Journal of
Clinical Medicine

Special Issue Reprint

New Advances in Dyslipidemia

Edited by
Nathan Wong

mdpi.com/journal/jcm

MDPI

New Advances in Dyslipidemia

New Advances in Dyslipidemia

Editor

Nathan Wong

MDPI

Basel • Beijing • Wuhan • Barcelona • Belgrade • Novi Sad • Cluj • Manchester

Editor
Nathan Wong
Division of Cardiology,
University of California
Irvine, USA

Editorial Office
MDPI
St. Alban-Anlage 66
4052 Basel, Switzerland

This is a reprint of articles from the Special Issue published online in the open access journal *Journal of Clinical Medicine* (ISSN 2077-0383) (available at: https://www.mdpi.com/journal/jcm/special_issues/advances_dyslipidemia).

For citation purposes, cite each article independently as indicated on the article page online and as indicated below:

Lastname, A.A.; Lastname, B.B. Article Title. *Journal Name* **Year**, *Volume Number*, Page Range.

ISBN 978-3-0365-9871-0 (Hbk)
ISBN 978-3-0365-9872-7 (PDF)
doi.org/10.3390/books978-3-0365-9872-7

Contents

Journal of
Clinical Medicine

MDPI

Editorial

Is Lipoprotein(a) the Most Important Predictor of Residual Atherosclerotic Cardiovascular Disease Risk?

Nathan D. Wong

Heart Disease Prevention Program, Division of Cardiology, University of California, Irvine, CA 92697, USA; ndwong@hs.uci.edu

Lipoprotein(a) is an underrecognized, but significant genetic risk factor for atherosclerotic cardiovascular disease (ASCVD), shown to be causal from data from prospective epidemiologic studies, Mendelian randomization, and genome wide association studies [1]. With therapies in development targeting reduction of lipoprotein(a), it is important to better understand the strength of its prediction, especially in relation to other lipid and non-lipid determinants of cardiovascular outcomes.

What is not clear is its relative importance to other prognostic factors in persons with ASCVD. Moreover, not well-described is the relative importance of lipoprotein(a) once LDL-C is well-controlled in statin-treated ASCVD patients, given that this is the current standard of care in such patients. Most studies have not quantitatively reported on the relative contribution of lipoprotein(a) with other risk factors for the prediction of ASCVD events, even though such analyses are available. We examined this issue in a secondary analysis of the previously reported "Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH)" clinical trial [2]. This trial studied 3414 participants aged 45 years or older with documented ASCVD including either coronary artery disease, cerebrovascular or carotid disease, or symptomatic peripheral arterial disease in addition to having atherogenic dyslipidemia defined as: (1) low density lipoprotein-cholesterol (LDL-C) of less than or equal to 160 mg/dL (4.1 mmol/L); (2) high density lipoprotein-cholesterol (HDL-C) of less than or equal to 40 mg/dL (1.0 mmol/L) for men or less than or equal to 50 mg/dL (1.3 mmol/L) for women; and (3) triglycerides greater than or equal to 150 mg/dL (1.7 mmol/L) and less than or equal to 400 mg/dL (4.5 mmol/L). Subjects were on statin therapy (40 mg simvastatin) and randomized to niacin versus placebo. The trial terminated early (at a mean follow-up of 3 years) due to a lack of efficacy for niacin in reducing ASCVD risk.

In our analysis of 3271 subjects with complete risk factor information, we created a 5-year risk prediction model (validated by 10-fold cross validation) for recurrent ASCVD events incorporating key variables of interest for the prediction of subsequent ASCVD events. We had follow-up for ASCVD events up to 6 years (mean 4.2 years), during which 16% of patients suffered a recurrent ASCVD event [3]. Our modelling considered key variables known to be associated with CVD and were available at baseline in our study, including age, sex, race, body mass index, blood pressure, LDL-C, HDL-C, triglycerides, lipoprotein(a), apolipoprotein A1, apolipoprotein B, smoking status, alcohol consumption, family history of cardiovascular disease (CVD), glycated hemoglobin, atrial fibrillation, serum creatine, homocysteine, specific ASCVD conditions (previous myocardial infarction, stroke, heart failure, carotid, or peripheral arterial disease), antihypertensive or diabetes drugs, aspirin use, previous use of higher versus lower intensity statins, body mass index, non-HDL-C, estimated glomerular filtration rate, pulse pressure, and treatment assignment. We allowed variables to enter if they were $p < 0.15$ in significance. *In the final prediction model, based on Wald Chi-square values, lipoprotein(a) was the strongest predictor of recurrent ASCVD events (Chi-sq = 18.2, $p < 0.0001$)*, followed by family history of cardiovascular disease (Chi-sq = 10.7, $p = 0.001$), homocysteine (Chi-sq = 9.5, $p = 0.002$), alcohol

Citation: Wong, N.D. Is Lipoprotein(a) the Most Important Predictor of Residual Atherosclerotic Cardiovascular Disease Risk? *J. Clin. Med.* **2022**, *11*, 4380. https://doi.org/10.3390/jcm11154380

Received: 19 July 2022
Accepted: 25 July 2022
Published: 28 July 2022

use (inversely) (Chi-sq = 6.0, $p = 0.014$), diabetes (Chi-sq = 5.9, $p = 0.015$), and male sex (Chi-sq = 5.0, $p = 0.025$). In our study, a 1 SD of lipoprotein(a) increment (37 nmol/L, or approximately 15 mg/dL) was associated with a 7% increase of ASCVD risk among our cohort of statin-treated patients with prior ASCVD. Of interest, neither age nor LDL-C entered the multivariable model; given that subjects were on statin therapy and LDL-C was well-controlled in many participants, the more limited range in LDL-C may have precluded its entry into the model. It is also possible other variables that were not available to us such as time since prior CVD event or number or severity of prior events could also have been important predictors of residual risk. To the best of our knowledge, our report is unique in quantifying lipoprotein(a) as the strongest predictor of ASCVD events, specifically in a secondary prevention population with known ASCVD on statin therapy.

As our study involved persons with ASCVD on statin therapy, it is possible that lipoprotein(a) is a stronger predictor of ASCVD in persons on statin therapy compared to not being on statin therapy. In a previously published meta-analysis of seven statin trials, Willeit et al. [4] showed lipoprotein(a) to predict future ASCVD event more strongly in those on statin treatment as compared to on placebo, with multivariable adjusted HR's for those with lipoprotein(a) $\geq$50 mg/dL vs. <50 mg/dL of 1.47 and 1.26, respectively ($p = 0.03$ for interaction). Moreover, in our subsequent report from the AIM-HIGH trial [5] we showed among statin-treated patients with ASCVD that compared to lipoprotein(a) <15 mg/dL, those with levels of $\geq$70 mg/dL had an adjusted HR for first recurrent events of 1.77 and total recurrent events of 1.51 (both $p < 0.0001$). Also, is lipoprotein(a) a stronger predictor in primary or secondary prevention? While our study included only persons with known ASCVD, in the UK Biobank [6] a lipoprotein(a) of $\geq$150 nmol/L was present in 12.2% of those without and 20.3% of those with pre-existing ASCVD and was associated with HR, 1.50 (95% CI, 1.44–1.56) and HR, 1.16 (95% CI, 1.05–1.27) for incident ASCVD, respectively, showing lipoprotein(a) to be a stronger risk factor in primary prevention. However, in this study lipoprotein(a) was a weaker predictor for those on statins compared to those not on statins (interaction $p < 0.0001$). In a more recent report among 413,734, participants from UK Biobank [7], adding Lp(a) to a prediction model containing traditional CVD risk factors in the primary prevention group improved the C-index by 0.0017 (95% CI 0.0008–0.0026) and population attributable fractions (PAF) in the whole cohort of 5.8% and 3.0% were associated with Lp(a) values above 100 nmol/L and above 175 nmol/L, respectively. Moreover, in a meta-analysis of 17 studies including 283,328 patients specifically with known coronary disease, elevated lipoprotein(a) level was independently associated with the future risk of cardiac events (RR 1.78; 95% CI 1.31–2.42) as well as overall cardiovascular events (RR 1.29; 95% CI 1.17–1.42) [8]. A smaller study of only 258 patients [9] who had severe carotid and/or lower extremity disease, a lipoprotein(a) level >30 mg/dL did appear to be among the strongest predictors of the primary and secondary composite cardiovascular disease endpoints in multivariable analysis, with only prior myocardial infarction and/or ischemic stroke (and not age, sex, or other risk factors) also predicting outcomes. However, these studies did not rank the order of importance of variables in the prediction of future cardiovascular outcomes. In a much older study of examining the relative strength of predictors of angiographically-defined coronary artery disease, age, family history, apolipoprotein B, and lipoprotein(a) (in that order) were identified to be the most important predictors of coronary disease [10].

While our analysis from the AIM-HIGH cohort is a selected clinical trial sample, it provides evidence, at least in persons with known ASCVD on statin therapy, that lipoprotein(a) may be among the most important predictors of future cardiovascular disease outcomes. Future studies should report the relative contribution of lipoprotein(a) with other predictors for cardiovascular disease outcomes both among primary and secondary prevention cohorts and according to use of statin therapy. A better understanding of the relative strength of lipoprotein(a) in relation to other risk factors for predicting ASCVD events can serve to help inform future efforts to improve screening for and potentially treating elevated lipoprotein(a).

Funding: No funding was received for preparation of this manuscript.

Conflicts of Interest: Nathan Wong receives research support through the University of California, Irvine from Novartis and Novo Nordisk.

References

1. Tsimikas, S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J. Am. Coll. Cardiol.* **2017**, *69*, 692–711. [CrossRef] [PubMed]
2. AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N. Engl. J. Med.* **2011**, *365*, 2255–2267. [CrossRef] [PubMed]
3. Wong, N.D.; Zhao, Y.; Xiang, P.; Coll, B.; López, J.A.G. Five-Year Residual Atherosclerotic Cardiovascular Disease Risk Prediction Model for Statin Treated Patients with Known Cardiovascular Disease. *Am. J. Cardiol.* **2020**, *137*, 7–11. [CrossRef] [PubMed]
4. Willeit, P.; Ridker, P.M.; Nestel, P.J.; Simes, J.; Tonkin, A.M.; Pedersen, T.R.; Schwartz, G.G.; Olsson, A.G.; Colhoun, H.M.; Kronenberg, F.; et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: Individual patient-data meta-analysis of statin outcome trials. *Lancet* **2018**, *392*, 1311–1320. [CrossRef]
5. Wong, N.D.; Zhao, Y.; Sung, J.; Browne, A. Relation of First and Total Recurrent Atherosclerotic Cardiovascular Disease Events to Increased Lipoprotein(a) Levels Among Statin Treated Adults with Cardiovascular Disease. *Am. J. Cardiol.* **2021**, *145*, 12–17. [CrossRef] [PubMed]
6. Patel, A.P.; Wang, M.; Pirruccello, J.P.; Ellinor, P.T.; Ng, K.; Kathiresan, S.; Khera, A.V. Lp(a) (Lipoprotein[a]) Concentrations and Incident Atherosclerotic Cardiovascular Disease: New Insights from a Large National Biobank. *Arterioscler. Thromb. Vasc Biol.* **2021**, *41*, 465–474. [CrossRef] [PubMed]
7. Welsh, P.; Welsh, C.; Celis-Morales, C.A.; Brown, R.; Ho, F.K.; Ferguson, L.D.; Mark, P.B.; Lewsey, J.; Gray, S.R.; Lyall, D.M.; et al. Lipoprotein(a) and cardiovascular disease: Prediction, attributable risk fraction, and estimating benefits from novel interventions. *Eur. J. Prev. Cardiol.* **2022**, *28*, 1991–2000. [CrossRef] [PubMed]
8. Wang, Z.; Zhai, X.; Xue, M.; Cheng, W.; Hu, H. Prognostic value of lipoprotein (a) level in patients with coronary artery disease: A meta-analysis. *Lipids Health Dis.* **2019**, *18*, 150. [CrossRef]
9. Ezhov, M.V.; Tmoyan, N.A.; Afanasieva, O.I.; Afanasieva, M.I.; Pokrovsky, S.N. Lipoprotein(a) and Cardiovascular Outcomes after Revascularization of Carotid and Lower Limbs Arteries. *Biomolecules* **2021**, *11*, 257. [CrossRef] [PubMed]
10. Hearn, J.A.; DeMaio S.J., Jr.; Roubin, G.S.; Hammarstrom, M.; Sgoutas, D. Predictive value of lipoprotein (a) and other serum lipoproteins in the angiographic diagnosis of coronary artery disease. *Am. J. Cardiol.* **1990**, *66*, 1176–1180. [CrossRef]

Journal of
Clinical Medicine

MDPI

Review

Global Trends in the Epidemiology and Management of Dyslipidemia

Tianxiao Liu, Dong Zhao * and Yue Qi *

Center for Clinical and Epidemiological Research, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, The Key Laboratory of Remodeling-Related Cardiovascular Diseases, Ministry of Education, Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing 100029, China
* Correspondence: deezhao@vip.sina.com (D.Z.); qiyue_bjcn@mail.ccmu.edu.cn (Y.Q.)

Abstract: Dyslipidemia, especially a circulating non-optimal level of cholesterol, is one of the most important risk factors for atherosclerotic cardiovascular disease (ASCVD), which accounts for the most deaths worldwide. Maintaining a healthy level of blood cholesterol is an important prevention strategy for ASCVD, through lifestyle intervention or cholesterol-lowering therapy. Over the past three decades, the epidemiology and management of dyslipidemia has changed greatly in many countries. Therefore, it is necessary to understand the current epidemiologic features of dyslipidemia and challenges from a global perspective.

Keywords: dyslipidemia; epidemiology; guidelines; therapy; management

Citation: Liu, T.; Zhao, D.; Qi, Y. Global Trends in the Epidemiology and Management of Dyslipidemia. *J. Clin. Med.* **2022**, *11*, 6377. https://doi.org/10.3390/jcm11216377

Academic Editor: Nathan D. Wong

Received: 9 September 2022
Accepted: 26 October 2022
Published: 28 October 2022

1. Introduction

Circulating non-optimal cholesterol, including increased low-density lipoprotein cholesterol (LDL-C) and remnant cholesterol carried by triglyceride-rich lipoproteins, comprises the main type of dyslipidemia worldwide and is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) [1]. It has been well demonstrated that atherosclerosis is causally associated with the retention of low-density lipoprotein (LDL) in the intima, which is the main deliverer of cholesterol to the focal areas of the artery wall. Cholesterol in LDL induces the activation of vascular endothelial cells, which subsequently recruit monocytes into the sub-endothelial space, and promote macrophage activation and inflammatory response in the arterial intima. Furthermore, these macrophages engulf LDL in the intima and turn into foam cells, giving rise to atherosclerotic lesions and eventually triggering ischemic heart disease (IHD), ischemic stroke, and other ASCVDs [2–4]. Additionally, remnant cholesterol carried by triglyceride-rich lipoproteins is also recognized to play a causal role in atherosclerosis development, similarly to LDL-C [5]. Non-high-density lipoprotein cholesterol (non-HDL-C), including LDL-C and remnant cholesterol, has been considered as cholesterol carried by both atherogenic lipoproteins. Therefore, LDL-C and non-HDL-C have been widely used as lipid-lowering targets. Effective treatment strategies for lowering LDL-C, including statin monotherapy, statin with ezetimibe, or statin with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have contributed to the reduction of further ASCVD events proportional to the absolute reduction in LDL-C [6–8]. However, ASCVD still remains the top cause of death globally, despite advances in controlling dyslipidemia in many countries. It is important to understand the global epidemiologic features and advances in the management of dyslipidemia, so as to identify the key issues or barriers of alleviating current and future burdens of dyslipidemia-related disease. Many studies have reported on the epidemiology trends in dyslipidemia and its management at the country or region level [9,10], and a few studies have analyzed lipid levels and changes overtime on a global scale [11,12]. However, a review article summarizing the current knowledge combined with the epidemiology and management of dyslipidemia

from a global perspective is lacking. Therefore, in this review, we will summarize the developments in global trends in the epidemiology and management of dyslipidemia.

The data presented in this review are mainly identified from four sources. The first data source is an open database of population-based data on risk factors collected by the Non-communicable diseases (NCD) Risk Factor Collaboration (NCD-RisC) [13], a worldwide network of health scientists that provides rigorous and timely data. The second data source is the open database of the Global Burden of Disease (GBD) study in the Global Health Data Exchange of the Institute for Health Metrics and Evaluation [14], with available information on the mortality rate, number, and proportion of deaths from various diseases at global, regional, and country levels. The third source is the MEDLINE database, which we searched for relevant publications regarding the epidemiology and management of dyslipidemia in the past 10 years, studies on the burden of disease associated with dyslipidemia, and country-specific guidelines on dyslipidemia management. The final source is the international guideline library of the Guidelines International Network (GIN) [15], which contains the latest guidelines across the globe.

Through investigation of the available data and published reports, we identify features of the global trends on the epidemiology and management of dyslipidemia worldwide, as described below.

2. Global Epidemiology of Dyslipidemia

The NCD-RisC study is the largest worldwide study so far on the global distribution of blood cholesterol and changing trends [13]. This study pooled data of 102.6 million individuals aged 18 years and older collected from 1127 population-based studies in 200 countries and territories, including 48 studies from Sub-Saharan Africa; 28 from Central Asia, the Middle East, and North Africa; 6 from South Asia; 16 from East and Southeast Asia; 17 from Oceania; 3 from high-income Asia-Pacific countries; 35 from Latin America and the Caribbean; 27 from high-income Western countries; and 20 from Central and Eastern Europe. The NCD-RisC study provided comparisons of the age-standardized mean total cholesterol (TC) and non-HDL-C among countries and regions from 1980 to 2018 [13]. Globally, little or no change was observed between 1980 and 2018 in the global age-standardized mean of TC and non-HDL-C, yet substantial differences exist among countries and regions, as reported in the latest two articles [11,12].

Based on the data from the NCD-RisC study, we summarized non-HDL-C levels and their changes across countries and exhibited the features for the global epidemiology of non-HDL-C levels. Over the past four decades, the median value of the global age-standardized mean non-HDL-C was almost unchanged in men rising from 3.36 mmol/L [interquartile range, 2.82–3.90 mmol/L] in 1980 to 3.37 mmol/L [3.04–3.59] in 2018, and decreased slightly in women from 3.44 mmol/L [interquartile range, 2.83–3.91 mmol/L] in 1980 to 3.34 mmol/L [3.08–3.54] in 2018 across the 200 countries. However, the majority of countries with the highest levels of age-standardized mean non-HDL-C in 1980 experienced significant declines. As shown in Figure 1A,B, the top 10 countries with the highest age-standardized mean levels of non–HDL-C levels in 1980 were mainly high-income countries in Western Europe and Singapore, which had age-standardized mean levels of non–HDL-C of >4.7 mmol/L in men and >4.5 mmol/L in women.

These countries underwent the largest reduction over the past four decades, with age-standardized mean levels of non-HDL-C decreasing more than 1.0 mmol/L from 1980 to 2018 (Figure 2).

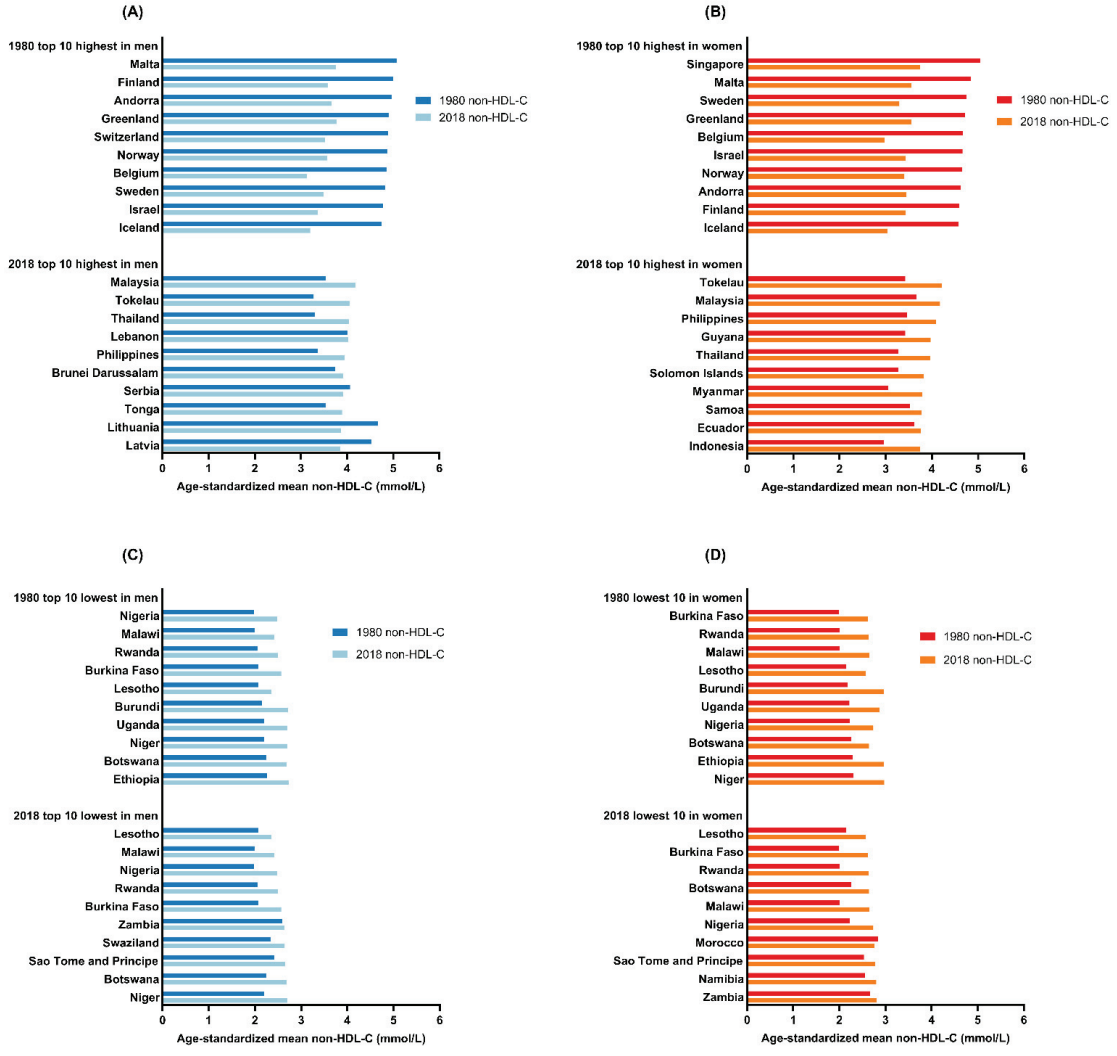

Figure 1. Top 10 countries with the highest and lowest age-standardized mean non-HDL-C levels in 1980 and 2018 for men and women. (**A**), Top 10 countries with the highest age-standardized mean non-HDL-C in men. (**B**), Top 10 countries with the highest age-standardized mean non-HDL-C in women. (**C**), Top 10 countries with the lowest age-standardized mean non-HDL-C in men. (**D**), Top 10 countries with the lowest age-standardized mean non-HDL-C for women. Data obtained from NCD-RisC study. Available online: https://www.ncdrisc.org (accessed on 1 July 2022) [13]. Abbreviations: non-HDL-C, non-high-density lipoprotein cholesterol.

The age-standardized mean levels of non-HDL-C in these European countries decreased to the global average level in 2018 (Figure 1A,B). By contrast, the age-standardized mean non–HDL-C in Singaporean women ranked the highest at 5.0 mmol/L in 1980 across 200 countries (Figure 1B), yet this number reduced to 3.7 mmol/L, which decreased to 11th, in 2018. On the other hand, the top 10 countries with the highest age-standardized mean non–HDL-C levels in 2018 were predominantly composed of developing countries from Southeast Asia, Western Asia, and Oceania. These countries had lower age-standardized mean non-HDL-C levels (<3.8 mmol/L) in 1980, and have experienced a large increase over

the past four decades (Figure 2). In addition to these countries, others have also experienced a substantial increase. In particular, age-standardized mean non-HDL-C in Chinese men increased 0.61 mmol/L over 40 years, ranking from 153rd in 1980 to 99th in 2018, which reached or surpassed the non-HDL-C levels of some Western countries. As for the top 10 countries with the lowest age-standardized mean non-HDL-C levels in 1980, many countries in Africa registered no such changes and are still below the global average level over the past four decades (Figure 1C,D). These changes in age-standardized mean non-HDL-C diminished the variation of non-HDL-C among countries from 1980 to 2018. The upper quartile of global age-standardized mean non-HDL-C from 1980 to 2018 decreased, for men from 3.90 mmol/L to 3.59 mmol/L, and for women from 3.91 mmol/L to 3.54 mmol/L, while the lower quartile of age-standardized mean non-HDL-C from 1980 to 2018 increased, for men from 2.82 mmol/L to 3.04 mmol/L, and for women from 2.83 mmol/L to 3.08 mmol/L. Additionally, the standard deviation of global age-standardized mean non-HDL-C among the 200 countries from 1980 to 2018 decreased from 0.76 mmol/L to 0.38 mmol/L in men and from 0.69 mmol/L to 0.31 mmol/L in women. Genetic and endemic factors also have a great influence on blood cholesterol level [16]. However, the data of the NCD-RisC study is collected at the national level, which cannot describe the epidemiology of dyslipidemia in ethnically and culturally heterogeneous populations. It is necessary to explore the influence of genetic and endemic factors on the epidemiology of dyslipidemia in the future.

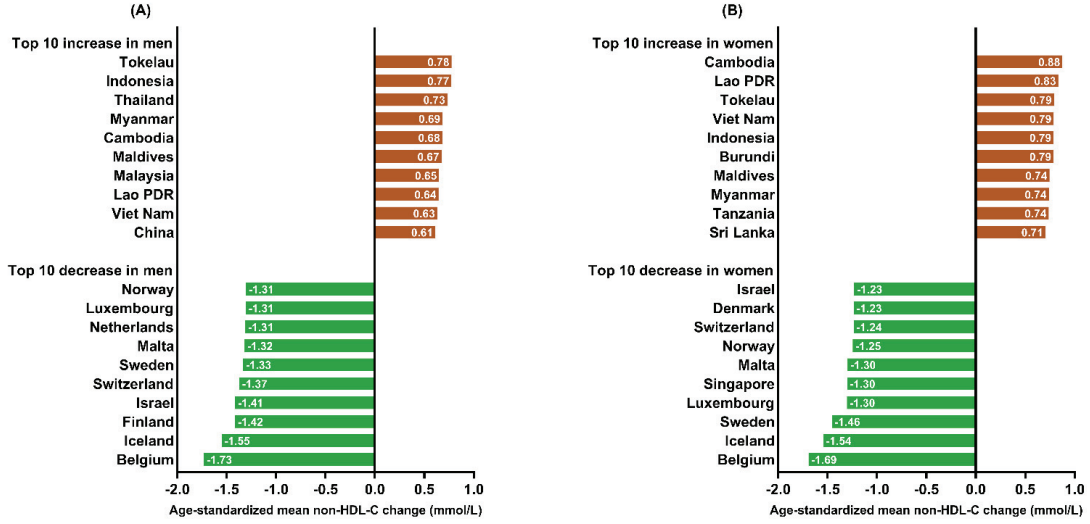

Figure 2. Top 10 countries with the largest increases and decreases of age-standardized mean non-HDL-C levels from 1980 to 2018 for men and women. (**A**), Top 10 countries with the largest increase and decrease of age-standardized mean non-HDL-C in men. (**B**), Top 10 countries with the largest increase and decrease of age-standardized mean non-HDL-C in women. Data obtained from NCD-RisC study. Available online: https://www.ncdrisc.org (accessed on 1 July 2022) [13]. Abbreviations: non-HDL-C, non-high-density lipoprotein cholesterol.

3. ASCVD Attributed to Dyslipidemia

The estimations of burden of ASCVD attributed to high LDL-C levels worldwide were based on data available in the GBD database [14]. According to the estimations of the GBD study in 2019, a total of 3.78 million deaths from IHD worldwide were attributable to high LDL-C levels, accounting for 44.3% of IHD deaths. While 0.61 million deaths from ischemic stroke were attributable to high LDL-C levels, accounting for 22.4% of ischemic stroke deaths [14]. Globally, these numbers have increased since 1990 (Figure 3).

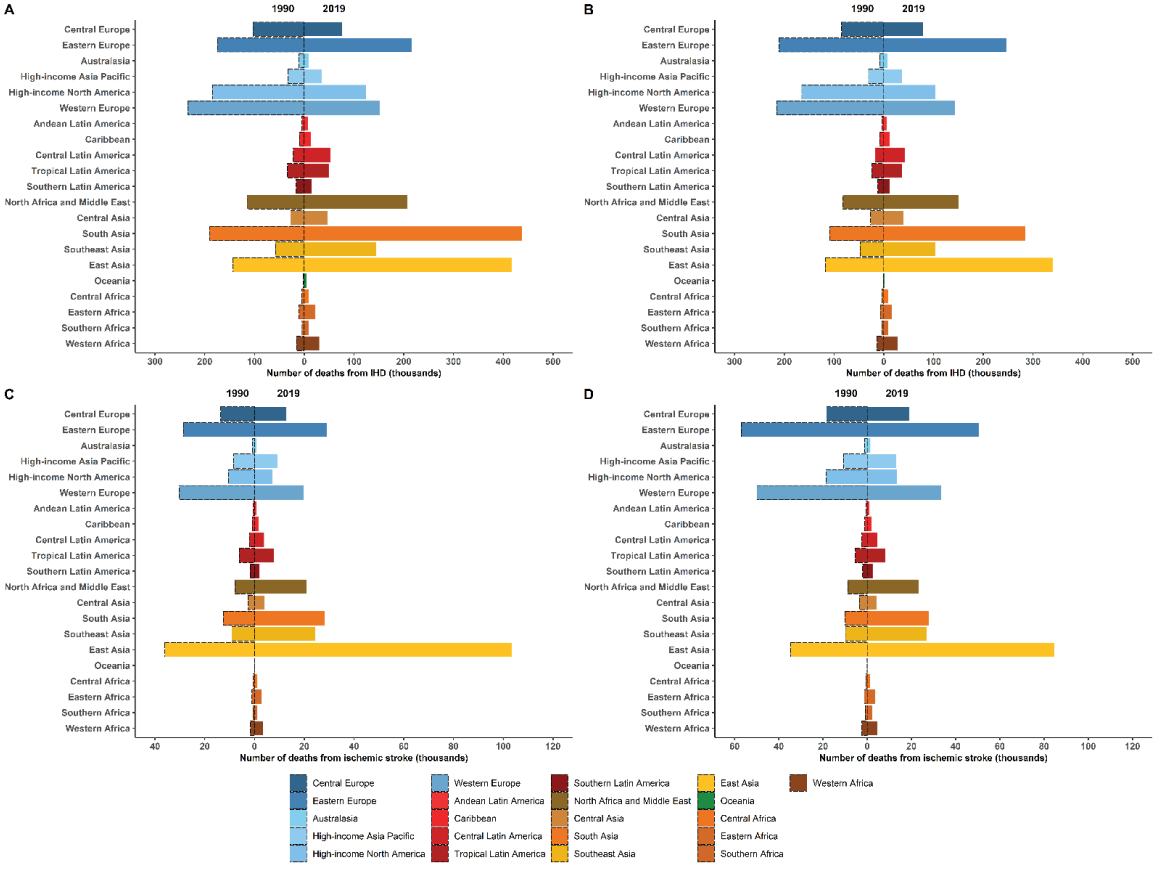

Figure 3. Change in deaths from ischemic heart disease and ischemic stroke attributable to high low-density lipoprotein cholesterol by region in 1990 and 2019. (**A**), Change in deaths from ischemic heart disease attributable to high low-density lipoprotein in men. (**B**), Change in deaths from ischemic heart disease attributable to high low-density lipoprotein in women. (**C**), Change in deaths from ischemic stroke attributable to high low-density lipoprotein in men. (**D**), Change in deaths from ischemic stroke attributable to high low-density lipoprotein in women. Data obtained from GBD database available on https://vizhub.healthdata.org/gbd-results/ (accessed on 1 July 2022) [14]. Abbreviations: IHD, ischemic heart disease.

The most important feature of this trend was the substantial increase in deaths attributable to high LDL-C levels in Asian countries. A consistent result was found in the NCD-RisC study [11]. The study reported that from 1990 to 2017, the number of deaths attributable to high non-HDL-C more than tripled in East Asia and more than doubled in Southeast Asia. The number of deaths attributable to high non-HDL-C in East, Southeast and South Asia accounted for 25% of deaths attributable to high non-HDL-C worldwide in 1990 and rose to about 50% in 2017.

Global age-standardized death rates (ASDRs) for IHD and ischemic stroke attributable to high LDL-C levels had a 35.1% reduction and 34.2% reduction in men, and a 38.1% reduction and 42.8% reduction in women over the last 30 years, respectively. Most Western countries/territories corresponded to the global trends, with a decrease in ASDRs attributable to high LDL-C over the past three decades. However, for Asian countries, the ASDRs for IHD and ischemic stroke attributable to high LDL-C did not decrease

over the same 30 years and even significantly increased in Central Asia and East Asia (Figures 4 and 5).

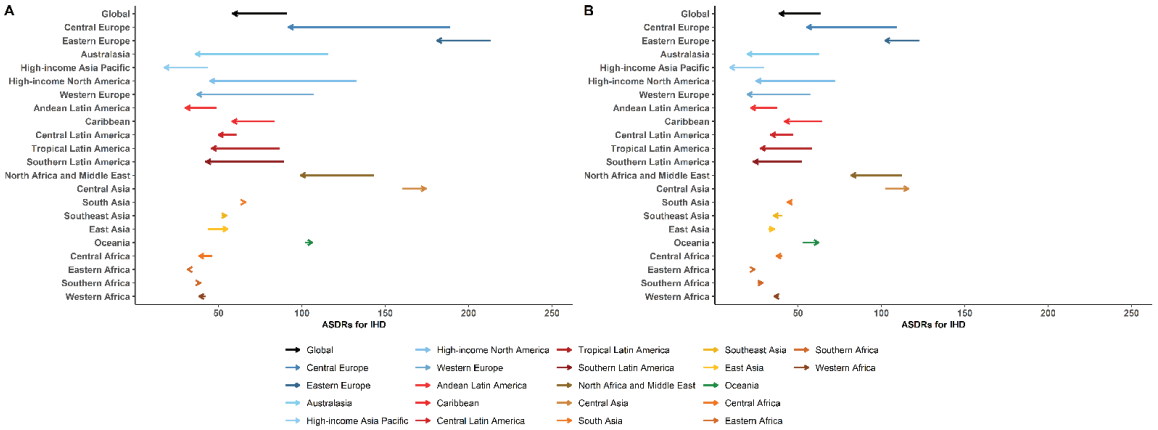

Figure 4. Change in age-standardized death rates per 100,000 of the general population from ischemic heart disease attributable to high low-density lipoprotein cholesterol between 1990 and 2019 by region for men (**A**) and women (**B**). Data obtained from the GBD database available on https://vizhub.healthdata.org/gbd-results/ (accessed on 1 July 2022) [14]. Abbreviations: ASDRs, age-standardized death rates; IHD, ischemic heart disease.

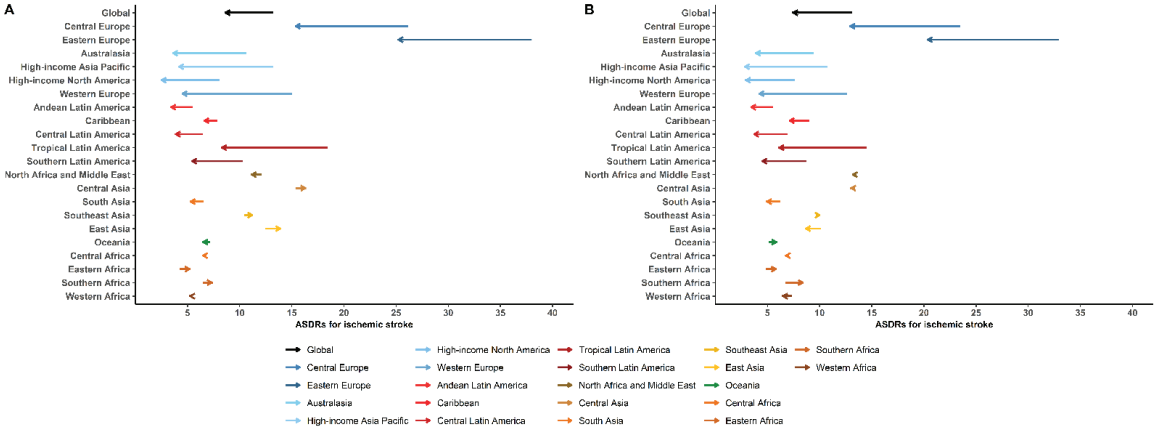

Figure 5. Change in age-standardized death rates per 100,000 of the general population from ischemic stroke attributable to high low-density lipoprotein cholesterol between 1990 and 2019 by region for men (**A**) and women (**B**). Data obtained from GBD database available on https://vizhub.healthdata.org/gbd-results/ (accessed on 1 July 2022) [14]. Abbreviations: ASDRs, age-standardized death rates.

On the other hand, many African countries have experienced no change in ASDRs attributable to high LDL-C since 1990, and remained low in 2019. Considerable heterogeneity exists both within and between populations worldwide, despite the similarly huge and growing burden of cardiovascular disease (CVD), reaffirming the need to reprioritize the global management and control of non-optimal cholesterol within populations.

4. Management of Dyslipidemia

From a global perspective, the use of lipid-lowering medications in high risk people has been recommended by all relevant CVD prevention guidelines issued by professional

societies of different countries or regions. The increasing availability and utility of statins have greatly contributed to the reduction of LDL-C related ASCVD burden. Education of the public to improve awareness about dyslipidemia-related CVD risk, increasing the opportunity for lipid testing and ASCVD risk assessment, and developing and updating clinical guidelines on dyslipidemia are also key issues to improve dyslipidemia management. In the past 20 years, such factors have resulted in considerable changes in lipid levels in many countries worldwide [17,18]. However, regions with different social demographic features show discrepancies in the management strategies of dyslipidemia.

4.1. Guidelines for Dyslipidemia Management

As highlighted in the data on the global epidemiology of dyslipidemia and burden of cardiovascular disease, there is considerable variation in dyslipidemia-related ASCVD risk across countries. Thus, the anticipated benefits in terms of CVD prevention as a consequence of effective implementation of either population-wide lifestyle change strategies or treatment of high risk individuals with cholesterol-lowering medication differ across ethnically and culturally heterogeneous populations. In this review, we summarize the differences in guidelines for the management of plasma lipid disorders issued by different countries or professional organizations [19–35]. Newly updated guidelines for most countries have been published after 2015 and are therefore based on relatively recent research evidence to provide time-sensitive guidance. Clinical guidelines have an essential role in guiding clinical practice by providing physicians with recommendation based on these latest data. As a guide to management strategies, there are some similarities in the guidelines issued by Western and non-Western countries.

All guidelines support lifestyle modification as an effective method to manage lipid level. Most clinical guidelines across countries recommend treatment strategies as a function of CVD risk assessment and untreated LDL-C levels for the purpose of keeping LDL-C within the specific target values. Almost all guidelines recommend LDL-C as the primary treatment target, and non-HDL-C and/or apolipoprotein B as the secondary treatment target [19–21,23,24,27,30,34]. Additionally, statins are the first-line agents in all guidelines. The addition of ezetimibe is recommended by most countries when the LDL-C goal is not achieved with the maximum tolerated dose of statins. Due to the successes of recent clinical trials, PCSK9 inhibitors are also recommended in some guidelines [19,21,24,27–30,34]. Besides the two nonstatin widely recommended in some guidelines, bile acid sequestrants may be considered as an add-on drug with statins to reduce LDL-C. Fibrates are recommended to lower triglyceride levels [21,23–25,27–30,34], but there are still no trials to show the cardiovascular benefit of fibrates except for meta-analysis of high triglyceride and low HDL-C groups [36], and recently the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes study has been discontinued as pemafibrate was reported to be unlikely to reduce CVD risk [37]. Additionally, niacin is recommended for treatment of hypertriglyceridemia in some guidelines, yet this agent is not recommended in combination with statin therapy due to a lack of additional benefits for CVD prevention in patients who have achieved LDL-C goals [29,30]. Pure eicosapentaenoic acid (EPA) can lower CVD risk in persons with moderately high triglyceride levels on statin therapy, which is the conclusion of the Japan EPA Lipid Intervention Study and the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial [38,39]. Icosapent Ethyl is recommended to be used in combination with statins for specific patients with moderately high triglyceride levels in some guidelines [23,34]. Many agents for dyslipidemia treatment are under study. For example, acyl-coenzyme A: cholesterol acetyltransferase (ACAT) inhibitor was reported to decrease cholesteryl ester accumulation in macrophages in animal studies [40]. However, randomized controlled trials (RCT) using non-selective ACAT inhibitors failed to show benefits in the changes in coronary atheroma volume and carotid intima-media thickness [40], and no evidence from RCT for CVD outcomes is available.

However, some differences are also observed between guidelines issued by different countries and organizations at various time points. First, risk assessments are based on different lists of risk factors in different guidelines, even though some of the risk factors have neither enough data for CVD risk prediction and have not been evaluated in most risk-predictive models, nor an available interventional approach. As reported in our previous review on cardiovascular risk assessment [41], among the 10 guidelines on dyslipidemia, the risk-factor list ranged from five risk factors (including age, sex, systolic blood pressure, TC, and smoking) to 13 risk factors. Second, these guidelines recommend different algorithms to categorize CVD risk, which might be based on considerations of feasibility and practicability in local practice. An exponential model including 186 countries evaluated that using the same CVD risk estimation to initiate statins use, irrespective of age, sex, and country, is not appropriate globally. Considering current characteristics of the national population and safety in medication treatment to determine treatment strategy might be the optimal solution [42]. Third, different guidelines recommended different definitions of 'high risk'. The varying recommendations for risk assessment among country-specific guidelines are generally central to treatment decision-making in clinical practice. However, these notable differences in the definition of high risk between guidelines may lead to an individual categorizing in a completely different risk bracket according to different guidelines developed by different organizations in different countries or regions, or even different guidelines developed in the same country or region. Fourth, the LDL-C treatment goals are also different among guidelines recommended by a comprehensive cardiovascular risk reduction strategy. In the 2019 European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias [34], the LDL-C target goal is <55 mg/dL for individuals with very high risk in primary or secondary prevention. In patients with ASCVD who experienced a second vascular event within 2 years, it is recommended to lower LDL-C to less than 40 mg/dL (Table S1), which is consistent with the recommendations for patients who have extreme risk of Polish Lipid Association published in 2021 [27]. This further risk stratification for patients with ASCVD is considered in more and more countries.

The initial doses of statins recommended by the guidelines also differ. Most country-specific guidelines recommend the dose of statins should be based on baseline ASCVD risk and expected LDL-C reduction of that risk [22,24,27,28,35], while some countries only mentioned the initial dose in very high and high risk individuals [25,26]. High-intensity statins or a maximally tolerated dose of statins are the most common therapeutic dose for individuals with very high and/or high CVD risk [20,21,25,30,32–34]. Moderate-intensity statins are recommended in Chinese guideline considering the safety of the high-intensity statins in the Chinese population [19].

Another aspect that merits special concern is the screening for genetic dyslipidemias. For example, as an important type of genetic dyslipidemias, screening for familial hypercholesterolemia (FH) has been recommended by the guidelines issued by the American Association of Clinical Endocrinologists and American College of Endocrinology, the National Institute for Health and Care Excellence, Japan Atherosclerosis Society, the Chinese Society of Cardiology and Philippine Heart Association [19,20,23–25,28–30,33–35]. However, the majority of national guidelines worldwide have no such recommendation, leaving room for enhanced detection of FH.

Inconsistencies in the recommendations for the management of dyslipidemia might be a contributing factor to low implementation in clinical practice. Additionally, for some countries in most parts of Africa and Eastern Europe, no local clinical practice guidelines exist for dyslipidemia.

4.2. Treatment and Control of Dyslipidemia

For the global population, advocating a healthy lifestyle, understanding the harm of dyslipidemia, and preventing the occurrence of dyslipidemia in early stages are the cornerstones of ASCVD prevention. For individuals with a high risk of ASCVD and

patients with established ASCVD, the key point is to ensure the use of lipid-lowering drugs and improve the treatment and control rate of dyslipidemia. However, the treatment and control rates show great differences across various countries.

Substantial decreases in non-HDL-C levels and subsequent reductions in the ASCVD burden in high-income Western countries during the past 30 years were partly owing to the contribution of lipid-lowering therapy. One study used data from the National Health and Nutrition Examination Survey from 2011 to 2012 and found that the treatment and control rate of dyslipidemia in the United States of America (USA) reached 54.1% and 66.0%, respectively [43]. The use of lipid-lowering drugs, especially statins has increased, which may be attributable to the availability of generic statins and reduced drug prices in health care systems. A retrospective longitudinal cohort study conducted from 2002 to 2013 in 157,000 adults aged 40 years and older in the USA [44] demonstrated that statins use in the general population increased 79.8%, especially the proportion of generic statins, from 8.4% in 2002–2003 to 81.8% in 2012–2013. However, the uptake of statins was suboptimal among patients with established ASCVD, at 49.8% in 2002–2003 and 58.1% in 2012–2013. The total expenditures and out-of-pocket expenditures associated with statins decreased, and further substitution of brand-name statins to generic statins may yield greater savings. In addition to the cornerstone role of statins in reducing ASCVD risk, the role of lipid lowering treatment beyond statins cannot be ignored. There is considerable evidence supporting the benefits of nonstatin cholesterol-lowering medications in combination with statins, especially cholesterol absorption inhibitors (ezetimibe) and PCSK9 inhibitors [45,46]. Nonstatin use in the USA adult population has also increased by 124%, from 2.5% in 2002–2003 to 5.6% in 2012–2013, and 15.9% of high-intensity statin users also used nonstatin in 2012–2013 [47].

By contrast, among countries in East and Southeast Asia (for example, China and Malaysia) that have had substantial increases in non-HDL-C levels and dyslipidemia-related ASCVD risk over the past 30 years, the treatment and control rates are unsatisfied. In the China Chronic Disease and Risk Factor Surveillance conducted among 163,641 Chinese adults aged > 18 years from 2013 to 2014, 11.2% were at high or very high risk of ASCVD. Among them, 74.5% individuals with high risk and 93.2% individuals with very high risk did not achieve their LDL-C lowering targets. Among the population with high and very high ASCVD risk that did not achieve their LDL-C lowering targets, only 5.5% and 14.5% received lipid-lowering drugs, respectively [48]. Although several studies have shown that the rate of statin utilization in Chinese patients with acute myocardial infarction during hospital admission has improved substantially in recent years [49], low adherence of statin use was found after discharge. A nationwide registry study with 192 participating hospitals from 2014 to 2018 among 6523 Chinese patients with acute coronary syndrome and a history of myocardial infarction or revascularization found that 50.8% were receiving lipid-lowering therapy before hospitalization (statin monotherapy in 98.4%, combination therapy in 1.2%), and only 30.1% of patients had LDL-C < 70 mg/dL at admission [50]. These studies suggest that statins use is inadequate in these regions. This seems to be related to many factors, including the availability and affordability of medications in hospitals or clinics at different levels, quality of care from medical service providers, and adherence to treatment by patients. The availability of medications is of utmost importance. One nationwide study assessed the availability of lipid-lowering medications in a survey of 3041 primary care institutions from 2016 to 2017, which included 145 community health centers, 384 community health stations from urban areas, 243 township health centers, and 2269 village clinics from rural areas in 31 Chinese provinces [51]. The availability of statins at these primary care institutions was only 49.7%, and village clinics had the lowest statin availability (43.7%) among the four types of institutions. This study was the first to address this important issue in a nationwide survey in these regions. The marked deficiencies in statins availability at primary care institutions are not consistent with the health needs of the population and have implications for patients' health, which may mostly restrict the impact of lipid-lowering medication on reducing the CVD burden. Except concerning

the marked underuse of lipid-lowering drugs for those meeting treatment criteria, more importantly, lipid-lowering therapy would certainly result in a higher economic burden from a public health perspective. In Western countries, statins therapy is cost-effective or cost-saving, especially in people with high CVD risk [52–54]. In China, with the intervention of government policy in recent years, the cost-effectiveness of lipid-lowering medication has significantly improved in Chinese population [55,56].

Effective community-based prevention strategies that promote lifestyle modification (e.g., dietary improvement and regular physical activity) are also needed to control dyslipidemia in the whole population and prevent the occurrence of dyslipidemia at an early stage. Understanding dyslipidemia related CVD risk and regular monitoring of blood lipids is also crucial. A large survey from 2007 to 2010 conducted in 43,368 Chinese adults aged $\geq$ 18 years reported that the awareness rate for dyslipidemia was 31.01% [57]. These data suggest the need to raise awareness of dyslipidemia among the general population and clinicians and increase the capacity of primary care institutions to screen and diagnose dyslipidemia in community residents.

5. Summary

This review provides a comprehensive overview of the global dyslipidemia epidemic and its management. The current features of epidemics of dyslipidemia include: (1) Differences in age-standardized non-HDL-C levels have been diminishing across countries over the past four decades, yet marked geographic differences in non-HDL-C levels still exist. (2) The global trend is that distribution of high non-optimal cholesterol has changed from high-income countries to some developing countries in East Asia and Southeast Asia. (3) Different countries and regions are in different stages of transition with respect to ASCVD burden, with decreased IHD and ischemic stroke deaths attributable to high LDL-C levels in high-income Western countries and a greatly increased burden of IHD and ischemic stroke deaths across Asian countries during this period. (4) This overview of cardiovascular risk assessment and dyslipidemia management from a global perspective can potentially guide countries in the development of their own risk assessment models and formulation of recommendations in their own guidelines according to the local requirements. (5) Notable differences exist in the treatment and control rate of dyslipidemia between different regions and countries, which emphasizes the need for consistent efforts to increase the compliance with medical treatment.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11216377/s1, Table S1: Differences of guideline recommendations for management of plasma lipid disorders [11,19–35,58].

Author Contributions: Conceptualization, T.L., Y.Q. and D.Z.; writing—original draft preparation, T.L.; writing—review and editing, Y.Q. and D.Z.; supervision, D.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sandesara, P.B.; Virani, S.S.; Fazio, S.; Shapiro, M.D. The Forgotten Lipids: Triglycerides, Remnant Cholesterol, and Atherosclerotic Cardiovascular Disease Risk. *Endocr. Rev.* **2019**, *40*, 537–557. [CrossRef]
2. Ference, B.A.; Ginsberg, H.N.; Graham, I.; Ray, K.K.; Packard, C.J.; Bruckert, E.; Hegele, R.A.; Krauss, R.M.; Raal, F.J.; Schunkert, H.; et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur. Heart J.* **2017**, *38*, 2459–2472. [CrossRef]
3. Boren, J.; Chapman, M.J.; Krauss, R.M.; Packard, C.J.; Bentzon, J.F.; Binder, C.J.; Daemen, M.J.; Demer, L.L.; Hegele, R.A.; Nicholls, S.J.; et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: Pathophysiological, genetic, and therapeutic insights: A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur. Heart J.* **2020**, *41*, 2313–2330. [CrossRef] [PubMed]
4. Chen, W.; Schilperoort, M.; Cao, Y.; Shi, J.; Tabas, I.; Tao, W. Macrophage-targeted nanomedicine for the diagnosis and treatment of atherosclerosis. *Nat. Rev. Cardiol.* **2021**, *19*, 228–249. [CrossRef]
5. Quispe, R.; Martin, S.S.; Michos, E.D.; Lamba, I.; Blumenthal, R.S.; Saeed, A.; Lima, J.; Puri, R.; Nomura, S.; Tsai, M.; et al. Remnant cholesterol predicts cardiovascular disease beyond LDL and ApoB: A primary prevention study. *Eur. Heart J.* **2021**, *42*, 4324–4332. [CrossRef] [PubMed]
6. Colhoun, H.M.; Betteridge, D.J.; Durrington, P.N.; Hitman, G.A.; Neil, H.A.W.; Livingstone, S.J.; Thomason, M.J.; Mackness, M.I.; Charlton-Menys, V.; Fuller, J.H. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet* **2004**, *364*, 685–696. [CrossRef]
7. Cannon, C.P.; Blazing, M.A.; Giugliano, R.P.; McCagg, A.; White, J.A.; Theroux, P.; Darius, H.; Lewis, B.S.; Ophuis, T.O.; Jukema, J.W.; et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N. Engl. J. Med.* **2015**, *372*, 2387–2397. [CrossRef] [PubMed]
8. Schwartz, G.G.; Steg, P.G.; Szarek, M.; Bhatt, D.L.; Bittner, V.A.; Diaz, R.; Edelberg, J.M.; Goodman, S.G.; Hanotin, C.; Harrington, R.A.; et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N. Engl. J. Med.* **2018**, *379*, 2097–2107. [CrossRef]
9. Al Rasadi, K.; Almahmeed, W.; AlHabib, K.F.; Abifadel, M.; Farhan, H.A.; AlSifri, S.; Jambart, S.; Zubaid, M.; Awan, Z.; Al-Waili, K.; et al. Dyslipidaemia in the Middle East: Current status and a call for action. *Atherosclerosis* **2016**, *252*, 182–187. [CrossRef] [PubMed]
10. Lee, Z.V.; Llanes, E.J.; Sukmawan, R.; Thongtang, N.; Ho, H.Q.T.; Barter, P.; Cardiovascular, RISk Prevention in Asia Network. Prevalence of plasma lipid disorders with an emphasis on LDL cholesterol in selected countries in the Asia-Pacific region. *Lipids Health Dis.* **2021**, *20*, 33. [CrossRef]
11. NCD Risk Factor Collaboration. Repositioning of the global epicentre of non-optimal cholesterol. *Nature* **2020**, *582*, 73–77. [CrossRef]
12. Pirillo, A.; Casula, M.; Olmastroni, E.; Norata, G.D.; Catapano, A.L. Global epidemiology of dyslipidaemias. *Nat. Rev. Cardiol.* **2021**, *18*, 689–700. [CrossRef]
13. NCD Risk Factor Collaboration. Available online: https://www.ncdrisc.org (accessed on 1 July 2022).
14. Global Burden of Disease Collaborative Network. GBD Results Tool. Available online: https://vizhub.healthdata.org/gbd-results/ (accessed on 1 July 2022).
15. Guidelines International Network. Available online: https://g-i-n.net/ (accessed on 1 July 2022).
16. Hoffmann, T.J.; Theusch, E.; Haldar, T.; Ranatunga, D.K.; Jorgenson, E.; Medina, M.W.; Kvale, M.N.; Kwok, P.Y.; Schaefer, C.; Krauss, R.M.; et al. A large electronic-health-record-based genome-wide study of serum lipids. *Nat. Genet.* **2018**, *50*, 401–413. [CrossRef]
17. Mortensen, M.B.; Falk, E.; Schmidt, M. Twenty-Year Nationwide Trends in Statin Utilization and Expenditure in Denmark. *Circ. Cardiovasc. Qual. Outcomes* **2017**, *10*. [CrossRef] [PubMed]
18. Vancheri, F.; Backlund, L.; Strender, L.E.; Godman, B.; Wettermark, B. Time trends in statin utilisation and coronary mortality in Western European countries. *BMJ Open* **2016**, *6*, e010500. [CrossRef]
19. Zhu, J.-R.; Gao, R.-L.; Zhao, S.-P.; Lu, G.-P.; Zhao, D.; Li, J.-J. 2016 Chinese guidelines for the management of dyslipidemia in adults. *J. Geriatr. Cardiol.* **2018**, *15*, 1–29. [CrossRef]
20. Gonzalez-Santos, L.E.; Oliva, R.; Jimeno, C.; Gonzales, E.; Margarita Balabagno, M.; Ona, D.; Cinco, J.E.; Baston, A.; Caole-Ang, I.; Fojas, M.; et al. Executive Summary of the 2020 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines. *J. ASEAN Fed. Endocr. Soc.* **2021**, *36*, 5–11. [CrossRef]
21. Malaysia Ministry of Health. Management of Dyslipidaemia 2017 5th Edition. Available online: http://www.acadmed.org.my/index.cfm?&menuid=67 (accessed on 1 July 2022).
22. Iyengar, S.S.; Puri, R.; Narasingan, S.N.; Wangnoo, S.K.; Mohan, V.; Mohan, J.C.; Misra, A.; Sriram, U.; Dalal, J.J.; Gupta, R.; et al. Lipid Association of India Expert Consensus Statement on Management of Dyslipidemia in Indians 2016: Part 1. *J. Assoc. Physicians India* **2016**, *64*, 7–52.

23. Kinoshita, M.; Yokote, K.; Arai, H.; Iida, M.; Ishigaki, Y.; Ishibashi, S.; Umemoto, S.; Egusa, G.; Ohmura, H.; Okamura, T.; et al. Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017. *J. Atheroscler. Thromb.* **2018**, *25*, 846–984. [CrossRef]
24. Rhee, E.J.; Kim, H.C.; Kim, J.H.; Lee, E.Y.; Kim, B.J.; Kim, E.M.; Song, Y.; Lim, J.H.; Kim, H.J.; Choi, S.; et al. 2018 Guidelines for the Management of Dyslipidemia in Korea. *J. Lipid Atheroscler.* **2019**, *8*, 78–131. [CrossRef]
25. Singapore Ministry of Health. MOH Clinical Practice Guidelines on Lipids. Available online: https://www.moh.gov.sg/hpp/doctors/guidelines/GuidelineDetails/cpgmed_lipids (accessed on 1 July 2022).
26. Ministry of Public Health Qatar. National Clinical Guideline: The Assessment and Management of Dyslipidaemia. Available online: https://www.moph.gov.qa/english/OurServices/eservices/Pages/Clinical-Guidelines.aspx (accessed on 1 July 2022).
27. Banach, M.; Burchardt, P.; Chlebus, K.; Dobrowolski, P.; Dudek, D.; Dyrbus, K.; Gasior, M.; Jankowski, P.; Jozwiak, J.; Klosiewicz-Latoszek, L.; et al. PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. *Arch. Med. Sci.* **2021**, *17*, 1447–1547. [CrossRef]
28. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2019**, *73*, e285–e350. [CrossRef] [PubMed]
29. Jellinger, P.S.; Handelsman, Y.; Rosenblit, P.D.; Bloomgarden, Z.T.; Fonseca, V.A.; Garber, A.J.; Grunberger, G.; Guerin, C.K.; Bell, D.S.H.; Mechanick, J.I.; et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease-Executive Summarycomplete Appendix to Guidelines. *Endocr. Pract.* **2017**, *23*, 479–497. [CrossRef]
30. Pearson, G.J.; Thanassoulis, G.; Anderson, T.J.; Barry, A.R.; Couture, P.; Dayan, N.; Francis, G.A.; Genest, J.; Gregoire, J.; Grover, S.A.; et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. *Can. J. Cardiol.* **2021**, *37*, 1129–1150. [CrossRef] [PubMed]
31. National Vascular Disease Prevention Alliance. Guidelines for Primary Cardiovascular Disease Prevention. Available online: https://www.heartfoundation.org.au/Conditions/Fp-Lipid-management (accessed on 1 July 2022).
32. Ministry of Health New Zealand. Cardiovascular Disease Risk Assessment and Management for Primary Care. Available online: https://www.health.govt.nz/system/files/documents/publications/cardiovascular-disease-risk-assessment-management-primary-care-feb18-v4_0.pdf (accessed on 1 July 2022).
33. National Institute for Health and Care Excellence. Cardiovascular Disease: Risk Assessment and Reduction, including Lipid Modification. Available online: https://www.nice.org.uk/guidance/cg181 (accessed on 1 July 2022).
34. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur. Heart J.* **2020**, *41*, 111–188. [CrossRef]
35. Klug, E.; Raal, F.J.; Marais, A.D.; Smuts, C.M.; Schamroth, C.; Jankelow, D.; Blom, D.J.; Webb, D.A. South African dyslipidaemia guideline consensus statement: 2018 update A joint statement from the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA). *S. Afr. Med. J.* **2018**, *108*, 973–1000. [CrossRef]
36. Marston, N.A.; Giugliano, R.P.; Im, K.; Silverman, M.G.; O'Donoghue, M.L.; Wiviott, S.D.; Ference, B.A.; Sabatine, M.S. Association Between Triglyceride Lowering and Reduction of Cardiovascular Risk Across Multiple Lipid-Lowering Therapeutic Classes: A Systematic Review and Meta-Regression Analysis of Randomized Controlled Trials. *Circulation* **2019**, *140*, 1308–1317. [CrossRef]
37. Kowa Research Institute, Inc. Available online: https://www.prnewswire.com/news-releases/kowa-to-discontinue-k-877-pemafibrate-prominent-cardiovascular-outcomes-study-301520956.html (accessed on 21 October 2022).
38. Yokoyama, M.; Origasa, H.; Matsuzaki, M.; Matsuzawa, Y.; Saito, Y.; Ishikawa, Y.; Oikawa, S.; Sasaki, J.; Hishida, H.; Itakura, H.; et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis. *Lancet* **2007**, *369*, 1090–1098. [CrossRef]
39. Bhatt, D.L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Ketchum, S.B.; Doyle, R.T., Jr.; Juliano, R.A.; Jiao, L.; Granowitz, C.; et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N. Engl. J. Med.* **2019**, *380*, 11–22. [CrossRef] [PubMed]
40. Hai, Q.; Smith, J.D. Acyl-Coenzyme A: Cholesterol Acyltransferase (ACAT) in Cholesterol Metabolism: From Its Discovery to Clinical Trials and the Genomics Era. *Metabolites* **2021**, *11*, 543. [CrossRef]
41. Zhao, D.; Liu, J.; Xie, W.; Qi, Y. Cardiovascular risk assessment: A global perspective. *Nat. Rev. Cardiol.* **2015**, *12*, 301–311. [CrossRef] [PubMed]
42. Yebyo, H.G.; Zappacosta, S.; Aschmann, H.E.; Haile, S.R.; Puhan, M.A. Global variation of risk thresholds for initiating statins for primary prevention of cardiovascular disease: A benefit-harm balance modelling study. *BMC Cardiovasc. Disord.* **2020**, *20*, 418. [CrossRef] [PubMed]
43. Lu, Y.; Wang, P.; Zhou, T.; Lu, J.; Spatz, E.S.; Nasir, K.; Jiang, L.; Krumholz, H.M. Comparison of Prevalence, Awareness, Treatment, and Control of Cardiovascular Risk Factors in China and the United States. *J. Am. Heart Assoc.* **2018**, *7*. [CrossRef] [PubMed]
44. Salami, J.A.; Warraich, H.; Valero-Elizondo, J.; Spatz, E.S.; Desai, N.R.; Rana, J.S.; Virani, S.S.; Blankstein, R.; Khera, A.; Blaha, M.J.; et al. National Trends in Statin Use and Expenditures in the US Adult Population from 2002 to 2013: Insights from the Medical Expenditure Panel Survey. *JAMA Cardiol.* **2017**, *2*, 56–65. [CrossRef] [PubMed]

45. Khan, S.U.; Yedlapati, S.H.; Lone, A.N.; Hao, Q.; Guyatt, G.; Delvaux, N.; Bekkering, G.E.T.; Vandvik, P.O.; Riaz, I.B.; Li, S.; et al. PCSK9 inhibitors and ezetimibe with or without statin therapy for cardiovascular risk reduction: A systematic review and network meta-analysis. *BMJ* **2022**, *377*, e069116. [CrossRef] [PubMed]
46. Kim, B.-K.; Hong, S.-J.; Lee, Y.-J.; Hong, S.J.; Yun, K.H.; Hong, B.-K.; Heo, J.H.; Rha, S.-W.; Cho, Y.-H.; Lee, S.-J.; et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): A randomised, open-label, non-inferiority trial. *Lancet* **2022**, *400*, 380–390. [CrossRef]
47. Salami, J.A.; Warraich, H.J.; Valero-Elizondo, J.; Spatz, E.S.; Desai, N.R.; Rana, J.S.; Virani, S.S.; Blankstein, R.; Khera, A.; Blaha, M.J.; et al. National Trends in Nonstatin Use and Expenditures among the US Adult Population From 2002 to 2013: Insights from Medical Expenditure Panel Survey. *J. Am. Heart Assoc.* **2018**, *7*, e007132. [CrossRef]
48. Zhang, M.; Deng, Q.; Wang, L.; Huang, Z.; Zhou, M.; Li, Y.; Zhao, Z.; Zhang, Y.; Wang, L. Prevalence of dyslipidemia and achievement of low-density lipoprotein cholesterol targets in Chinese adults: A nationally representative survey of 163,641 adults. *Int. J. Cardiol.* **2018**, *260*, 196–203. [CrossRef]
49. Li, J.; Li, X.; Wang, Q.; Hu, S.; Wang, Y.; Masoudi, F.A.; Spertus, J.A.; Krumholz, H.M.; Jiang, L. ST-segment elevation myocardial infarction in China from 2001 to 2011 (the China PEACE-Retrospective Acute Myocardial Infarction Study): A retrospective analysis of hospital data. *Lancet* **2015**, *385*, 441–451. [CrossRef]
50. Xing, Y.; Liu, J.; Hao, Y.; Liu, J.; Huo, Y.; Smith, S.C., Jr.; Ge, J.; Ma, C.; Han, Y.; Fonarow, G.C.; et al. Prehospital statin use and low-density lipoprotein cholesterol levels at admission in acute coronary syndrome patients with history of myocardial infarction or revascularization: Findings from the Improving Care for Cardiovascular Disease in China (CCC) project. *Am. Heart J.* **2019**, *212*, 120–128. [CrossRef]
51. Lu, Y.; Zhang, H.; Lu, J.; Ding, Q.; Li, X.; Wang, X.; Sun, D.; Tan, L.; Mu, L.; Liu, J.; et al. Prevalence of Dyslipidemia and Availability of Lipid-Lowering Medications Among Primary Health Care Settings in China. *JAMA Netw. Open* **2021**, *4*, e2127573. [CrossRef] [PubMed]
52. Lazar, L.D.; Pletcher, M.J.; Coxson, P.G.; Bibbins-Domingo, K.; Goldman, L. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. *Circulation* **2011**, *124*, 146–153. [CrossRef]
53. McConnachie, A.; Walker, A.; Robertson, M.; Marchbank, L.; Peacock, J.; Packard, C.J.; Cobbe, S.M.; Ford, I. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: A record linkage study. *Eur. Heart J.* **2014**, *35*, 290–298. [CrossRef] [PubMed]
54. Heller, D.J.; Coxson, P.G.; Penko, J.; Pletcher, M.J.; Goldman, L.; Odden, M.C.; Kazi, D.S.; Bibbins-Domingo, K. Evaluating the Impact and Cost-Effectiveness of Statin Use Guidelines for Primary Prevention of Coronary Heart Disease and Stroke. *Circulation* **2017**, *136*, 1087–1098. [CrossRef] [PubMed]
55. Wang, M.; Liu, J.; Bellows, B.K.; Qi, Y.; Sun, J.; Liu, J.; Moran, A.E.; Zhao, D. Impact of China's Low Centralized Medicine Procurement Prices on the Cost-Effectiveness of Statins for the Primary Prevention of Atherosclerotic Cardiovascular Disease. *Glob. Heart* **2020**, *15*, 43. [CrossRef]
56. Yang, H.; Li, N.; Zhou, Y.; Xiao, Z.; Tian, H.; Hu, M.; Li, S. Cost-Effectiveness Analysis of Ezetimibe as the Add-on Treatment to Moderate-Dose Rosuvastatin versus High-Dose Rosuvastatin in the Secondary Prevention of Cardiovascular Diseases in China: A Markov Model Analysis. *Drug Des. Dev. Ther.* **2020**, *14*, 157–165. [CrossRef]
57. Pan, L.; Yang, Z.; Wu, Y.; Yin, R.X.; Liao, Y.; Wang, J.; Gao, B.; Zhang, L.; China National Survey of Chronic Kidney Disease Working, Group. The prevalence, awareness, treatment and control of dyslipidemia among adults in China. *Atherosclerosis* **2016**, *248*, 2–9. [CrossRef]
58. Writing Committee; Lloyd-Jones, D.M.; Morris, P.B.; Ballantyne, C.M.; Birtcher, K.K.; Covington, A.M.; DePalma, S.M.; Minissian, M.B.; Orringer, C.E.; Smith, S.C., Jr.; et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. *J. Am. Coll. Cardiol.* **2022**, *80*, 1366–1418. [CrossRef]

Journal of
Clinical Medicine

MDPI

Review

Lipid-Lowering Nutraceuticals for an Integrative Approach to Dyslipidemia

Brian Cheung [1,2], Geeta Sikand [2], Elizabeth H. Dineen [1,2], Shaista Malik [1,2] and Ailin Barseghian El-Farra [1,2,*]

[1] Susan Samueli Integrative Health Institute, 856 Health Sciences Road, Irvine, CA 92617, USA
[2] Division of Cardiology, University of California, Irvine, CA 92521, USA
* Correspondence: barsegha@hs.uci.edu

Abstract: Dyslipidemia is a treatable risk factor for atherosclerotic cardiovascular disease that can be addressed through lifestyle changes and/or lipid-lowering therapies. Adherence to statins can be a clinical challenge in some patients due to statin-associated muscle symptoms and other side effects. There is a growing interest in integrative cardiology and nutraceuticals in the management of dyslipidemia, as some patients desire or are actively seeking a more natural approach. These agents have been used in patients with and without established atherosclerotic cardiovascular disease. We provide an updated review of the evidence on many new and emerging nutraceuticals. We describe the mechanism of action, lipid-lowering effects, and side effects of many nutraceuticals, including red yeast rice, bergamot and others.

Keywords: apolipoprotein B; atherosclerosis; cardiometabolic; cardiovascular disease; cardiovascular risk reduction; complementary medicine; integrative medicine; lipoprotein (a)

Citation: Cheung, B.; Sikand, G.; Dineen, E.H.; Malik, S.; Barseghian El-Farra, A. Lipid-Lowering Nutraceuticals for an Integrative Approach to Dyslipidemia. *J. Clin. Med.* **2023**, *12*, 3414. https://doi.org/10.3390/jcm12103414

Academic Editor: Dean G. Karalis

Received: 31 December 2022
Revised: 7 February 2023
Accepted: 10 February 2023
Published: 11 May 2023

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) refers to the accumulation of plaque in arteries, leading to cardiovascular disease, cerebrovascular disease, and peripheral arterial disease. The complex interplay of many factors can lead to the pathogenesis of ASCVD. Chronic inflammation is one of these important aspects and is also involved in the erosion and rupture of unstable plaque [1]. Endothelial dysfunction is another important aspect in the pathogenesis of ASCVD and is primarily mediated by nitric oxide and prostacyclins [2,3]. It can be non-invasively evaluated via flow-mediated dilation (FMD), but further research is needed to elucidate how dyslipidemia affects FMD values [3]. Diabetes mellitus type 2 (DM2) is also a risk factor associated with microvascular and macrovascular disease. It is also associated with lower high-density lipoprotein cholesterol (HDL-C) and elevated triglycerides (TG), nitrotyrosine, nitrated low-density lipoprotein-cholesterol (LDL-C), and nitrated HDL-C, which are associated with an increased risk for cardiovascular disease [4].

Dyslipidemia is an important treatable risk factor for ASCVD, and the estimated global prevalence of elevated cholesterol, according to the World Health Organization, is about 40% [5]. It is strongly associated with a lifetime exposure to elevated LDL-C in longitudinal studies [1,6,7]. Patients with a LDL-C $\geq$ 4.91 mmol/L ($\geq$190 mg/dL) should be evaluated for familial hypercholesterolemia, which is frequently underdiagnosed, as about 85% of those with the autosomal dominant genetic disorder are unaware of their diagnosis [8]. Other derangements in the lipid profile may be considered risk-enhancing factors, which may favor initiation or intensification of therapy in certain patients. Such factors include persistently elevated TG of $\geq$2.0 mmol/L ($\geq$175 mg/dL), apolipoprotein B (apoB) $\geq$ 130 mg/dL, or lipoprotein (a) (Lp(a)) $\geq$ 50 mg/dL or 125 nmol/L [1].

Statins, which are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are the cornerstone in the management of dyslipidemia and are frequently

first-line therapeutics [9]. Robust evidence demonstrates that statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors substantially reduce ASCVD risk [6,7,9,10].

However, adherence to statin therapy can be a clinical challenge because some patients can develop side effects, such as statin-associated muscle symptoms (SAMS) [11]. Some degree of statin intolerance is reported in 5–30% of patients and contributes to reduced statin adherence [10]. Furthermore, some patients are hesitant to starting a statin due to concern for potential side effects.

More patients are actively seeking integrative therapies, including nutraceuticals, from clinicians with expertise in integrative cardiology [12]. The estimated global prevalence of dietary supplement and nutraceutical use in patients with cardiovascular disease is 36% [13]. Nutraceuticals can be considered in the management of dyslipidemia for their lipid-lowering effects in patients who are not on statins or other LDL-lowering therapies due to a desire for a more natural approach. They can also be considered as adjunctive treatments to conventional LDL-lowering therapies that have not achieved lipid thresholds. Nutraceuticals can also be considered in patients with SAMS or other side effects, although they are not without their own side effects. Thus, clinicians have a need for high-quality evidence-based recommendations relating to the use of nutraceuticals [14,15].

Due to the growing interest in the field of integrative cardiology, many new clinical trials, systemic reviews, and meta-analyses have recently been published on nutraceuticals. We review the updated literature on novel and emerging nutraceuticals used in the management of dyslipidemia and their lipid-lowering effects.

2. Methods

A literature review was performed searching Pubmed, Scopus, and Google Scholar. A search for the most recent published meta-analysis, systemic reviews, and randomized control trials (RCT) was performed for each nutraceutical. Publications not written in English or lacking accompanying English translations were excluded.

The level of evidence and strength of recommendations for particular lipid-lowering therapies were evaluated and graded according to predefined scales in the legend of Table 1, which also shows a summary of LDL-lowering effects of nutraceuticals [16].

Table 1. Nutraceuticals and their LDL-Lowering Effects.

Nutraceutical	Class	Level of Evidence	Mechanism of Action	Daily Dose	Lipid Lowering Effect	Safety	Drug Interactions
Anthocyanins	IIb	A	Downregulates the mRNA of SREBP-1c and fatty acid synthase, resulting in less fat accumulation in adipocytes [17]	100 to 450 mg [18]	LDL-C: −5 to −10% [16]	Well tolerated [16] Precautions during pregnancy (polyhydramnios) [19]	No known drug interactions [16]
Artichoke Leaf Extract	IIa	A	Inhibit HMG-CoA reductase [16,20], induce pathways involving SREBP and ACAT, [20] increase excretion of bile acids [21]	500 to 2800 mg [21]	LDL-C: −5 to −15% [16]	GI discomfort, skin reactions, and asthma exacerbations [16,22] Insufficient data in pregnant or breastfeeding patients [22]	Antidiabetic drugs, antihypertensive drugs, and CYP2B6 and CPY2C19 inducers and inhibitors [22]

Table 1. *Cont.*

Nutraceutical	Class	Level of Evidence	Mechanism of Action	Daily Dose	Lipid Lowering Effect	Safety	Drug Interactions
Berberine	I	A	PCSK9-I [23], upregulates the hepatic LDL receptor by activing the Jun amino-terminal kinase and extracellular signal regulated kinases [16,24] Decreased GI reabsorption of cholesterol, enhanced fecal excretion, increased hepatic bile acid formation, [25] activates AMPK, [26,27] inhibits NADPH [28]	200 to 1500 mg [29]	LDL-C: −15 to −20% [16]	GI symptoms, headaches, and elevated transaminases [30,31] No serious liver injury [16,29,31] Kernicterus in infants [31] Pregnant women, breastfeeding mothers, and infants should avoid [22]	Anticoagulants, anti- platelets, antidiabetic drugs, antihypertensive drugs, central nervous system depressants, cyclosporine, CYP substrates (CYP2C9, CYP2D6, CYP3A4), dextromethorphan, and tacrolimus [22]
Bergamot	IIa	A	Inhibits HMG-CoA reductase, ACAT [16] pancreatic cholesterol ester hydrolase, [32] activates AMPK, [26] radical-scavenging activity, [16] increases fecal excretion of bile acids [16,33]	200 to 1500 mg [16]	LDL-C: −7 to −40% [34]	GI discomfort and muscle cramps Little safety data in patients who are pregnant or breastfeeding [22]	Antidiabetic drugs due to hypoglycemia [22]
L-carnitine	IIb	A	Decreases TG synthesis by decreasing available free fatty acids, increases mitochondrial oxidation of long chain fatty acids, and increases production of apolipoprotein A1 [35]	500 mg to 6 g [35]	LDL-C: −0.14 mmol/L; 95% CI, –0.22 to −0.06 TG: −0.11 mmol/L; 95% CI, –0.18 to −0.03 [35]	Fishy body odor, minor nausea, or GI discomfort [22,36] Safe in patients who are pregnant or breastfeeding Parenteral carnitine supplementation is safe in infants [22,37,38]	Thyroid hormones and warfarin [22]
Chromium	III	A	Upregulates gene expression of PPAR-γ and LDL receptor [39]	40 to 1000 mcg [39]	TC: −0.17 mmol/L; 95% CI, –0.27 to −0.07 [40]	Weight loss, hypoglycemia, anemia, thrombocytopenia, elevated transaminases, elevated creatinine, rhabdomyolysis, and dermatitis Safe during pregnancy and in women breastfeeding [41]	Levothyroxine, insulin, metformin, and other antidiabetic medication [41]

Table 1. *Cont.*

Nutraceutical	Class	Level of Evidence	Mechanism of Action	Daily Dose	Lipid Lowering Effect	Safety	Drug Interactions
Chitosan	IIb	A	Interferes with GI absorption by binding to negatively charged fatty acids and bile acids and disrupting the emulsification of neutrally charged cholesterol [42]	0.3 to 3 g [43]	LDL-C: −5% [16]	Should not be used in patients with allergies to crustaceans or shellfish [42] GI discomfort Insufficient data on use in patients who are pregnant or breastfeeding [22]	Acyclovir or warfarin [22]
Coenzyme Q10	III	A	Reduce oxidative stress and restores coenzyme Q10 [44]	30 to 250 mg [45]	TG: −0.0032 mmol/L; 95% CI, –0.0063 to −0.0001 [45] HDL-C: 0.03 mmol/L; 95% CI, 0.01 to 0.06 [46]	Insomnia, GI discomfort, dizziness, headache, dyspepsia, photophobia, irritability, and fatigue [47]	Anticoagulants, insulin, and cancer treatments Beta-blockers can inhibit enzyme reactions involving coenzyme Q10 [47]
Conjugated Linoleic Acid	IIb	A	Promotes cholesterol efflux by increasing expression of ABCA1 and ABCG1 [48]	0.5 to 7 g [49]	LDL-C: −5% [16]	GI discomfort, hepatotoxicity [50] Safe in patients who are pregnant [51] Insufficient data in patients breastfeeding [22]	Anticoagulants, anti- platelet drugs, and anti-hypertensives [22]
Curcumin	IIb	A	Inhibits intestinal NPC1L1 cholesterol transporter expression by inhibiting the SREBP2 transcription factor, [52] downregulates PCSK9 expression, [53] upregulates ABCA1 expression [54]	50 mg to 6 g [55]	LDL-C: −5% [16]	GI discomfort [22,56] Precautions in patients who are pregnant or breastfeeding as levels greater than dietary levels may be unsafe [22]	Alkylating agents, amlodipine, anticoagulants, anti- platelets, antidiabetic drugs, CYP3A4 substrates, sulfasalazine, tacrolimus, talinolol, tamoxifen, and warfarin [22]
Soluble Fiber							
Glucomannan	IIa	A	Inhibits HMG-CoA reductase, reduces GI cholesterol absorption, [57] increases the conversion of bile acids into cholesterol through increased 7-α- hydroxylase activity [16]	1 to 15 g per day [16,58]	LDL: −0.35 mmol/L; 95% CI, –0.46 to −0.25 [58]	GI discomfort, obstructions in the bowel or esophagus, [22,58] reduce absorption of vitamin E Insufficient data in patients who are pregnant or breastfeeding [22]	May be issues with absorption of medicines [22]

Table 1. *Cont.*

Nutraceutical	Class	Level of Evidence	Mechanism of Action	Daily Dose	Lipid Lowering Effect	Safety	Drug Interactions
β-Glucan	IIa	A	Viscosity reduces cholesterol absorption, increases bile acid excretion [59]	3 to 25 g [16,60]	LDL-C: −0.27 mmol/L; 95% CI, −0.35 to −0.20 [60]	Insufficient data in patients who are pregnant or breastfeeding [22]	antihypertensives and immunosup-pressant drugs [22]
Guar Gum	IIa	A	Prevents GI cholesterol absorption, increases bile acid extraction [61]	30 to 100 g [61]	LDL-C: −0.45 mmol/L; 95% CI, –0.61 to −0.29 [61]	GI discomfort, obstruction of the esophagus or bowel [22,61] Safe during pregnancy as it treats intrahepatic cholestasis of pregnancy [62] Insufficient data in patients who are breastfeeding [22]	Penicillin, metformin, estradiol, and digoxin May inhibit the absorption of oral drugs [22]
Psyllium	IIa	A	Reduces GI absorption cholesterol, binds to bile acids [63]	2 to 20 g per day [63]	LDL-C: −0.33 mmol/L; 95% CI, –0.38 to −0.27 [63]	GI discomfort, mild anaphylactic allergic reactions, bowel obstructions, and esophageal obstructions [16,22,64] Safe during pregnancy or while breastfeeding [65]	Carbamazepine, digoxin, estradiol, lithium, metformin, and olanzapine [22]
Garlic Extract	IIa	A	Inhibits HMG-CoA reductase, acetyl-CoA synthetase, squalene-monooxygenase, and potentially non-acetylated CoA, [66] GI absorption of fatty acids and cholesterol, increases the excretion of bile acids [16]	0.3 to 20 g [16,67]	LCL-C: −5 to −10% [16]	GI symptoms, body odor, garlicy breath, aftertaste, and increased bleeding risk [16,68] Possibly unsafe when used in higher levels in patients who are pregnant or breastfeeding [22]	Anti-hypertensive drugs, anti-diabetic drugs, atazanavir, CYP2E1/CYP3A4 inducers and inhibitors, isoniazid, protease inhibitors, saquinavir, tacrolimus, and warfarin [22]

Table 1. *Cont.*

Nutraceutical	Class	Level of Evidence	Mechanism of Action	Daily Dose	Lipid Lowering Effect	Safety	Drug Interactions
Green Tea	IIa	A	Inhibits expression of nitric oxide synthase, [69] activates AMPK, inhibits HMG-CoA reductase, [16,69] inhibits the reabsorption of bile acids [16,70]	100 mg to 20 g per day [16,69]	LCL-C: −5 [16]	GI discomfort, transitory blood pressure elevations, rashes thrombotic thrombocytopenic purpura, hepatotoxicity, hypokalemia, [16,22,69] Higher doses associated with iron and folate deficiency; use with precaution in pregnant patients [16,71]	5-fluorouracil, adenosine, anticoagulants, antiplatelets, antidiabetic drugs, statins, beta agonists, bortezomib, carbamazepine, cimetidine, clozapine, lisinopril, lithium, stimulants, verapamil, and valproate acid [22]
Alpha Lipoic Acid	IIb	A	Modulates fat synthesis, mitochondrial β-oxidation of fat, clearance of TG-rich lipoproteins in the liver, and adipose TG accumulation [72]	300 to 1800 mg [73]	LDL-C: −0.28 mmol/L; 95% CI, −0.50 to −0.06 [73]	GI discomfort, skin rash, and rarely insulin autoimmune syndrome Safe during pregnancy [74] Insufficient data in patients breastfeeding [22]	Alkylating agents, anticoagulants, anti- platelet drugs, antidiabetic drugs, antitumor antibiotics, and levothyroxine [22]
Lupin Protein	IIa	A	Inhibits HMG-CoA receptor and PCSK9 activity. Refs. [75,76], upregulates SREBP-2 via phosphatidylinositol-3- kinase, alpha serine/threonine-protein kinase, and glycogen synthase kinase-3 beta kinase pathways [77]	≤35 g [78]	LDL-C: −5 to −12% [16]	GI discomfort Likely safe to use in patients who are pregnant or breastfeeding [22]	No known interactions with drugs [22]
Magnesium	III	A	Regulates HMG-CoA reductase expression, upregulates cholesterol 7α-hydroxylase and LCAT expression [79]	35 to 500 mg [80]	LDL-C: −0.18 mmol/L; 95% CI, –0.30 to −0.05 [81]	GI discomfort, flushing, confusion, hypotension, hyperreflexia, respiratory depression, hyperkalemia, hypocalcemia, pulmonary edema, and cardiac arrest [82,83] Safe during pregnancy at appropriate doses [22,83] Appears safe to use during breastfeeding [22]	Aminoglycosides, antacids, bisphosphonates, calcium channel blockers, digoxin, ketamine, levodopa, carbidopa, potassium-sparing diuretics, quinolones, sulfonylurea, and tetracyclines [22]

Table 1. *Cont.*

Nutraceutical	Class	Level of Evidence	Mechanism of Action	Daily Dose	Lipid Lowering Effect	Safety	Drug Interactions
Niacin	IIb	A	Inhibits diacylglycerol acyltransferase-2, which decreases TG synthesis and LDL-C by increasing hepatic apoB degradation, raises HDL-C by stimulating hepatic apolipoprotein A-I production [84]	≤2 g daily [85,86]	TG: −28.6%; LDL-C: −12.0% [86]	GI hemorrhage, peptic ulcers, myopathy, rhabdomyolysis, gout, flushing, skin lesions, skin infections, lower respiratory infections, and increased incidence of diabetes and hospitalizations for diabetes [85] No restrictions for pregnant or breast feeding patients [87]	Statins, isoniazid, and pyrazinamide [1,88]
Nigella Sativa	IIb	A	Reduces GI cholesterol absorption, increases biliary excretion, reduces cholesterol synthesis, inhibits lipid oxidation, upregulates LDL receptors [89]	200 mg to 3 g for powders, capsules, and extracts 1 to 5 mL for oil suspensio ns [90]	LDL-C: −0.48 mmol/L; 95% CI, –0.58 to −0.37 [90]	GI discomfort, elevated alkaline-phosphate, AST, ALT, gamma-glutamyl transferase [89] Safe to use during pregnancy [91] Insufficient data during breastfeeding [22]	anticoagulants, anti- platelets, antidiabetic drugs, antihyper-tensives, cyclosporine, diuretics, immunosuppres-sants, and serotonergic drugs [22]
Olive Extract	IIb	B	Reduces lipid peroxidation, increases bile excretion, and inhibits HMG-CoA reductase and ACAT [92]	136.2 mg oleuropei n and 6.4 mg hydroxyty rosol [93]	LDL-C: –0.19 ± SD 0.56 mmol/L [93]	No known adverse effects of olive extract No known data on about the levels consumed through olive extract in those who are pregnant or breastfeeding [94]	No known interactions [94]
Gamma-oryzanol	IIb	A	Inhibits GI absorption, increases excretion of bile acids, inhibits HMG-CoA reductase, inhibits platelet aggregation, [95] alters the gut microbiome [96]	100 to 300 mg [16,22]	LDL-C: −5 to −10% [16]	No reported side effects [10,97] No safety data on patients who are pregnant or breastfeeding [22]	No known drug interactions [22]

Table 1. *Cont.*

Nutraceutical	Class	Level of Evidence	Mechanism of Action	Daily Dose	Lipid Lowering Effect	Safety	Drug Interactions
Pantethine	IIb	B	Inhibits HMG-CoA reductase and acetyl-CoA carboxylase, which are involved in TG synthesis and lipoprotein metabolism [98]	600 to 1200 mg [98]	LDL-C: −11% [98]	gastrointestinal symptom [98] Safe in children and in patients with chronic kidney disease, including dialysis [99,100] Insufficient data in patients who are pregnant or breastfeeding [22]	No known drug interactions [22]
Polyunsaturated n-3 Fatty Acids	I	A	Reduces synthesis of hepatic VLDL, endogenous fatty acids, substrates available for TG synthesis, and activity of diacylglycerol acyltransferase or phosphatidic acid phosphohydrolase, which are involved in TG synthesis, promotes β-oxidation of fatty acids and increase phospholipid synthesis [101]	≤4 g [102,103]	TG: −0.36 mmol/L [104]	GI discomfort, new- onset atrial fibrillation and atrial flutter, fishy aftertaste [103,105] Safe to use in pregnancy [106] Likely safe during breastfeeding [22]	Anticoagulants, anti- platelet drugs, antihyper-tensives, contraceptives, cyclosporine, and tacrolimus [22]
Pectin	IIb	B	Decreases GI cholesterol absorption, increases bile acid excretion, [107,108] decreases HMG-CoA reductase, increases cholesterol 7-α- hydroxylase in the liver, modulates gut microbiome [108]	6 g [107]	LDL-C: −5 to −10% [16]	GI discomfort [107] Precaution in patients who are pregnant (binds to vitamin B12) [109] Safe in patients who are breastfeeding [22]	Digoxin, lovastatin, and tetracyclines [22]
Phytosterols	IIa	A	Inhibit cholesterol absorption in GI tract by competing with dietary cholesterol in the formation of dietary micelles, decreasing apoB secretion from enterocytes and hepatocytes, increases expression of ABCA1 and ABCG1 level [110–112]	400 mg to 3 g [16,110]	LDL-C: −8 to −16% [16,69]	Well tolerated and safe [16,69] Safe to use in pregnancy [113] Insufficient data on their use in those breastfeeding [22]	No known drug interactions [22]

Table 1. *Cont.*

Nutraceutical	Class	Level of Evidence	Mechanism of Action	Daily Dose	Lipid Lowering Effect	Safety	Drug Interactions
Policosanol	IIb	A	Promotes bile acid production and lipolysis via inhibiting the expression of farnesoid X receptor-small heterodimer partner and activating the Takeda G- coupled protein receptor 5-AMPK signaling pathway, which inhibits HMG-CoA reductase activity [114,115]	5 to 20 mg [116]	LDL-C: −0.71 mmol/L; 95% CI, –1.02 to −0.40 [116]	GI discomfort, tachycardia, myalgia, hypertension, headache, dizziness, somnolence, insomnia, polydipsia, nocturia, dry skin, rashes, and weight gain [116] Safe to use in pregnancy [117,118] Insufficient data in breastfeeding [22]	Antidiabetic drugs, beta-blockers, nitroprusside, and warfarin [22]
Probiotics	IIb	A	*Lactobacillus* and *Bifidobacterium* increase bile acid excretion [119] *Lacticaseibacillus* decreases NPC1L1 cholesterol transporter expression and increase cholesterol efflux via increased expression of ABCA1 [120] *Lactobacillus rhamnosus* JL1 activates the AMPK pathway and inhibits PPAR-γ and SREBP-1C gene expression [121]	1 to 6 g [16,122]	LDL-C: −5% [16]	GI discomfort, infections from yeast *Saccharomyces cervisiae* Safe in infants and patients who are pregnant or breastfeeding [123]	Insufficient data [16]
Red Yeast Rice Extract	I	A	HMG-CoA reductase inhibitor [124]	<3 mg of monacolin K) [14]	LDL-C: −15% to −25% [16]	Gastrointestinal discomfort, rashes, and allergic reactions [17,20,21] Formulations with citrinin are nephrotoxic and hepatotoxic [14,20,21] No elevations in transaminases or kidney impairment [14,17,20,21] Precautions with pregnancy [125] Unknown if safe to use during breastfeeding [126]	CYPP450 inducers or inhibitors, antifungals, macrolides, cyclosporine, fibrates, niacin, nefazodone, protease inhibitors, statins, and verapamil [16,126]

Table 1. *Cont.*

Nutraceutical	Class	Level of Evidence	Mechanism of Action	Daily Dose	Lipid Lowering Effect	Safety	Drug Interactions
Resveratrol	III	A	Activates silent information regulation 2 homolog 1, suppresses hepatic upregulation of genes associated in lipogenesis and prevent the downregulation of genes involved with lipolysis, [127] suppresses foam cell formation [128]	250 to 3000 mg [129,130]	LDL-C: −0.147 mmol/L; 95% CI, –0.286 to −0.008 [131]	Increase bleeding Likely safe to consume during pregnancy and breastfeeding provided not consumed from alcohol. In patients with malignancies that grow in response to estrogen, such as breast cancer, uterine cancer, ovarian cancer, it is advised that patients should limit intake [129]	Garlic, ginger, ginkgo, nattokinase, anticoagulants, anti- platelet drugs and those involving the cytochrome P450 system, such as CYP1A1, CYP1A2, CYP1B1, CYP2C19, CYP2E1, and CYP3A4 [129]
Sea Buckthorn	IIb	A	Increases expression of PPAR-α, PPAR-γ, and ABCA1, decreases expression of SREBP-2, promotes expression of CPT1A, which is involved in increasing lipolysis and β-oxidation [132]	0.75 mL [133]	LDL-C: −0.40 mmol/L; 95% CI, –0.76 to −0.04 [133]	Well tolerated Safe to use in pregnancy [134] Little data in patients who breastfeed [22]	Anticoagulants, anti- platelets, and antihyper-tensives [22]
Silymarin	IIb	A	Increases lipolysis and β- oxidation via the upregulation of CPT1, [135] increases cholesterol efflux via increases expression of ABCA1 [136]	140 to 700 mg [137]	LDL-C: −0.27 mmol/L; 95% CI, –0.49 to −0.05 [137]	GI discomfort, headache, ureteric calculi, and hemolytic anemia, transient ischemia attack, myocardial infarction, and cardiovascular death [137] Insufficient data in patients who are pregnant or breastfeeding [138]	Antidiabetic drugs, morphine, tamoxifen, sirolimus, and warfarin [22]
Spirulina	IIa	A	Activates heme oxygenase-1 (atheroprotective enzyme involved in heme catabolic pathway in endothelial cells), [16,69] antioxidant, anti- inflammatory, and radical-scavenging properties, [16] alters gut microbiome [139]	1 to 10 g [69]	LDL-C: −5 to −15% [16,69]	GI discomfort, bleeding, rashes, elevated transaminases, and cholestasis [22,140] Little safety data in patients who are pregnant or breastfeeding [22]	Anticoagulants, anti- platelets, antidiabetic drugs, and immunosuppres-sant drugs [22]

Table 1. *Cont.*

Nutraceutical	Class	Level of Evidence	Mechanism of Action	Daily Dose	Lipid Lowering Effect	Safety	Drug Interactions
Soybean Protein	IIa	A	Inhibits HMG-CoA reductase, reduces PCSK9 protein, [141] increases bile acid excretion, cholesterol synthesis inhibition, increases transcription of the LDL receptor, [142,143] increases apoB receptor activity, decreases hepatic synthesis of cholesterol and lipoprotein secretion, [143] alters the gut microbiome [144]	25 to 120 mg [16,69]	LDL-C: −3 to −10% [16]	GI discomfort, menstrual complaints, headaches, dizziness, and rashes [22] Chronic use of higher doses of soy protein may affect fertility and thyroid function [16,69] Decreased absorption of divalent and trivalent metals, such as calcium, copper, iron, magnesium, and zinc [143] Avoid during pregnancy Use of soy is likely safe during breastfeeding [22]	Antidiabetic drugs, antihypertensive drugs, diuretics, estrogens, progesterone, tamoxifen, levothyroxine, monoamine oxidase inhibitors, and warfarin [22]
Vitamin E	IIb	A	Inhibits HMG-CoA reductase, promotes scavenging for free radicals, and activates PPAR -α, -β, and -γ receptors [145–147]	400 to 800 UI [16]	HDL-C: 0.15 mmol/L; 95% CI, 0.07 to 0.23 [148]	Bleeding, heart failure, hemorrhagic cerebral vascular accidents, prostate cancer, and all- cause mortality [147,149] Safe in pregnancy [106] Likely safe during breastfeeding [22]	Alkylating agents, anticoagulants, anti- platelets, cyclosporine, CYP3A4 substrates, niacin, and selumetinib [22]

Definition of level of evidence. Level A: Data derived from multiple randomized clinical trials or their meta-analysis. Level B: Data derived from a single randomized clinical trial or large nonrandomized studies. Level C: Consensus or opinion of experts and/or small studies, retrospectives studies, or registries. Definition of classes of recommendation. Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective. Is recommended/ is indicated. Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. Class IIa: Weight of evidence/opinion is in favor of usefulness/ efficacy. Should be considered. Class IIb: Usefulness/efficacy is less well established by evidence/opinion. May be considered. Class III Evidence or general agreement that the given treatment or procedure is not useful/ effective and, in some cases, may be harmful. Is not recommended (no efficacy on lipid profile). Abbreviations: Acyl-coenzyme A cholesterol acyltransferase (ACAT), adenosine triphosphate-binding cassette (ABC), alanine-aminotransferase (ALA), adenosine monophosphate-activated protein kinase (AMPK), aspartate-aminotransferase (AST), carnitine palmitoyl transferase 1 (CPT1), gastrointestinal reabsorption (GI), high-density lipoprotein cholesterol (HDL-C), 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), lecithin cholesterol acyltransferase (LCAT), low-density lipoprotein cholesterol (LDL-C), messenger ribonucleic acid (mRNA), nicotinamide adenine dinucleotide phosphate (NADPH), Niemann-Pick C1-like 1 (NPC1L1), peroxisome proliferator-activated receptor (PPAR), proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9I), red yeast rice (RYR), sterol regulatory element-binding proteins (SREBP), total cholesterol (TC), triglycerides (TG).

3. Nutraceuticals and Their Main Effects on LDL-C

3.1. Red Yeast Rice Extract

Red yeast rice (RYR) extract is a traditional Chinese supplement that is produced via fermenting yeast (*Monascus purpureus*) grown on white rice and contains sterols, isoflavones,

and polyketides such as monacolin K [14–16,126]. The lactone form of monacolin K is structurally identical to lovastatin and requires conversion into the active hydroxyl acid form via the small intestine and liver [16,126]. RYR extract consumption results in the reduction of circulating atherogenic LDL-C particles, which is associated with a substantial reduction in the risk of cardiovascular events. Thus, RYR extract formulations may have a role in preventing cardiovascular disease. Besides monacolin K, RYR extract contains a wide (and variable) range of chemical constituents and several monacolins (M, L, J, and X) that may also contribute in varying degrees to the lipid-lowering effect [14]. Monacolin K is an HMG-CoA reductase inhibitor and increases clearance of serum LDL-C [124]. The typical dosage of RYR extract ranges from 1.2 to 2.4 g daily. This is equivalent to about 4.8 to 10 mg of monacolin K, depending on the formulation [16]. The International Lipid Expert Panel (ILEP) recommends a daily dose of <3 mg monacolins [14].

The expected LDL-C reduction is about −15% to −25% [16]. In a recent meta-analysis of 30 RCTs, 5440 participants were treated with RYR extract compared to placebo. Those in the RYR extract arm experienced a reduction in total cholesterol (TC) (−0.74 mmol/L; 95% confidence interval [CI], −0.71 to −0.22), TG (−0.45 mmol/L; 95% CI, −0.70 to −0.21), LDL-C (−0.42 mmol/L; 95% CI, −0.78 to −0.06) and an increase in HDL-C (0.14 mmol/L; 95% CI, 0.09 to 0.20) [150]. In another meta-analysis of 15 RCTs with 1012 participants, RYR extract lowered apoB (-5.45×10^{-4} mmol/L; 95% CI, -6.90×10^{-4} to -4.00×10^{-4}) compared to placebo [151].

Another meta-analysis investigated RYR extract's impact on cardiovascular outcomes, and it included a total of seven RCTs in China with 10,699 participants with dyslipidemia who were not on statins. The authors found that RYR extract reduces the risk of a non-fatal myocardial infarction (MI) (relative risk [RR] = 0.42; 95% CI, 0.34 to 0.52), revascularization (percutaneous coronary intervention and coronary artery bypass graft) (RR = 0.58; 95% CI, 0.48 to 0.71), and sudden death (RR = 0.71; 95% CI, 0.53 to 0.94) when compared to placebo. However, there was no significant difference in fatal MI [152].

Some of the more common adverse side effects can include gastrointestinal discomfort, rashes, and allergic reactions [125,151,152]. The prevalence of increased liver transaminases or muscle symptoms in RYR extract is comparable to that of statins [14,151,152]. Although citrinin is a nephrotoxic and hepatotoxic metabolite produced during the fermentation of RYR, a meta-analysis of 53 RCTs with 8535 participants did not demonstrate significant kidney impairment or elevated transaminases with RYR extract [14,126,151,152]. There are rare reports of rhabdomyolysis in patients with a prior history of rhabdomyolysis or polypharmacy use with RYR extract, statins, and antidepressants [126]. However, multiple meta-analyses of RCTs have shown no serious adverse reactions from RYR extract requiring hospitalizations when compared to statins and placebo [14,151,152].

Although the United States (US) Food and Drug Administration (FDA) has released a statement that statins may be considered in certain pregnant patients, such as those with homozygous familial hypercholesterolemia, special precautions should be taken with the use of RYR extract during pregnancy [125]. Citrinin-free formulations should be used, as citrinin is teratogenic [16]. The IELP recommends a minimum dose of citrinin. The no-observed-adverse-effect level is $\leq$0.2 μg/kg body weight per day, which is $\leq$14 μg/day for a 70 kg person [14]. It is unknown if RYR extract is safe during breastfeeding. Special precautions should also be taken in patients with hepatobiliary disorders [126]. Other potential interactions include those with food, CYPP450 inducers or inhibitors, antifungals, macrolides, cyclosporine, fibrates, niacin, nefazodone, protease inhibitors, statins, and verapamil [16,126].

Formulations containing RYR extract, however, have been the subject of greater regulatory scrutiny—particularly in regions where lovastatin is only available as a prescription. Some believe selling a product containing monacolin K is equivalent to selling a prescription pharmaceutical product. The US FDA determined in 1998 that RYR products that contain more than trace amounts of monacolin K are unapproved new drugs and cannot be sold legally as dietary supplements [14]. The European Food Safety Authority (EFSA)

does not permit the sale or supply of RYR preparations that contain ≥3 mg of monacolin K [153]. The 2021 European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice recommend against using RYR extract [154].

In summary, RYR preparations have been shown to be safe and effective in improving lipid profiles and, to some extent, in reducing the risk of cardiovascular events. However, they should not replace conventional treatments (statins, ezetimibe, and PCSK9 inhibitors), as higher-quality long-term outcomes data exist. Of note, RYR extract may be considered in: (1) patients with statin intolerance, (2) patients with dyslipidemia ineligible for statin therapy, and (3) patients with a strong preference for RYR extract over conventional treatment. When recommending RYR products to patients, it is important to ensure that the product has been produced according to the principles of good manufacturing practice, to ensure consistency of dose of the active ingredient and the absence of harmful contaminants [14].

3.2. Berberine

Berberine is a quaternary benzylisoquinoline alkaloid used in China [16,25]. It can be isolated from the bark, fruit, root, rhizome, and stem of various plant genera, including *Berberis*, *Coptis*, and *Hydrastis* [16]. Berberine inhibits PCSK9, resulting in less degradation of the hepatic LDL receptor and improved clearance of serum LDL-C [23]. Berberine also upregulates the hepatic LDL receptor and thus serum LDL-C clearance at the level of the messenger ribonucleic acid by activating the Jun amino-terminal kinase and extracellular signal regulated kinases [16,24]. Other secondary mechanisms involve decreased gastrointestinal reabsorption of cholesterol, enhanced fecal excretion, and increased hepatic bile acid formation [25]. Berberine activates adenosine monophosphate-activated protein kinase (AMPK), which inhibits cholesterol and triglyceride synthesis, promotes hepatic fatty acid oxidation, and reduces lipogenic gene expression [26,27]. Berberine also inhibits nicotinamide adenine dinucleotide phosphate, which is involved in cholesterol synthesis [28]. The typical dosage of berberine is 200 to 1500 mg per day [29].

The expected LDL-C reduction is about −15 to −20% [16]. A meta-analysis of 19 RCTs and cross-sectional trials with 1372 participants found that berberine reduced TC (−1.17 mmol/L; 95% CI, −1.28 to −1.06), LDL-C (−1.06 mmol/L; 95% CI, −1.17 to −0.96) and TG (−0.60 mmol/L; 95% CI, −0.71 to −0.50) and increased HDL-C (0.24 mmol/L; 95% CI, 0.14–0.34) [29].

Side effects include gastrointestinal symptoms, headaches, and elevated transaminases [30,31]. No serious liver injury was reported in adults [16,29,31]. Kernicterus may be more common in infants taking berberine [31]. Pregnant women, breastfeeding mothers, and infants should avoid berberine. Interactions are possible with anticoagulants, antiplatelets, antidiabetic drugs, antihypertensive drugs, central nervous system depressants, cyclosporine, CYP substrates (CYP2C9, CYP2D6, and CYP3A4), dextromethorphan, and tacrolimus [22].

3.3. Bergamot (*Citrus bergamia*)

Bergamot (*Citrus bergamia Risso*) is a Mediterranean citrus fruit that is rich in flavonoids, which can be purified from the peel to produce bergamot polyphenolic fraction (BPF) [16,33]. These flavonoids can inhibit HMG-CoA reductase and acyl-coenzyme A cholesterol acyltransferase, which are involved in cholesterol production and transportation, respectively [16]. BPF inhibits pancreatic cholesterol ester hydrolase, which is involved in the esterification of cholesterol [32]. Other flavonoids, such as melitidin, neoeriocitrin, and rutin, have been shown to inhibit LDL-C oxidation and to inhibit cholesterol triglyceride synthesis via AMPK [26]. These flavonoids may potentially have anti-atherosclerotic properties through radical-scavenging activity [16]. BPF may also reduce intestinal absorption of cholesterol via increased fecal excretion of bile acids [16,33]. The typical dosage is 500 to 1500 mg per day [16].

The expected LDL-C reduction is about −7 to −40%. In a systematic review of 12 studies with 870 participants, BPF decreased TC (−12.3 to −31.3%), LDL-C (−7.6 to

−40.8%), and TG (−11.5 to −39.5%) and increased HDL-C (1.0 to 6.5%). The authors found a dose-dependent response, with higher doses of BPF associated with increased lipid-lowering reductions [34].

Bergamot is associated with gastrointestinal discomfort and muscle cramps. Safety data on patients who are pregnant or breastfeeding are scant. There may be interactions with antidiabetic drugs due to hypoglycemia [22].

3.4. Garlic Extract

Garlic is an herb used in traditional Indian and Chinese medicine and is sold as raw garlic, extracted oil, or powdered tablets. It contains allicin (diallyl thiosulfinate), which inhibits HMG-CoA reductase, acetyl-CoA synthetase, squalene-monooxygenase, and potentially non-acetylated CoA [66]. Garlic may inhibit intestinal absorption of fatty acids and cholesterol and increase the excretion of bile acids [16]. The typical dosage ranges from about 0.3 to 20 g [16,67].

The expected LDL-C reduction is −5 to −10% [16]. In a recent network meta-analysis of 26 RCTs with 1620 participants, those in the garlic arm showed a decrease in TC (−0.25 mmol/L; 95% CI, −0.38 to −0.11), LDL-C (−0.21 mmol/L; 95% CI, −0.31 to −0.11), and TG (−0.14 mmol/L; 95% CI, −0.22 to −0.05) and an increase in HDL-C (0.03 mmol/L; 95% CI, 0.00 to 0.07) compared to placebo [15]. In another meta-analysis of six trials, garlic extract was shown to increase serum Lp(a) (54.59%; 95% CI, 30.47 to 78.71) in the trials that lasted longer than 12 weeks [155].

Garlic extract has been shown to affect coronary plaque. In an RCT, 55 participants with metabolic syndrome were randomized to supplementation with aged garlic extract versus placebo and followed for a year. There was a relative reduction of about 30% in mean low-attenuation plaque percent (−1.5% ± 2.3; $p < 0.01$) on cardiac computed tomography angiography, when compared to baseline. However, there were no changes in the total plaque volume, dense calcium, or non-calcified plaque between the two groups [156]. Another recent RCT focused on aged garlic extract in participants with DM2. After 1 year follow up, those in the supplementation arm saw a similar 29% relative reduction in low-attenuation plaque percent compared to their baseline on cardiac computed tomography angiography. When compared to placebo, those in the supplementation arm also had a higher reduction in median low-attenuation plaque percent (−0.02% ± 18.8; $p = 0.0415$). However, there were no changes in the volumes of total plaque, fibrous plaque, or fibrofatty plaque between the two arms [157].

Garlic extract is associated with gastrointestinal symptoms, body odor, garlicy breath, aftertaste, and increased bleeding risk [16,68]. It is possibly unsafe when used in higher levels in patients who are pregnant or breastfeeding. Garlic extract may have potential interactions with anti-hypertensive drugs, anti-diabetic drugs, atazanavir, CYP2E1/CYP3A4 inducers and inhibitors, isoniazid, protease inhibitors, saquinavir, tacrolimus, and warfarin [22].

3.5. Artichoke Leaf Extract

Artichokes are native to the Mediterranean region and can be a part of the Mediterranean diet. Many antioxidants can be derived from artichoke leaf extract, including caffeic acid, flavonoids, volatile sesquiterpene, and mono- and dicaffeoylquinic acid (cynarin and chlorogenic acid) [16,21,158]. There are two proposed mechanisms of action. Flavonoids, such as luteolin, may inhibit HMG-CoA reductase, which is involved in cholesterol synthesis [16,20]. They may also induce pathways involving the sterol regulatory element-binding proteins (SREBP) and the acyl-coenzyme A cholesterol acyltransferase, resulting in a reduction in cholesterol [20]. There may also be an increase in the gastrointestinal excretion of bile acids. The typical dosage for artichoke leaf extract can range from 500 to 2800 mg per day [21].

The expected LDL-C reduction is about −5 to −15% [16]. A network meta-analysis of 11 RCTs of artichoke leaf extract with 775 participants found a reduction in TC (−0.46 mmol/L;

95% CI, −0.69 to −0.23), LDL-C (−0.39 mmol/L; 95% CI, −0.54 to −0.24), and TG (−0.19 mmol/L; 95% CI, −0.32 to −0.06). There were no significant changes with HDL-C [15].

Reported side effects include gastrointestinal discomfort, skin reactions, and potential asthma exacerbations [16,22]. However, there are no reports of significant side effects [21]. Data on use in pregnant or breastfeeding patients are insufficient. There may be interactions with antidiabetic drugs, antihypertensive drugs, and CYP2B6 and CPY2C19 inducers and inhibitors [22].

3.6. Green Tea

Green tea is derived from the leaves of the *Camellia sinensis* plant and can be consumed as tea or green tea extract. Green tea is rich in catechins, which are flavonoids and include epicatechin, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate, gallocatechin, catechin gallate, and gallocatechin gallate [159]. There are multiple potential mechanisms of action for green tea. It inhibits the expression of inducible nitric oxide synthase [69]. Green tea also activates AMPK and inhibits HMG-CoA reductase [16,69]. It is postulated that green tea inhibits the reabsorption of bile acids in the ilium, resulting in the increased biliary excretion of cholesterol and higher LDL receptor expression on the liver [16,70]. The typical dosage ranges from 100 to 500 mg per day [16,69].

The average expected decrease in LDL-C is about −5% [16]. A network meta-analysis of 25 RCTs with 1487 participants comparing green tea extract versus placebo revealed that those in the green tea arm had a significant decrease in TC (−0.18 mmol/L; 95% CI, −0.33 to −0.04) and LDL-C (−0.17 mmol/L; 95% CI, −0.28 to −0.07). There were no significant changes in HDL-C or TG [15].

Green tea extract is generally well tolerated. Common side effects include gastrointestinal discomfort, transitory blood pressure elevations, and rashes [16,69]. Rare serious adverse effects include thrombotic thrombocytopenic purpura, hepatotoxicity, or hypokalemia [22]. At higher doses, green tea may lead to iron and folate deficiency by binding and reducing their absorption. In turn, special precautions may need to be taken in pregnant patients [16]. There may be an increased risk of miscarriage when consuming 200 mg or more of caffeine per day [71]. There may be some interactions with 5-fluorouracil, adenosine, anti-coagulants, anti-platelet drugs, antidiabetic drugs, statins, beta agonists, bortezomib, carbamazepine, cimetidine, clozapine, lisinopril, lithium, stimulants, verapamil, valproate acid, and more [22].

3.7. Olive Extract

Olive trees (*Olea europaea*) are native to the Mediterranean, and their fruits and leaves can be used to create olive extract [93,94]. The extract contains phenolic compounds, such as hydroxytyrosol, L-tyrosol, and secoiridoid oleuropein [93]. Olive extract reduces lipid peroxidation, increases bile excretion, and inhibits HMG-CoA reductase and acetyl-CoA cholesterol acyltransferase activity [92]. The typical dosage can range up to about 136.2 mg oleuropein and 6.4 mg hydroxytyrosol per day [93].

In a randomized, double-blind, controlled, crossover trial, 60 participants with hypertension were randomized into the placebo versus the olive leaf extract arm for 6 weeks. Participants then underwent a 4 week washout period and were assigned to the crossover arm for an additional 6 weeks. The authors found that olive leaf extract resulted in reductions of TC (−0.32 ± SD 0.70 mmol/L; $p = 0.002$), LDL-C (−0.19 ± SD 0.56 mmol/L; $p = 0.017$) and TG (−0.18 ± SD 0.48; $p = 0.008$) compared to the control arm. However, there were no significant changes in HDL-C [93].

There are no known adverse effects of olive extract. Although presumably safe to consume during pregnancy and while breastfeeding, there are no known data on the levels consumed through olive extract. There are no known interactions with medications [94].

3.8. Gamma-Oryzanol

Gamma-oryzanol is extracted from the bran of rice (*Oryza sativa* L.), which has been used in Islamic traditional medicine. The main mechanism of cholesterol reduction is via inhibition of gastrointestinal cholesterol absorption and increased fecal excretion of bile acids. Gamma-oryzanol has been shown to inhibit HMG-CoA reductase and platelet aggregation [95]. Gamma-oryzanol may also affect serum lipid levels by altering the gut microbiome [96]. The typical dosage ranges from 100 to 300 mg daily [16,22].

The expected LDL-C reduction is about −5 to −10% [16]. In a meta-analysis of 14 studies with 270 participants being treated with rice bran oil, those in the nutraceutical arm had a decrease in TG (−0.10 mmol/L; 95% CI, −0.20 to −0.004), TC (−0.19 mmol/L; 95% CI, −0.29 to −0.11), and LDL-C (−0.20 mmol/L; 95% CI, −0.29 to −0.04). There was no significant change in HDL-C [97].

There are no reported side effects with gamma-oryzanol [16,97]. There are no safety data on patients who are pregnant or breastfeeding, and there are no known drug interactions [22].

3.9. Soybean Protein

Soybean, also known as *Glycine max*, is a legume that traditionally has been consumed in Asian countries but has seen an increased adoption in the West. It contains high protein, polyunsaturated fatty acid (PUFA), and fiber [160]. Soy protein has many potential lipid-lowering mechanisms. β-conglycinin, a soy peptide, inhibits HMG-CoA reductase and reduces the amount of PCSK9 protein in the liver [141]. Soybean protein hydrolysate has been shown to reduce cholesterol absorption via increased bile acid excretion, cholesterol synthesis inhibition, and increased transcription of the LDL receptor [142,143]. Soy protein has been shown to increase apoB receptor activity and to decrease hepatic synthesis of cholesterol and lipoprotein secretion [143]. Soybeans have also been shown to alter the gut microbiome by increasing *Bifidobacteriaceae*, *Deferribacteraceae*, and *Clostridiales*, which may play a role in soy protein's lipid-lowering properties [144]. The typical dosage ranges from 25 to 120 mg daily [16,69].

The expected LDL-C reduction is about −3 to −10% [16]. A meta-analysis of 43 clinical trials with 2607 total participants that were given either dietary or supplementary soy versus placebo found that those in the soy arm experienced a decrease in TC (−0.17 mmol/L; 95% CI, −0.24 to −0.09) and LDL-C (−0.12 mmol/L; 95% CI, −0.17 to −0.07). The authors did not find a dose-dependent correlation with the lipid-lowering effect [161]. Another meta-analysis of 10 RCTs with 973 participants found that soy isoflavone supplementation did not significantly change Lp(a) [162].

Common side effects include gastrointestinal discomfort, menstrual complaints, headaches, dizziness, and rashes [22]. Chronic use of higher doses of soy protein may affect fertility and thyroid function [16,69]. There may be decreased absorption of divalent and trivalent metals, such as calcium, copper, iron, magnesium, and zinc, due to phytic acid in soybeans [143]. Due to the potential estrogen effects, supplemental soy protein should be avoided during pregnancy. However, there are no limitations in dietary soy. Use of soy is likely safe during breastfeeding. There may be interactions with antidiabetic drugs, antihypertensive drugs, diuretics, estrogens, progesterone, tamoxifen, levothyroxine, monoamine oxidase inhibitors, and warfarin [22].

3.10. Lupin Protein

Lupin is another legume that grows natively in Australia, the Mediterranean region, and South America. Lupin protein inhibits both HMG-CoA receptor and PCSK9 activity [75,76]. It upregulates SREBP-2 via phosphatidylinositol-3-kinase, alpha serine/threonine-protein kinase, and glycogen synthase kinase-3 beta kinase pathways in the liver [77]. The typical dosage is about 35 g or less per day [78].

The expected LDL-C reduction is about –5 to −12% [16]. In an RCT where 33 patients with dyslipidemia were randomized to receive 25 g per day of lupin protein isolate versus placebo, LDL-C (−0.35 ± 0.54 mmol/L) decreased in patients with TC > 6.6 mmol/L [78].

The most common side effects include gastrointestinal discomfort. It is likely safe to use in patients who are pregnant or breastfeeding. There are no known interactions with drugs [22].

3.11. Policosanol

Policosanol is extracted from sugarcane (*Saccharum officinarum* L.) wax, wheat germ, beeswax, and rice. It is a mixture of aliphatic alcohols, including tetratriacontanol, dotriacontanol, triacontanol, tetracosanol, hexacosanol, heptacosanol, octacosanol, and nonacosanol [116]. Policosanol promotes bile acid production and lipolysis via inhibiting the expression of farnesoid X receptor-small heterodimer partner and activating the Takeda G-coupled protein receptor 5-AMPK signaling pathway, which inhibits HMG-CoA reductase activity [114,115]. The typical dose ranges from 5 to 20 mg [116].

In a meta-analysis of 22 RCTs with 1886 participants with dyslipidemia, policosanol supplementation was associated with a decrease in TC (−0.58 mmol/L; 95% CI, −0.87 to −0.30) and LDL-C (−0.71 mmol/L; 95% CI, −1.02 to −0.40) and an increase in HDL-C (0.13 mmol/L; 95% CI, 0.09 to 0.16). There was no significant change in TG [116].

Common side effects of policosanols include gastrointestinal discomfort, tachycardia, myalgia, hypertension, headache, dizziness, somnolence, insomnia, polydipsia, nocturia, dry skin, rashes, and weight gain [116]. Animal models appear to show that policosanol is safe to use in pregnancy [117,118]. Data on the safety of policosanol in patients who are breastfeeding remain insufficient. There are possible interactions with antidiabetic drugs, beta-blockers, nitroprusside, and warfarin [22].

3.12. Phytosterols

Phytosterols are plant-derived compounds that are found in all plant foods, particularly in vegetable oils, nuts, seeds, and grains [163]. Phytosterol is a broad term that encompasses both plant sterols and stanols, and the most common phytosterols are campesterol, sitosterol, and stigmasterol [110,163]. Their structure is similar to that of cholesterol. Phytosterols inhibit cholesterol absorption in the gastrointestinal tract by competing with dietary cholesterol in the formation of dietary micelles, decreasing secretion of apoB from enterocytes and hepatocytes, and increasing cholesterol efflux via increased expression of adenosine triphosphate-binding cassette (ABC) protein A1 and ABCG1 levels [110–112]. The typical dosage ranges from 400 mg to 3 g per day [16,110].

The expected LDL-C reduction is about –8 to −16% [16,69]. In a meta-analysis of eight RCTs with 297 participants with dyslipidemia, plant sterol and stanol supplementation was found to lower LDL-C (−0.31 mmol/L; 95% CI, −0.39 to −0.23). The authors found that there were no significant differences between supplemented or dietary phytosterols [110]. In another larger meta-analysis of 51 clinical trials with 3786 participants who were randomized to dietary phytosterols versus placebo, there was a decrease in LDL-C (−0.34 mmol/L; 95% CI, −0.38 to −0.30) and TG (−0.05 mmol/L; 95% CI, −0.09 to −0.01) in the phytosterol arm. The increase in HDL-C was not significant [163].

Plant sterols/stanols had the highest certainty of evidence as assessed by the Journal of Clinical Epidemiology (JCE) Grading of Recommendations Assessment, Development and Evaluation (GRADE) [15]. This was also reflected in recent ILEP guidelines that gave IIa recommendations, which acknowledged the moderate effects and quality of trials [69].

Phytosterols are generally well tolerated and safe [16,69]. Phytosterols are safe to use in pregnancy [113]. However, data on their use in those breastfeeding are insufficient. There are no known drug interactions that are clinically significant [22].

3.13. Viscous Dietary Fibers

Viscous dietary fibers are an umbrella term used for a variety of complex polysaccharides found in oats, barley, legumes (lentils, lima beans, kidney beans, and pinto beans), fruits (apples, pears, plums, and citrus fruits), and vegetables (broccoli, Brussels sprouts, carrots, and green peas), seeds, and nuts that are resistant to digestion in the small intestine [164]. The US FDA and EFSA have both confirmed the lipid-lowering capabilities of soluble fiber [60,165]. Soluble fibers have different mechanisms of action and efficacy in their lipid lowering capacity [164].

3.13.1. β-Glucan

β-glucan is a soluble fiber found in the endospermic cell walls of oats and is produced during the ripening process. Due to the increased viscosity of β-glucan, this reduces the absorption of cholesterol from the gastrointestinal tract. It also increases gastrointestinal elimination via bile acid excretion [59]. Typical daily consumption ranges from 3 to 25 g [16,60].

In a meta-analysis of 13 RCTs that randomized 927 patients with dyslipidemia to receive a diet enriched with oat β-glucan versus placebo, the authors found a decrease in TC (−0.24 mmol/L; 95% CI, −0.28 to −0.20) and LDL-C (−0.27 mmol/L; 95% CI, −0.35 to −0.20). However, there was no significant change in TG or HDL-C [60].

β-glucans are typically well tolerated. Data on their use in patients who are pregnant or breastfeeding are insufficient. There may be interactions with antihypertensives and immunosuppressant drugs [22].

3.13.2. Psyllium

The husk of *Plantago* seed contains psyllium, which is a soluble fiber that forms a viscous gel. Psyllium reduces absorption of cholesterol via the gastrointestinal tract and binds to bile acids, which increases intestinal excretion of cholesterol and increases hepatic LDL receptor expression. Typical consumption can range from 2 to 20 g per day [63].

In a meta-analysis of 28 clinical trials involving 1924 patients with and without dyslipidemia, the authors found a reduction in LDL-C (−0.33 mmol/L; 95% CI, −0.38 to −0.27), non-HDL-C (−0.39 mmol/L; 95% CI, −0.50 to −0.27), and apoB (−0.05 g/L; 95% CI, −0.08 to −0.03) [63].

Side effects include gastrointestinal discomfort, mild anaphylactic allergic reactions, bowel obstructions, and esophageal obstructions [16,22,64]. Increased water consumption reduces obstructions [164]. Psyllium is safe to use during pregnancy or while breastfeeding [65]. There may be drug interactions with carbamazepine, digoxin, estradiol, lithium, metformin, and olanzapine [22].

3.13.3. Glucomannan

Glucomannan is a dietary fiber found in the tuber root of *Amorphophallus konjac*, which has been used as both food and medicine in Asia. It inhibits HMG-CoA reductase and reduces absorption of cholesterol in the gastrointestinal tract [57]. Glucomannan also increases the conversion of bile acids into cholesterol through increased 7-α-hydroxylase activity [16]. The typical dosage ranges from 1 to 15 g per day [16,58].

In a meta-analysis of 12 RCT with 370 participants with and without dyslipidemia that were treated with dietary glucomannan versus placebo, the authors found a decrease in LDL-C (−0.35 mmol/L; 95% CI, −0.46 to −0.25) and non-HDL-C (−0.32 mmol/L; 95% CI, −0.46 to −0.19). However, there was no significant change in apoB [58].

Glucomannan is associated with gastrointestinal discomfort and obstructions in the bowel or esophagus [22,58]. It may also reduce the absorption of vitamin E. Data on its use in patients who are pregnant or breastfeeding are insufficient. There may be issues with the absorption of other medicines when glucomannan is used [22].

3.13.4. Guar Gum

Guar, also known as *Cyamopsis tetragonoloba* or *Cyamopsis psoraloides*, is natively grown in India, Pakistan, North Africa, and South America [61,166]. It contains guar gum, which is a fermentable and soluble fiber consisting of galactose and mannose. Guar gum has a wide range of applications, as it is used in food (emulsifiers or thickeners), cosmetics, paper, textiles, toiletry, water treatment, and solar cells [166]. It works by preventing absorption of cholesterol in the gastrointestinal tract and increasing bile acid extraction. The typical dosage ranges from 30 to 100 g per day [61].

In a meta-analysis of 25 clinical trials with 1095 participants, there was a decrease in TC (−0.53 mmol/L; 95% CI, −0.69 to −0.36) and LDL-C (−0.45 mmol/L; 95% CI, −0.61 to −0.29). There was no significant change in TG or HDL-C [61].

Guar gum is generally well tolerated, and side effects include gastrointestinal discomfort and obstruction of the esophagus or bowel [22,61]. It is safe to use during pregnancy, as it treats intrahepatic cholestasis of pregnancy [62]. However, data on its use in patients who are breastfeeding remain insufficient. There may be interactions with penicillin, metformin, estradiol, and digoxin. It also may inhibit the absorption of other oral drugs [22].

3.13.5. Pectin

Pectins are soluble fibers that are found in citrus and apples. They can be commercially extracted from the pulp waste in the juice pressing process. They are used as thickeners and food stabilizers in jams, marmalades, yogurts, desserts, and more [107]. Pectins work by decreasing cholesterol absorption in the gastrointestinal tract and increasing excretion of bile acids [107,108]. They also decrease HMG-CoA reductase and increase cholesterol 7-α-hydroxylase in the liver. Pectins also modulate the gut microbiome by increasing *Lactobacillus*, *Bifidobacterium*, and *Bacteroides* [108]. Typical consumption can be about 6 g per day [107].

Various degrees of esterification of pectins, molecular weight, and sourcing from apples or citrus can impact the lipid-lowering capacity of pectins [107]. The expected LDL-C reduction is about −5 to −10% [16,107]. In a randomized, crossover design trial of 90 participants with dyslipidemia, the authors found a decrease in TC (−5.41 ± 7.27%) and LDL-C (−8.05 ± 9.31%) in patients treated with pectins from citrus with high degrees of esterification. Similarly, there was a decrease in TC (−6.54 ± 6.49%) and LDL-C (−9.26 ± 9.71%) with pectins from apples with high degrees of esterification. The authors found that pectins with higher degrees of esterification lowered TC and LDL-C more effectively than pectins with lower degrees of esterification. They also found that there was no significant difference in the TC and LDL-C lowering capabilities of pectins from citrus or apples. There was no significant change in TG or HDL-C from any type of pectin [107].

Pectins are generally well tolerated. Gastrointestinal discomfort is common in citrus pectins with higher degrees of esterification compared to pectins from apples [107]. Precautions should be taken in patients who are pregnant, as pectins bind to vitamin B12. This may exacerbate vitamin B12 deficiencies and potentially lead to higher risks of spina bifida in fetuses [109]. Pectins should be safe to use in patients who are breastfeeding. There may be interactions with digoxin, lovastatin, and tetracyclines [22].

3.14. Nigella Sativa

Nigella sativa (*N. sativa*), also known as black caraway, black cumin, or black seed, is a flower that is grown natively in Eastern Europe, the Middle East, North Africa, and South Asia [90]. It has been used as Islamic traditional medicine and has many modern applications, as it is used in cosmetics, food, and pharmaceuticals. *N. sativa* contains thymoquinone, flavonoids, and PUFAs such as linoleic and oleic acids. These can be made into a powder, extract, or oil suspension [89,90]. *N. sativa* works by reducing gastrointestinal absorption of cholesterol, increasing biliary excretion, reducing cholesterol synthesis, inhibiting lipid oxidation, and upregulating LDL receptors [89]. Typical daily doses can range from 200 mg to 3 g for powders, capsules, and extracts or 1 to 5 mL for oil suspensions [90].

In a meta-analysis of 37 trials with 2531 participants, *N. sativa* supplementation was associated with a reduction in TC (−0.43 mmol/L; 95% CI, −0.54 to −0.32), LDL-C (−0.48 mmol/L; 95% CI, −0.58 to −0.37), and TG (−0.18 mmol/L; 95% CI, −0.23 to −0.12) and an increase in HDL-C (0.05 mmol/L; 95% CI, 0.03 to 0.07) [90].

N. sativa is well tolerated and generally safe. It may be associated with gastrointestinal discomfort and elevated alkaline-phosphate, aspartate-aminotransferase, alanine-aminotransferase, and gamma-glutamyl transferase [89]. Despite this, *N. sativa* appears to be safe to use during pregnancy [91]. The data on its use during breastfeeding remain insufficient. There may be possible drug interactions with anticoagulants, anti-platelet drugs, antidiabetic drugs, antihypertensives, cyclosporine, diuretics, immunosuppressants, and serotonergic drugs [22].

3.15. Silymarin

Silymarin contains a group of flavonolignans, including silibinin, silybin, silydianin, silychristin, and isosilybin [137]. It is extracted from the fruit of *Silybum marianum*, also known as milk thistle, which is native to Europe [138]. Silymarin has been shown to increase lipolysis and β-oxidation via the upregulation of carnitine palmitoyl transferase 1 (CPT1) [135]. It has also been shown to increase cholesterol efflux via the increased expression of ABCA1 [136]. The typical dosage ranges from 140 to 700 mg per day [137].

In a meta-analysis of 11 RCTs of 816 participants with diabetes or liver disease, silymarin supplementation was found to decrease TC (−0.45 mmol/L; 95% CI, −0.80 to −0.10), LDL-C (−0.27 mmol/L; 95% CI, −0.49 to −0.05), and TG (−0.29 mmol/L; 95% CI, −0.53 to −0.05) and to increase HDL-C (0.09 mmol/L; 95% CI, 0.02 to 0.15) [137].

Silymarin is typically well tolerated. However, side effects of silymarin include gastrointestinal discomfort, headache, ureteric calculi, and hemolytic anemia. Reported serious adverse events include transient ischemia attack, MI, and cardiovascular death [137]. Safety data on its use in patients who are pregnant or breastfeeding are not available [138]. There are possible interactions with antidiabetic drugs, morphine, tamoxifen, sirolimus, and warfarin [22].

3.16. Sea Buckthorn

Sea buckthorn (*Hippophae rhamnoides* L.) is a plant found natively in northeastern Europe, Russia, China, Tibet, and Mongolia. It has been used in traditional Tibetan medicine and has been gaining popularity as a fruit juice [133]. It contains flavonoids, including isorhamnetin, kaempferol, and quercetin [132,133]. They increase the expression of peroxisome proliferator-activated receptor (PPAR)-α, PPAR-γ, and ABCA1 and decrease the expression of SREBP-2. Sea buckthorn promotes the expression of CPT1A, which is involved in increasing lipolysis and β-oxidation [132]. The typical dose of sea buckthorn seed oil is about 0.75 mL [133].

In a meta-analysis of 13 RCTs with 1167 participants, sea buckthorn supplementation decreased TC (−0.35 mmol/L; 95% CI, −0.64 to −0.05), TG (−0.72 mmol/L; 95% CI, −1.13 to −0.32), and LDL-C (−0.40 mmol/L; 95% CI, −0.76 to −0.04) and increased HDL-C (0.37 mmol/L; 95% CI, 0.06 to 0.68) [133].

Sea buckthorn is generally well tolerated. Animal models appear to show that sea buckthorn is safe to use in pregnancy [134]. However, there are limited data on its use in patients who breastfeed. There may be drug interactions with anticoagulants, anti-platelets, and antihypertensives [22].

3.17. Anthocyanins

Anthocyanins are antioxidants and are red, blue, or purple pigmented flavonoids [18]. They are used in food coloring and are found in fruits, flowers, roots, stems, leaves, and vegetables of blueberries, black rice, cherries, purple cabbage, purple grapes, and raspberries [16,18]. They have been shown to downregulate the messenger ribonucleic

acid expression of SREBP-1c and fatty acid synthase, resulting in less fat accumulation in adipocytes [17]. Typical dosages range from 100 to 450 mg daily [18].

The expected LDL-C reduction is about −5 to −10% [16]. In a meta-analysis of 20 trials with 1311 participants, the authors found a decrease in LDL-C (−0.19 mmol/L; 95% CI, −0.31 to −0.06) and TG (−0.20 mmol/L; 95% CI, −0.33 to −0.07) and an increase in HDL-C (0.09 mmol/L; 95% CI, 0.02 to 0.15). There was no significant change in TC [18].

Anthocyanins are generally well tolerated [16]. However, precautions should be taken with anthocyanins during pregnancy. There was a single case report of polyhydramnios discovered at 37 weeks of gestation from the prenatal closure of the ductus arteriosus after the maternal ingestion of MonaVie, which is a juice blend containing anthocyanins [19].

3.18. Spirulina

Arthrospira maxima, known commercially as spirulina, is a cyanobacterium containing amino acids, beta-carotene, polyphenols, vitamins, and PUFA [140]. C-phycocyanin, the main component involved in the lipid-lowering effect of spirulina, is a photosynthetic pigment that is used as a natural blue food coloring. The mechanism of action involves activating heme oxygenase-1, which is an atheroprotective enzyme involved in the heme catabolic pathway in endothelial cells [16,69]. C-phycocyanin also has antioxidant, anti-inflammatory, and radical-scavenging properties [16]. PUFAs from spirulina affect the gut microbiome, which may alter lipid metabolism [139]. The typical dosage ranges from 1 to 10 g per day [69].

The average expected decrease in LDL-C is about −5 to −15% [16,69]. One meta-analysis of eight clinical trials with 420 patients with diabetes found a decrease in TC (−0.30 mmol/L; 95% CI, −0.55 to −0.05), TG (−0.19 mmol/L; 95% CI, −0.34 to −0.04), and LDL-C (−0.24 mmol/L; 95% CI, −0.41 to −0.07). However, there was no significant change in HLD-C [15].

Side effects include gastrointestinal discomfort, bleeding, rashes, elevated transaminases, and cholestasis [22,140]. There are limited data on the safety in patients who are pregnant or breastfeeding. There may be interactions with anticoagulants, anti-platelet drugs, antidiabetic drugs, or immunosuppressant drugs [22].

3.19. Probiotics

Probiotics are live bacteria and yeast that are typically found in fermented foods and may alter the gut microbiome [122,123]. The most common microorganisms found in probiotics include *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, *Escherichia*, and *Bacillus* [123]. *Lactobacillus* and *Bifidobacterium* have been shown to increase the excretion of bile acids from the gastrointestinal tract via bile salt hydrolase enzymatic activity. This makes bile acids less water-soluble and thus more easily excreted by removing the amino acid moiety through deconjugation [119]. *Lacticaseibacillus* has also been shown to decrease Niemann–Pick C1-like 1 (NPC1L1) cholesterol transporter expression and increase cholesterol efflux via increased expression of ABCA1 [120]. *Lactobacillus rhamnosus* JL1 has also been shown to activate the AMPK pathway and inhibit PPAR-γ and SREBP-1C gene expression [121]. Probiotics can be delivered via capsules, yogurt, or fermented milk [122]. The typical dosage in capsules can range from 1 to 6 g per day [16,122].

The expected LDL-C reduction by probiotics is about −5% [16]. In a meta-analysis of 16 RCTs with 1429 non-obese participants with dyslipidemia, probiotics were associated with a decrease in TC (−0.34 mmol/L; 95% CI, −0.45 to −0.23) and LDL-C (−0.26 mmol/L; 95% CI, −0.36 to −0.17). No significant change was observed in TG or HDL-C [122].

Probiotics are generally safe and well tolerated. Side effects include gastrointestinal discomfort and infection, especially with probiotic formulations containing the yeast *Saccharomyces cerevisiae*. Probiotics are safe to use in infants and patients who are pregnant or breastfeeding [123].

3.20. Alpha Lipoic Acid

Alpha lipoic acid (ALA), also known as thioctic acid, is an antioxidant found in spinach, broccoli, tomatoes, red meat, and liver [72]. It is an essential cofactor for mitochondrial pyruvate dehydrogenase and α-ketoglutarate dehydrogenase [167]. ALA has been shown to modulate fat synthesis, mitochondrial β-oxidation of fat, clearance of TG-rich lipoproteins in the liver, and adipose TG accumulation [72]. The typical dosage ranges from 300 to 1800 mg per day [73].

In a meta-analysis of 12 RCTs with 548 patients, those in the ALA arm saw a decrease in TC (−0.28 mmol/L; 95% CI, −0.54 to −0.02), LDL-C (−0.28 mmol/L; 95% CI, −0.50 to −0.06), and TG (−0.35 mmol/L; 95% CI, −0.56 to −0.14). No significant changes in HDL-C were observed [73].

Adverse effects of ALA include gastrointestinal discomfort, skin rash, and rarely, insulin autoimmune syndrome. ALA is safe to use in patients who are pregnant [74]. However, there are insufficient data on its use in patients who are breastfeeding. ALA may interact with alkylating agents, anticoagulants, anti-platelet drugs, antidiabetic drugs, antitumor antibiotics, and levothyroxine [22].

3.21. Conjugated Linoleic Acid

Conjugated linoleic acid is a trans-fatty acid produced by bacteria in the gastrointestinal tract of ruminant animals via the metabolism of PUFAs and monounsaturated fatty acids. It is found in dairy products and meats from cows and sheep [49]. Conjugated linoleic acid promotes cholesterol efflux by increasing expression of cholesterol transporters ABCA1 and ABCG1 [48]. Typical dosages range from 0.5 to 7 g per day [49].

The expected LDL-C reduction is about −5% [16]. In a meta-analysis of 15 clinical trials, conjugated linoleic acid supplementation was associated with a decrease in LDL-C (−0.22 mmol/L; 95% CI, −0.36 to −0.08). There were no significant changes in TC, TG, or HDL-C [49].

Conjugated linoleic acid is associated with gastrointestinal discomfort and hepatotoxicity [50]. It is safe to use in patients who are pregnant [51]. However, there are insufficient data on its use in patients who are breastfeeding. Possible drug interactions include those with anticoagulants, anti-platelet drugs, and antihypertensives [22].

3.22. Chitosan

Chitosan is a polysaccharide derived from chitin, which is found in crustaceans [42,43]. Due to its positively charged amino group, chitosan interferes with gastrointestinal absorption by binding to negatively charged fatty acids and bile acids and disrupting the emulsification of neutrally charged cholesterol [42]. Typical dosages range from 0.3 to 3 g per day [43].

The expected LDL-C reduction is about –5% [16]. In a meta-analysis of 11 RCTs with 1011 participants, chitosan supplementation was associated with a decrease in TC (−1.39 mmol/L; 95% CI, −2.17 to −0.62), LDL-C (−0.83 mmol/L; 95% CI, −1.64 to −0.01), and TG (−1.06 mmol/L; 95% CI, −1.67 to −0.45). There was no significant change in HDL-C [43].

Chitosan should not be used in patients with allergies to crustaceans or shellfish [42]. Other side effects include gastrointestinal discomfort. There are insufficient data on its use in patients who are pregnant or breastfeeding. Possible drug interactions include those with acyclovir or warfarin [22].

3.23. Pantethine

Pantethine is a compound produced endogenously via pantothenic acid, which is also known as vitamin B5 [16,98]. The mechanism of action is believed to include cysteamine and involves the inhibition of HMG-CoA reductase and acetyl-CoA carboxylase, which are involved in TG synthesis and lipoprotein metabolism. However, further research is needed to elucidate the full mechanism. The typical dosage is about 600 to 1200 mg per day [98].

In a triple-blinded RCT with 30 participants, those in the pantethine arm saw a decrease in TC (−6%), LDL-C (−11%), and apoB (−8%). However, there were no significant changes in HDL-C, TG, or Lp(a). The main side effect of pantethine is gastrointestinal symptom [98]. Pantethine can be used in children and in patients with chronic kidney disease, including those on dialysis [99,100]. There are insufficient data on its use in patients who are pregnant or breastfeeding. There are no known drug interactions [22].

4. Nutraceuticals and Their Effects on Other Lipid Targets

4.1. Polyunsaturated n-3 Fatty Acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain PUFAs that are found naturally in fish, krill, squid, eggs, algae, flaxseeds, walnuts, clary sage, and various other edible seeds. The EFSA acknowledges that consumption of EPA and DHA may lower serum triglyceride levels [102]. These PUFAs work by reducing the synthesis of hepatic VLDL, endogenous fatty acids, substrates available for TG synthesis, and the activity of diacylglycerol acyltransferase or phosphatidic acid phosphohydrolase, which are involved in TG synthesis. They also promote β-oxidation of fatty acids and increase phospholipid synthesis [101].

Formulations can include over-the-counter supplements, which can contain higher levels of saturated fat. Prescriptions are purified pharmaceutical-grade formulations that contain less saturated fats. Both supplements and prescription formulations can contain a combination of EPA and DHA. However, only prescription formulations contain solely EPA. It should be noted that the over-the-counter supplements are not equivalent to the prescription formulations, as only purified EPA has also been shown to reduce plaque volume [168]. For both supplements and prescription formulations, the typical dosage is $\leq$4 g per day of EPA and DHA [102,103]. For prescription formulations containing only EPA, the typical dosage is $\leq$4 g per day [105].

In a meta-analysis of 46 RCTs with 4991 participants with DM2, those in the fish oil supplementation arm saw a decrease in TC (−0.22 mmol/L; 95% CI, −0.32 to −0.11) and TG (−0.36 mmol/L; 95% CI, −0.48 to −0.25) and an increase in HDL-C (0.05 mmol/L; 95% CI, 0.02 to 0.08). There was no significant change in LDL-C [169]. Another meta-analysis of 33 RCTs with 2704 participants with metabolic syndrome investigated the individual effects of DHA and EPA supplementation versus control. Those in the EPA supplementation arm saw a decrease in TC (−0.24 mmol/L; 95% CI, −0.43 to −0.05) and LDL-C (−0.13 mmol/L; 95% CI, −0.25 to −0.01). There was no significant change in HDL-C with EPA supplementation. In the DHA supplementation arm, there was a decrease in TG (−0.29 mmol/L; 95% CI, −0.37 to −0.21) and an increase in TC (0.14 mmol/L; 95% CI, 0.03 to 0.25), LDL-C (0.26 mmol/L; 95% CI, 0.15 to 0.38) and HDL-C (0.07 mmol/L; 95% CI, 0.04 to 0.09) [104].

There are strong data supporting the use of prescription EPA formulations. The Japan EPA Lipid Intervention Study (JELIS) trial was a large open-label RCT with 18,645 participants of Japanese descent with dyslipidemia. All patients were on 10 mg of pravastatin or 5 mg of simvastatin. They were randomized to receive 1.8 g per day of prescription EPA or placebo. The authors found a significant reduction in TG (23%) and major adverse cardiovascular events (MACE) (HR, 0.81; 95% CI, 0.69 to 0.95) in the EPA arm [170].

Another landmark RCT, the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), further cemented the use of prescription EPA formulations in treating elevated triglycerides. A total of 8179 participants who had fasting TG between 1.53 to 5.64 mmol/L (135 to 499 mg/dL) and were already on a statin were randomized to 4 g of prescription EPA. The authors found a reduction in TG (−18.3%), HDL-C (−2.6%), non-HDL-C (−3.6%), high sensitive-CRP (−13.9), and MACE (HR, 0.75; 95% CI, 0.68 to 0.83) in the EPA arm [105].

Similar results have not been reproduced with omega-3 fatty acids containing both EPA and DHA. The Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial was

a large RCT with 13,078 patients who were at high risk of cardiovascular disease. They were randomized to 4 g of omega-3 FA, consisting of both prescription EPA and DHA versus corn oil. This trial was terminated early due to futility as no difference was observed in MACE (HR, 0.99; 95% CI, 0.90 to 1.09; $p = 0.84$) despite a significant decrease in TG (−19.0%; 95% CI, −39.2 to −6.4%) [103].

Prescription and supplemental DHA and EPA are associated with gastrointestinal discomfort and new-onset atrial fibrillation and atrial flutter. Those sourced from fish or krill can have a fishy aftertaste [103,105]. DHA and EPA are safe to use in pregnancy, as they are frequently in prenatal vitamins [106]. They are also likely safe to use during breastfeeding. Possible drug interactions include those with anticoagulants, anti-platelet drugs, antihypertensives, contraceptives, cyclosporine, and tacrolimus [22].

4.2. Niacin

Many clinicians use nicotinic acid (niacin or vitamin B_3) in patients who are statin intolerant in the management of hypertriglyceridemia, despite it no longer being recommended for LDL-C reduction [1,7]. It inhibits diacylglycerol acyltransferase-2, which decreases TG synthesis and LDL-C by increasing hepatic apoB degradation. It raises HDL-C by stimulating hepatic apolipoprotein A-I production [84]. Typical dosages are ≤2 g daily [85,86].

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial was a large multicenter RCT that was terminated early due to the lack of efficacy. A total of 3414 participants with cardiovascular disease on simvastatin (and ezetimibe if LDL-C was >2.07 mmol/L [80 mg/dL]) were randomized to receive 1500 to 2000 mg niacin versus placebo. After 3 years, there was no difference in MACE (HR, 1.02; 95% CI, 0.87 to 1.21; $p = 0.79$) despite the niacin group experiencing an increase in HDL-C (25.0%) and a decrease in TG (−28.6%) and LDL-C (−12.0%) [86].

In the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial, 25,673 participants with established atherosclerotic cardiovascular disease were randomized to 2 g extended release niacin and laropiprant (used to minimize flushing from niacin) versus placebo. All participants received simvastatin (and ezetimibe if TC was ≥135 mg/dL or 3.5 mmol/L). Despite an increase in HDL-C (0.16 mmol/L) and a reduction in LDL-C (−0.25 mmol/L) and TG (−0.37 mmol/L) in the niacin arm, there were no significant differences in composite major vascular events (HR, 0.96; 95% CI, 0.90 to 1.03; $p = 0.29$). The authors did find a 10% reduction in revascularization procedures (RR, 0.90; 95% CI, 0.82 to 0.99; $p = 0.03$) in the niacin arm [85].

A meta-analysis of 17 studies with 35,760 participants with cardiovascular disease or dyslipidemia found that niacin monotherapy reduced the risk of acute coronary syndrome (RR, 0.74; 95% CI, 0.58 to 0.96), cerebral vascular accident (RR, 0.74; 95% CI, 0.59 to 0.94), and revascularization (RR, 0.79; 95% CI, 0.64 to 0.98) compared to participants not on statins [171]. Another meta-analysis of 14 RCTs with 9013 participants found that those in the niacin arm experienced a reduction in Lp(a) (−22.9%, 95% CI, −27.3 to −18.5) [172].

Due to the AIM-HIGH and HPS2-THRIVE trials, the US FDA withdrew the indication for extended-release niacin for co-administration with statins [173]. The European Medicines Agency has suspected all use of extended-release niacin and laropiprant, and niacin is no longer recommended to treat dyslipidemia in the European Union [7,174]. Similarly, the American multisociety guidelines recommend against using niacin for its LDL-C lowering capacity, but it may be considered in patients with severe hypertriglyceridemia [1].

Niacin is associated with increased gastrointestinal hemorrhage, peptic ulcers, myopathy, rhabdomyolysis, gout, flushing, skin lesions, skin infections, and lower respiratory infections. There is also an increased incidence of diabetes and hospitalizations for diabetes complications [85]. There are no restrictions with niacin for pregnant or breast feeding patients, as it is associated with a lower risk of congenital abnormalities [87]. There may be interactions with statins, isoniazid, and pyrazinamide [1,88].

4.3. L-Carnitine

L-carnitine is a hydrophilic quaternary ammonium cation that is found in meat, fish, poultry, and dairy. It is synthesized in the brain, liver, and kidneys [35]. L-carnitine supplementation, when concomitantly given with coenzyme Q10, may reduce SAMS [175]. L-carnitine decreases TG synthesis by decreasing available free fatty acids, increases mitochondrial oxidation of long-chain fatty acids, and increases production of apolipoprotein A1. The typical oral dosage ranges from 500 mg to 3 g and can be as high as 6 g per day [35].

In a meta-analysis of 55 RCTs with 3058 participants, those in the L-carnitine supplementation arm saw a reduction in TC (−0.22 mmol/L; 95% CI, −0.35 to −0.09), LDL-C (−0.14 mmol/L; 95% CI, −0.22 to −0.06), and TG (−0.11 mmol/L; 95% CI, −0.18 to −0.03) and an increase in HDL-C (0.04 mmol/L; 95% CI, 0.01 to 0.07). The authors found that higher doses of L-carnitine (≥2 g) yielded a greater reduction in TC and LDL-C [35]. Another meta-analysis of four RCTs with 218 participants found that oral L-arginine supplementation lowered Lp(a) (−0.09 mmol/L; 95% CI, −0.10 to −0.08) [176].

L-carnitine is generally well-tolerated. Patients may have fishy body odor, minor nausea, or other gastrointestinal discomfort [22,36]. L-carnitine supplementation in those who are pregnant and breastfeeding is safe, and parenteral carnitine supplementation is safe in infants [22,37,38]. There may be drug interactions with thyroid hormones and warfarin [22].

4.4. Vitamin E

Vitamin E is a fat-soluble vitamin with antioxidant properties. It has been shown to slow atherosclerotic plaque progression in patients with dyslipidemia when supplemented with vitamin C [177]. There are eight distinct chemical compounds, including α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol [16]. Vitamin E lowers lipids by inhibiting HMG-CoA reductase, promoting scavenging for free radicals, and activating the PPAR -α, -β, and -γ receptors [145–147]. The typical dosage ranges from 400 to 800 UI per day [16].

In a meta-analysis of 16 RCTs with 803 participants, the authors found that vitamin E increased HDL-C (0.15 mmol/L; 95% CI, 0.07 to 0.23) compared to placebo. They found a dose-dependent response, with higher doses of vitamin E supplementation correlating with higher increases in HDL-C. There were no significant changes in TC, LDL-C, or TG [148].

Vitamin E supplementation is associated with an increased risk of bleeding, heart failure, hemorrhagic cerebral vascular accidents, prostate cancer, and all-cause mortality [147,149]. Vitamin E supplementation is safe in pregnant women, as it is frequently used in prenatal vitamins [106]. It is also likely safe during breastfeeding. There are possible drug interactions with alkylating agents, anticoagulants, anti-platelet drugs, cyclosporine, CYP3A4 substrates, niacin, and selumetinib [22].

5. Inconsistent Data Regarding Nutraceuticals and Dyslipidemia

5.1. Resveratrol

Resveratrol (3,5,40-trihydroxystilbene) is a non-flavonoid polyphenol compound primarily found in red grapes, raspberries, mulberries, blueberries, knotweed, and peanuts. It is also found in some juices and wines made from these fruits [129,130]. It potentially has antioxidant, anti-inflammatory, anti-apoptotic, and anti-cancer properties [130]. Resveratrol is an activator of the silent information regulation 2 homolog 1 and has been shown to suppress the hepatic upregulation of genes associated with lipogenesis and prevent the downregulation of genes involved in lipolysis [127]. It also may inhibit atherosclerosis by suppressing foam cell formation [128]. Typical dosages range from 250 to 3000 mg per day [129,130].

The LDL-C lowering effects of resveratrol have been mixed. One meta-analysis performed by Akbari et al. with 31 RCTs and 1722 participants investigated resveratrol in patients with metabolic syndrome and other related risk factors. Akbari et al. found a significant reduction in TC (−0.20 mmol/L; 95% CI, −0.33 to −0.06) but not in LDL-C, TG, or HDL-C. Notably, this meta-analysis included other pill combinations that contained other

nutraceuticals in addition to resveratrol [178]. In another recent meta-analysis, Cao et al. only included RCTs where resveratrol was the sole nutraceutical used. Studies including other nutraceutical combinations with resveratrol were excluded. A total of 17 RCTs and 968 participants with metabolic syndrome and similar risk factors were included in their analysis. Cao et al. found in the resveratrol arm a significant reduction in TC (−0.27 mmol/L; 95% CI, −0.33 to −0.17), TG (−0.10 mmol/L; 95% CI, −0.14 to −0.05), and LDL-C (−0.147 mmol/L; 95% CI, −0.286 to −0.008) but not HDL-C. They also found a dose-dependent response with a higher reduction in LDL-C in those taking resveratrol for 12 weeks or longer and in those with diabetes [131].

Resveratrol may increase bleeding. It is likely safe to consume during pregnancy and breastfeeding, provided that the resveratrol is not consumed from beverages with alcohol. In patients with malignancies that grow in response to estrogen, such as breast, uterine, and ovarian cancer, it is advised that patients limit their intake due to resveratrol potentially acting on estrogen receptors. Resveratrol may have interactions with garlic, ginger, ginkgo, nattokinase, anticoagulants, anti-platelet drugs, and those involving the cytochrome P450 system, such as CYP1A1, CYP1A2, CYP1B1, CYP2C19, CYP2E1, and CYP3A4 [129].

5.2. Curcumin

Curcumin is a yellow polyphenolic compound found in the dried rhizomes of turmeric (*Curcuma longa*), which is natively grown in Southeast Asia [55,56]. It has been used in traditional Chinese and Indian medicine and has commercial applications, such as being used as a food additive or in cosmetics [179]. Curcumin inhibits intestinal NPC1L1 cholesterol transporter expression by inhibiting the SREBP2 transcription factor [52]. It also increases LDL-C clearance by increasing LDL receptor expression through the downregulation of PCSK9 expression [53]. Lastly, curcumin increases cholesterol efflux by upregulating ABCA1 expression [54]. Typical dosages can range from 50 mg to 6 g per day [55].

The expected LDL-C reduction is about −5% [16]. In a meta-analysis by Sahebkar et al. of five RCTs and 133 participants from a heterogeneous population, curcumin supplementation did not significantly change TC, TG, LDL-C or HDL-C [55]. However, another meta-analysis, by Altobelli et al., focused on patients with diabetes and included five RCTs with 476 participants. In the curcumin arm, there was a decrease in TC (−0.30 mmol/L; 95% CI, −0.53 to −0.07), LDL-C (−0.28 mmol/L; 95% CI, −0.52 to −0.04), and TG (−0.57 mmol/L; 95% CI, −0.83 to −0.31). However, there was no significant change in HDL-C [180]. Another meta-analysis, which included 10 RCTs with 683 participants, focused on patients with nonalcoholic fatty liver disease. Here, Khalili et al. found a decrease in TC (−0.81 mmol/L; 95% CI, −1.34 to −0.27) and TG (−0.49 mmol/L; 95% CI, −0.71 to −0.27) in the curcumin arm compared to placebo. However, no significant changes in LDL-C or HDL-C were found [179].

Curcumin supplementation is generally well tolerated and safe, and the most common side effect is gastrointestinal discomfort [22,56]. However, precautions should be taken in patients who are pregnant or breastfeeding, as levels greater than dietary levels may be unsafe. There may be drug interactions with alkylating agents, amlodipine, anticoagulants, anti-platelet drugs, antidiabetic drugs, CYP3A4 substrates, sulfasalazine, tacrolimus, talinolol, tamoxifen, and warfarin [22].

5.3. Magnesium

Magnesium is a naturally occurring mineral. Intravenous magnesium has been linked to lower left ventricular failure, lower mortality from ischemic heart disease, and lower all-cause mortality [82]. Magnesium downregulates HMG-CoA reductase expression and upregulates cholesterol 7α-hydroxylase and lecithin cholesterol acyltransferase expression [79]. Typical oral dosages can range from 35 to 500 mg per day [80].

In a meta-analysis of 12 RCTs with 677 participants with diabetes, magnesium supplementation lowered LDL-C (−0.18 mmol/L; 95% CI, −0.30 to −0.05) but did not significantly

affect TC, HDL-C, or TG [80]. Other studies have not found a significant change in the lipid profile of patients without diabetes [81].

Side effects of hypermagnesemia include gastrointestinal discomfort, flushing, confusion, hypotension, hyperreflexia, respiratory depression, hyperkalemia, hypocalcemia, pulmonary edema, and cardiac arrest [82,83]. Magnesium is safe to use during pregnancy and actually has therapeutic indications when given at appropriate doses [22,83]. It appears safe when the total oral intake does not exceed 350 mg per day. There may be an increase in fetal mortality when intravenously used for tocolysis. There were no increases in fetal mortality when given for preeclampsia or eclampsia. When given intravenously or intramuscularly for more than 5 to 7 days, there may be an increased risk for neonatal fractures or osteopenia. Magnesium appears safe to use during breastfeeding. There may be drug interactions with aminoglycosides, antacids, bisphosphonates, calcium channel blockers, digoxin, ketamine, levodopa, carbidopa, potassium-sparing diuretics, quinolones, sulfonylurea, and tetracyclines [22].

5.4. Chromium

Chromium(III) is an essential trace mineral found in fruits, vegetables, grains, meat, beer, and wine [41]. It is involved in lipid metabolism, and chromium deficiency is associated with dyslipidemia [181]. Chromium upregulates gene expression of PPAR-γ and LDL receptor. Typical dosages range from 40 to 1000 mcg per day [39].

In a meta-analysis with 40 RCTs and 1966 participants, chromium supplementation was associated with only a decrease in TC (-0.17 mmol/L; 95% CI, -0.27 to -0.07). There were no significant changes in LDL-C, TG, or HDL-C [39]. In another meta-analysis with 24 RCTs focusing on 1418 patients with diabetes, chromium supplementation was found to decrease TC (-0.20 mmol/L; 95% CI, -0.29 to -0.11) and increase HDL-C (0.06 mmol/L; 95% CI, 0.01 to 0.11). There was no significant change in LDL-C or TG [40].

Chromium supplementation may lead to weight loss, hypoglycemia, anemia, thrombocytopenia, elevated transaminases, elevated creatinine, rhabdomyolysis, and dermatitis. Chromium supplementation is safe during pregnancy and in women breastfeeding. Drug interactions include those with levothyroxine, insulin, metformin, and other anti-diabetic medications [41].

5.5. Coenzyme Q10

Coenzyme Q10 (ubidecarenone, ubiquinone, or vitamin Q10) is a benzoquinone compound produced in the body. The highest concentrations are found in the heart, liver, kidneys, and pancreas [47]. Statins can lower coenzyme Q10 levels, and the National Lipid Association has endorsed coenzyme Q10 supplementation in a select group of patients who develop SAMS [47,182]. L-carnitine can be used in addition to coenzyme Q10 to help with SAMS [175]. Coenzyme Q10 is thought to reduce oxidative stress and replenish low coenzyme Q10 stores [44]. Typical dosages of coenzyme Q10 can range from 30 to 250 mg per day [45].

There are conflicting data on its lipid-lowering effects, which are minimal if present. In a meta-analysis of eight RCTs with 526 patients with known coronary artery disease, participants were randomized to placebo versus coenzyme Q10. In the arm with coenzyme Q10 supplementation, there was a decrease in TC (-0.03 mmol/L; 95% CI, -0.05 to -0.01) and an increase in HDL-C (0.03 mmol/L; 95% CI, 0.01 to 0.06). However, there were no significant changes in LDL-C, TG, or Lp(a) [46]. Conversely, a larger meta-analysis of 21 controlled trials with 1039 participants with metabolic syndrome found conflicting results. In the intervention arm, those being treated with coenzyme Q10 experienced a reduction in TG (-0.0032 mmol/L; 95% CI, -0.0063 to -0.0001). However, there were no significant changes in TC, HLD-C, or LDL-C [45].

In the Intervention With Selenium and Q10 on Cardiovascular Mortality and Cardiac Function in the Elderly Population in Sweden (KiSel-10) study, 443 Swedish participants between the ages of 70 to 87 years were randomized to receive placebo versus 200 mg coen-

zyme Q10 and 200 μg selenium supplementation for 4 years. Participants were followed for 12 years, and those in the supplement arm had a significant reduction in cardiovascular mortality compared to the placebo arm (HR 0.59; 95% CI, 0.42 to 0.81; $p = 0.001$) [183,184].

Coenzyme Q10 is generally well tolerated with no serious adverse events. Insomnia, gastrointestinal discomfort, dizziness, headache, dyspepsia, photophobia, irritability, and fatigue have been reported. Coenzyme Q10 may have interactions with anticoagulants, insulin, and certain cancer treatments. Beta-blockers can inhibit enzyme reactions involving coenzyme Q10 [47].

6. Lifestyle Changes and the Impact on Dyslipidemia

The Mediterranean Diet

The Mediterranean diet mimics the food pattern typically consumed in areas surrounding the Mediterranean Sea. It can consist of plentiful fruits, vegetables, nuts, and grains. It can also comprise low to moderate amounts of dairy, poultry, fish, and eggs. The primary source of fat is derived from olive oil. Red or processed meats are less frequently consumed [185]. The Mediterranean diet is endorsed by the guidelines from multiple societies, including the European Society of Cardiology, European Association of Preventive Cardiology, American College of Cardiology, American Heart Association, and others [154,186].

In a meta-analysis of 38 studies with 4658 participants, those who had a Mediterranean diet showed a decrease in TC (−0.15 mmol/L; 95% CI, −0.26 to −0.04), TG (−0.14 mmol/L; 95% CI, −0.18 to −0.10), and LDL-C (−0.21 mmol/L; 95% CI, −0.35 to −0.08). There was also an increase in HDL-C (0.03 mmol/L; 95% CI, 0.01 to 0.06) [187].

In the Prevención con Dieta Mediterránea (PREDIMED) trial, 7447 participants from Spain with high cardiovascular risk were randomized into three arms, including Mediterranean diet supplemented with extra-virgin olive oil, Mediterranean diet supplemented with nuts, or a low-fat diet (control). Martınez-Gonzalez et al. followed the participants for about 5 years. Compared to the control arm, participants in the arms where their Mediterranean diets were supplemented with extra-virgin olive oil and nuts, respectively, experienced a 30% and 28% reduction in the combined endpoints of MI, stroke, and cardiovascular death. However, this was largely driven by the reduction in stroke, as there were no significant reductions in MI or cardiovascular death [188]. Martınez-Gonzalez et al. performed a post hoc analysis on the same PREDIMED cohort that focused on a "provegetarian" plant-based food pattern compared to those mostly consuming meat, fish, eggs, and dairy products. They found that those in the highest quintile for vegetable consumption had a 41% reduction in all-cause mortality compared to those with the lowest vegetable consumption [189].

Similarly, another meta-analysis of seven prospective cohort studies with 37,879 participants from Europe and the US also found a smaller but significant (15%) reduction in all-cause mortality in those following the Mediterranean diet. However, there was no significant reduction in cardiovascular mortality with the Mediterranean diet versus control. A subgroup analysis focusing on those consuming a Mediterranean diet also found that those living in the Mediterranean area had a more significant reduction in all-cause mortality compared to those from non-Mediterranean areas (14% versus 5%) [190].

7. Discussion

Nutraceuticals are a wide variety of compounds with various mechanisms of action, including inhibiting HMG-CoA reductase activity, inhibiting acyl-coenzyme A cholesterol acyltransferase, preventing cholesterol absorption from the gastrointestinal tract, promoting lipolysis, and more. The lipid-lowering effects of many nutraceuticals have been investigated in many rigorous clinical trials, systemic reviews, and meta-analyses. Many of these studies focused on primary prevention in patients with dyslipidemia, metabolic syndrome, and diabetes.

7.1. Comparisons of the Effectiveness of Nutraceuticals

Although a large amount of data regarding nutraceutical interventions exists, questions still remain regarding the comparative efficacy of nutraceuticals; this is attributed to the paucity of head-to-head trials comparing various nutraceuticals. A network meta-analysis (NMA) is considered the highest level of evidence-based medicine because it enables simultaneous comparison of interventions and provides indirect evidence of the comparative efficacy of various nutraceuticals [191].

A recent NMA by Osadnik et al. included 131 RCTs with over 13,062 participants and ranked the lipid-lowering effects of 10 nutraceuticals, including artichoke leaf extract, berberine, bergamot, garlic, green tea extract, policosanols, plant sterols and stanols, RYR extract, spirulina, and silymarin. Each nutraceutical was ranked according to *p*-score values. This NMA demonstrated that all analyzed nutraceuticals, except for policosanols in studies outside of Cuba, were more effective in lowering LDL-C than placebo [15].

Bergamot, RYR extract, artichoke, berberine, and plant sterols were ranked as the most effective in lowering LDL-C and TC by Osadnik et al. Bergamot was the most effective in lowering LDL-C and TC compared to the other nutraceuticals, and RYR extract was ranked as the second most effective supplement. Berberine and artichoke leaf extract were almost equally effective at reducing LDL-C and TC. In comparison with RYR and bergamot, berberine and artichoke leaf extract were ranked as slightly less effective.

Bergamot, berberine, and RYR extract were the three nutraceuticals that effectively raised HDL-C in the NMA performed by Osadnik et al. Bergamot was the most effective at raising HDL-C, followed by berberine and then RYR extract in terms of their effectiveness. Bergamot, RYR extract, silymarin, berberine, spirulina, artichoke leaf extract, and garlic were all shown to decrease TG levels, with bergamot being the most effect at lowering TG.

Osadnik et al. reported that the lipid-lowering effect of phytosterols was modest and ranked them fifth in their NMA. They might be more effective when combined with other nutraceuticals and exert a synergistic effect due to their various mechanisms of action. Phytosterols had the highest certainty of evidence as assessed by GRADE. Of note, Osadnik et al. reported that the results of Cuban trials on policosanols were questionable because similar results were not able to be reproduced in trials outside of Cuba. These disparate results reveal that more research is needed to investigate the true lipid-lowering potential of phytosterols [15].

7.2. Outcomes Data

RYR extract has the most data to support its use in patients with dyslipidemia. RYR extract supplementation is associated with a reduction in non-fatal MI, coronary revascularization, and sudden death [152]. These studies were primarily conducted in patients of Han Chinese descent, and caution should be taken when extrapolating to other patient populations.

Coenzyme Q10 can be used in patients who develop SAMS [182]. Despite the inconsistent data on the lipid-lowering efficacy, the KiSel-10 study demonstrated that Swedish patients between the ages of 70 to 87 years experienced a reduction in cardiovascular mortality when supplemented with both coenzyme Q10 and selenium [183,184]. Caution should be exercised when trying to extrapolate these results to other patient populations.

Mediterranean diets that are high in extra-virgin olive oil and nuts are the food patterns with the strongest evidence for reduction of MACE, due primarily to a reduction in stroke [188]. Similarly, the plant-based Mediterranean diet has also been shown to reduce all-cause mortality but currently is not shown to reduce cardiovascular mortality [189,190]. When examining those who follow the Mediterranean diet, those living in the Mediterranean had a higher reduction in all-cause mortality than those living outside of the Mediterranean, suggesting that other factors may be at play in reducing all-cause mortality [190].

Aged garlic extract has been shown to reduce the low-attenuation plaque percentage in patients with metabolic syndrome and DM2. These reductions were seen in serial imaging on cardiac computed tomography angiography after only 1 year of supplementation [156,157].

Further studies are needed to investigate the potential MACE reduction in patients taking aged garlic extract.

Niacin is no longer recommended for LDL-C reduction but may be considered for the treatment of hypertriglyceridemia in patients who are statin-intolerant [1,7]. Older studies have shown that niacin can reduce the risk of acute coronary syndrome, cerebral vascular accident, and revascularization in patients not on statins. Because statins were not used, those older studies do not reflect modern methodology and likely do not represent current-day patients receiving the standard-of-care [171]. The AIM-HIGH and HPS2-THRIVE trials confirmed this by showing that there was no benefit in the reduction of cardiovascular and cerebrovascular events when niacin was added on top of statin therapy [85,86]. The HPS2-THRIVE trial did show a reduction in coronary revascularization procedures [85].

Many nutraceuticals lack outcomes data. In turn, it should be highlighted that nutraceuticals do not replace the use of statins or detract from the importance of other lipid-lowering therapies. The controversial Supplements, Placebo or Rosuvastatin Study (SPORT) trial showed that rosuvastatin quickly lowered LDL-C more than either fish oil, cinnamon, garlic, turmeric, plant sterol, or red yeast rice extract over a 4 week period. The authors did not find a significant change in LDL-C with all six nutraceuticals compared to placebo. However, this study may have been underpowered, as it only had 190 participants among eight parallel arms in the follow-up period of 4 weeks [192].

7.3. Regulation of Nutraceuticals/Supplements

Nutraceutical preparations are often marketed as "food supplements". Therefore, they are not regulated in the same manner as pharmaceuticals, so long as manufacturers do not make any specific health-related efficacy claims about their nutraceutical products. A common concern is the wide variation in quality, as there may be potential contaminants in formulations. There also may be differences in the amount of the actual marketed nutraceutical between different manufacturers or even within each single manufacturer due to batch-to-batch variations. Therefore, the results from one study may not be extrapolated to the exact nutraceutical formulation purchased by patients. Greater regulation is likely to result in the more widespread availability of high-quality preparations [14,15].

7.4. Future Research

There is a need for more high-quality RCTs, systematic reviews, and meta-analyses that investigate the lipid-lowering effects of nutraceuticals. Some nutraceutical studies are not as rigorous as pharmaceutical clinical trials, as they may have fewer patients enrolled. More work is needed to explore the impact of many nutraceuticals on biomarkers such as apoB, apolipoprotein A1, Lp(a), and others. In addition, more research is specifically needed to investigate the potential effects on plaque burden, MACE, and other outcomes. Furthermore, caution should be exercised when extrapolating the results to various ethnic groups or target populations with different medical conditions. Although many trials were run in primary prevention patients, more research is needed to investigate the use of nutraceuticals in secondary prevention. However, nutraceuticals may still serve an important role in the management of dyslipidemia, especially in patients with statin intolerance. They can also be used in patients who are interested in a more integrative approach with compounds that are extracted or purified from naturally occurring fruits, vegetables, plants, and meats. They can be added on top of statins and other conventional lipid-lowering therapies.

8. Conclusions

Bergamot and RYR extract appear to be the most effective nutraceuticals in terms of LDL-C reduction [15]. There are a wide variety of nutraceuticals that exhibit their lipid-lowering effects via different mechanisms of action [16,69]. A plant-based Mediterranean diet can also be incorporated into a patient's lifestyle in order to provide a holistic approach

to addressing dyslipidemia [187]. These integrative therapies may potentially help mitigate modifiable cardiovascular risk factors and potentially lower a patient's ASCVD risk burden.

There is an ever-growing body of research on the lipid-lowering effects of nutraceuticals, as there are many clinical trials, systematic reviews, and meta-analyses. Interestingly, the SPORT trial has raised more questions about the potential lipid-lowering effects of nutraceuticals [192]. It is important to highlight that statins cannot be replaced by nutraceuticals, as statins remain the cornerstone of lipid-lowering therapy [16,69]. More studies are needed to investigate the lipid-lowering effects using robust modern clinical trial methodology involving statins.

Only a few integrative therapies have data on cardiovascular outcomes. Aged garlic extract has been shown to reduce low-attenuation plaque [156,157]. However, only RYR extract, coenzyme Q10 (when supplemented with selenium), and the Mediterranean diet have been shown to have some mortality benefits [152,183,184,188]. Hence, more research is needed to investigate the impact of other nutraceuticals on cardiovascular risk on a long-term basis using modern clinical research methodology.

Nutraceuticals used to treat dyslipidemia have been gaining popularity with both patients and clinicians [12]. They can be used in patients who have SAMS or other side effects from statins. They can be considered in patients with dyslipidemia but who are ineligible for statin therapy. Nutraceuticals can also be used when patients have a strong preference over conventional therapies. They can be used as the initial therapy or as an adjunct therapy on top of pharmaceuticals or other nutraceuticals [14,16,69]. Since many nutraceuticals come from all around the world, some patients may prefer nutraceuticals for cultural, ritualistic, or religious reasons. It is important that clinicians be able to provide culturally competent care that aligns with their patients' values and beliefs.

Integrative cardiologists are uniquely equipped to guide this emerging field of medicine and the use of nutraceuticals in the management of dyslipidemia. There is a potential opportunity to reduce ASCVD risk and to promote cardiovascular prevention [12]. Clinicians can help patients obtain accurate information and continue to generate the science to support the clinical use of nutraceuticals. There is a lot of exciting work to be done to further explore the evolving story of lipid management.

Author Contributions: Conceptualization, A.B.E.-F.; Writing—Original Draft Preparation, B.C.; Writing—Review and Editing, B.C., G.S., E.H.D., S.M. and A.B.E.-F.; Supervision, E.H.D., S.M. and A.B.E.-F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 aha/acc/aacvpr/aapa/abc/acpm/ada/ags/apha/aspc/nla/pcna guideline on the management of blood cholesterol: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *J. Am. Coll. Cardiol.* **2019**, *73*, e285–e350. [CrossRef] [PubMed]
2. Ambrosino, P.; Bachetti, T.; D'Anna, S.E.; Galloway, B.; Bianco, A.; D'Agnano, V.; Papa, A.; Motta, A.; Perrotta, F.; Maniscalco, M. Mechanisms and clinical implications of endothelial dysfunction in arterial hypertension. *J. Cardiovasc. Dev. Dis.* **2022**, *9*, 136. [CrossRef] [PubMed]
3. Mućka, S.; Miodońska, M.; Jakubiak, G.K.; Starzak, M.; Cieślar, G.; Stanek, A. Endothelial function assessment by flow-mediated dilation method: A valuable tool in the evaluation of the cardiovascular system. *Int. J. Env. Res. Public Health* **2022**, *19*, 11242. [CrossRef]
4. Jakubiak, G.K.; Cieślar, G.; Stanek, A. Nitrotyrosine, nitrated lipoproteins, and cardiovascular dysfunction in patients with type 2 diabetes: What do we know and what remains to be explained? *Antioxidants* **2022**, *11*, 856. [CrossRef] [PubMed]

5. Raised Cholesterol. Available online: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3236 (accessed on 23 October 2022).
6. Ference, B.A.; Ginsberg, H.N.; Graham, I.; Ray, K.K.; Packard, C.J.; Bruckert, E.; Hegele, R.A.; Krauss, R.M.; Raal, F.J.; Schunkert, H.; et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the european atherosclerosis society consensus panel. *Eur. Heart J.* **2017**, *38*, 2459–2472. [CrossRef] [PubMed]
7. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; et al. 2019 esc/eas guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur. Heart J.* **2020**, *41*, 111–188. [CrossRef] [PubMed]
8. Gidding, S.S.; Champagne, M.A.; de Ferranti, S.D.; Defesche, J.; Ito, M.K.; Knowles, J.W.; McCrindle, B.; Raal, F.; Rader, D.; Santos, R.D.; et al. The agenda for familial hypercholesterolemia: A scientific statement from the american heart association. *Circulation* **2015**, *132*, 2167–2192. [CrossRef]
9. Grundy, S.M.; Stone, N.J.; Guideline, G. Writing Committee for the Cholesterol. 2018 cholesterol clinical practice guidelines: Synopsis of the 2018 american heart association/american college of cardiology/multisociety cholesterol guideline. *Ann. Intern Med.* **2019**, *170*, 779–783. [CrossRef]
10. Cheeley, M.K.; Saseen, J.J.; Agarwala, A.; Ravilla, S.; Ciffone, N.; Jacobson, T.A.; Dixon, D.L.; Maki, K.C. Nla scientific statement on statin intolerance: A new definition and key considerations for ascvd risk reduction in the statin intolerant patient. *J. Clin. Lipidol.* **2022**, *16*, 361–375. [CrossRef]
11. Bytyci, I.; Penson, P.E.; Mikhailidis, D.P.; Wong, N.D.; Hernandez, A.V.; Sahebkar, A.; Thompson, P.D.; Mazidi, M.; Rysz, J.; Pella, D.; et al. Prevalence of statin intolerance: A meta-analysis. *Eur. Heart J.* **2022**, *43*, 3213–3223. [CrossRef]
12. Cheung, B. The intersection of the two complimentary fields of preventive cardiology and integrative cardiology: A fellow's voice. *Am. J. Prev. Cardiol.* **2022**, *12*. [CrossRef]
13. Bin, Y.S.; Kiat, H. Prevalence of dietary supplement use in patients with proven or suspected cardiovascular disease. *Evid.-Based Complement. Alternat. Med.* **2011**, *2011*, 632829. [CrossRef] [PubMed]
14. Banach, M.; Catapano, A.L.; Cicero, A.F.G.; Escobar, C.; Foger, B.; Katsiki, N.; Latkovskis, G.; Rakowski, M.; Reiner, Z.; Sahebkar, A.; et al. Red yeast rice for dyslipidaemias and cardiovascular risk reduction: A position paper of the international lipid expert panel. *Pharmacol. Res.* **2022**, *183*, 106370. [CrossRef] [PubMed]
15. Osadnik, T.; Golawski, M.; Lewandowski, P.; Morze, J.; Osadnik, K.; Pawlas, N.; Lejawa, M.; Jakubiak, G.K.; Mazur, A.; Schwingschackl, L.; et al. A network meta-analysis on the comparative effect of nutraceuticals on lipid profile in adults. *Pharmacol. Res.* **2022**, *183*, 106402. [CrossRef] [PubMed]
16. Cicero, A.F.G.; Colletti, A.; Bajraktari, G.; Descamps, O.; Djuric, D.M.; Ezhov, M.; Fras, Z.; Katsiki, N.; Langlois, M.; Latkovskis, G.; et al. Lipid-lowering nutraceuticals in clinical practice: Position paper from an international lipid expert panel. *Nutr. Rev.* **2017**, *75*, 731–767. [CrossRef] [PubMed]
17. Park, S.; Kang, S.; Jeong, D.Y.; Jeong, S.Y.; Park, J.J.; Yun, H.S. Cyanidin and malvidin in aqueous extracts of black carrots fermented with aspergillus oryzae prevent the impairment of energy, lipid and glucose metabolism in estrogen-deficient rats by ampk activation. *Genes Nutr.* **2015**, *10*, 455. [CrossRef] [PubMed]
18. Araki, R.; Yada, A.; Ueda, H.; Tominaga, K.; Isoda, H. Differences in the effects of anthocyanin supplementation on glucose and lipid metabolism according to the structure of the main anthocyanin: A meta-analysis of randomized controlled trials. *Nutrients* **2021**, *13*, 2003. [CrossRef] [PubMed]
19. Kapadia, V.; Embers, D.; Wells, E.; Lemler, M.; Rosenfeld, C.R. Prenatal closure of the ductus arteriosus and maternal ingestion of anthocyanins. *J. Perinatol.* **2010**, *30*, 291–294. [CrossRef] [PubMed]
20. Rangboo, V.; Noroozi, M.; Zavoshy, R.; Rezadoost, S.A.; Mohammadpoorasl, A. The effect of artichoke leaf extract on alanine aminotransferase and aspartate aminotransferase in the patients with nonalcoholic steatohepatitis. *Int. J. Hepatol.* **2016**, *2016*, 4030476. [CrossRef]
21. Sahebkar, A.; Pirro, M.; Banach, M.; Mikhailidis, D.P.; Atkin, S.L.; Ciceo, A.F.G. Lipid-lowering activity of artichoke extracts: A systematic review and meta-analysis. *Crit. Rev. Food Sci. Nutr.* **2018**, *58*, 2549–2556. [CrossRef]
22. Natural Medicines. 2022. Available online: https://naturalmedicines.therapeuticresearch.com/ (accessed on 18 August 2022).
23. Li, H.; Dong, B.; Park, S.W.; Lee, H.S.; Chen, W.; Liu, J. Hepatocyte nuclear factor 1alpha plays a critical role in pcsk9 gene transcription and regulation by the natural hypocholesterolemic compound berberine. *J. Biol. Chem.* **2009**, *284*, 28885–28895. [CrossRef] [PubMed]
24. Abidi, P.; Zhou, Y.; Jiang, J.D.; Liu, J. Extracellular signal-regulated kinase-dependent stabilization of hepatic low-density lipoprotein receptor mrna by herbal medicine berberine. *Arter. Thromb. Vasc. Biol.* **2005**, *25*, 2170–2176. [CrossRef]
25. Li, X.Y.; Zhao, Z.X.; Huang, M.; Feng, R.; He, C.Y.; Ma, C.; Luo, S.H.; Fu, J.; Wen, B.Y.; Ren, L.; et al. Effect of berberine on promoting the excretion of cholesterol in high-fat diet-induced hyperlipidemic hamsters. *J. Transl. Med.* **2015**, *13*, 278. [CrossRef] [PubMed]
26. Loh, K.; Tam, S.; Murray-Segal, L.; Huynh, K.; Meikle, P.J.; Scott, J.W.; van Denderen, B.; Chen, Z.; Steel, R.; LeBlond, N.D.; et al. Inhibition of adenosine monophosphate-activated protein kinase-3-hydroxy-3-methylglutaryl coenzyme a reductase signaling leads to hypercholesterolemia and promotes hepatic steatosis and insulin resistance. *Hepatol. Commun.* **2019**, *3*, 84–98. [CrossRef] [PubMed]

27. Kim, W.S.; Lee, Y.S.; Cha, S.H.; Jeong, H.W.; Choe, S.S.; Lee, M.R.; Oh, G.T.; Park, H.S.; Lee, K.U.; Lane, M.D.; et al. Berberine improves lipid dysregulation in obesity by controlling central and peripheral ampk activity. *Am. J. Physiol. Endocrinol. Metab.* **2009**, *296*, E812–E819. [CrossRef]
28. Wang, C.; Li, J.; Lv, X.; Zhang, M.; Song, Y.; Chen, L.; Liu, Y. Ameliorative effect of berberine on endothelial dysfunction in diabetic rats induced by high-fat diet and streptozotocin. *Eur. J. Pharmacol.* **2009**, *620*, 131–137. [CrossRef]
29. Bertuccioli, A.; Moricoli, S.; Amatori, S.; Rocchi, M.B.L.; Vici, G.; Sisti, D. Berberine and dyslipidemia: Different applications and biopharmaceutical formulations without statin-like molecules-a meta-analysis. *J. Med. Food* **2020**, *23*, 101–113. [CrossRef]
30. Ju, J.; Li, J.; Lin, Q.; Xu, H. Efficacy and safety of berberine for dyslipidaemias: A systematic review and meta-analysis of randomized clinical trials. *Phytomedicine* **2018**, *50*, 25–34. [CrossRef]
31. Linn, Y.C.; Lu, J.; Lim, L.C.; Sun, H.; Sun, J.; Zhou, Y.; Ng, H.S. Berberine-induced haemolysis revisited: Safety of rhizoma coptidis and cortex phellodendri in chronic haematological diseases. *Phytother. Res.* **2012**, *26*, 682–686. [CrossRef]
32. Musolino, V.; Gliozzi, M.; Carresi, C.; Maiuolo, J.; Mollace, R.; Bosco, F.; Scarano, F.; Scicchitano, M.; Maretta, A.; Palma, E.; et al. Lipid-lowering effect of bergamot polyphenolic fraction: Role of pancreatic cholesterol ester hydrolase. *J. Biol. Regul. Homeost. Agents* **2017**, *31*, 1087–1093.
33. Cappello, A.R.; Dolce, V.; Iacopetta, D.; Martello, M.; Fiorillo, M.; Curcio, R.; Muto, L.; Dhanyalayam, D. Bergamot (*Citrus bergamia* risso) flavonoids and their potential benefits in human hyperlipidemia and atherosclerosis: An overview. *Mini Rev. Med. Chem.* **2016**, *16*, 619–629. [CrossRef] [PubMed]
34. Lamiquiz-Moneo, I.; Gine-Gonzalez, J.; Alisente, S.; Bea, A.M.; Perez-Calahorra, S.; Marco-Benedi, V.; Baila-Rueda, L.; Jarauta, E.; Cenarro, A.; Civeira, F.; et al. Effect of bergamot on lipid profile in humans: A systematic review. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 3133–3143. [CrossRef]
35. Askarpour, M.; Hadi, A.; Symonds, M.E.; Miraghajani, M.; Sadeghi, O.; Sheikhi, A.; Ghaedi, E. Efficacy of l-carnitine supplementation for management of blood lipids: A systematic review and dose-response meta-analysis of randomized controlled trials. *Nutr. Metab. Cardiovasc. Dis.* **2019**, *29*, 1151–1167. [CrossRef] [PubMed]
36. Cruciani, R.A.; Dvorkin, E.; Homel, P.; Malamud, S.; Culliney, B.; Lapin, J.; Portenoy, R.K.; Esteban-Cruciani, N. Safety, tolerability and symptom outcomes associated with l-carnitine supplementation in patients with cancer, fatigue, and carnitine deficiency: A phase i/ii study. *J. Pain Symptom. Manag.* **2006**, *32*, 551–559. [CrossRef] [PubMed]
37. Seong, S.H.; Cho, S.C.; Park, Y.; Cha, Y.S. L-carnitine-supplemented parenteral nutrition improves fat metabolism but fails to support compensatory growth in premature korean infants. *Nutr. Res.* **2010**, *30*, 233–239. [CrossRef] [PubMed]
38. Keller, U.; Van Der Wal, C.; Seliger, G.; Scheler, C.; Röpke, F.; Eder, K. Carnitine status of pregnant women: Effect of carnitine supplementation and correlation between iron status and plasma carnitine concentration. *Eur. J. Clin. Nutr.* **2009**, *63*, 1098–1105. [CrossRef]
39. Tarrahi, M.J.; Tarrahi, M.A.; Rafiee, M.; Mansourian, M. The effects of chromium supplementation on lipid profile in humans: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res.* **2021**, *164*, 105308. [CrossRef]
40. Asbaghi, O.; Naeini, F.; Ashtary-Larky, D.; Moradi, S.; Zakeri, N.; Eslampour, E.; Kelishadi, M.R.; Naeini, A.A. Effects of chromium supplementation on lipid profile in patients with type 2 diabetes: A systematic review and dose-response meta-analysis of randomized controlled trials. *J. Trace Elem. Med. Biol.* **2021**, *66*, 126741. [CrossRef]
41. Chromium Fact Sheet for Health Professionals. NIH. 2022. Available online: https://ods.od.nih.gov/factsheets/Chromium-HealthProfessional/#h2 (accessed on 11 September 2022).
42. Ylitalo, R.; Lehtinen, S.; Wuolijoki, E.; Ylitalo, P.; Lehtimäki, T. Cholesterol-lowering properties and safety of chitosan. *Arzneimittelforschung* **2002**, *52*, 1–7. [CrossRef]
43. Moraru, C.; Mincea, M.M.; Frandes, M.; Timar, B.; Ostafe, V. A meta-analysis on randomised controlled clinical trials evaluating the effect of the dietary supplement chitosan on weight loss, lipid parameters and blood pressure. *Medicina* **2018**, *54*, 109. [CrossRef]
44. Arenas-Jal, M.; Sune-Negre, J.M.; Garcia-Montoya, E. Coenzyme q10 supplementation: Efficacy, safety, and formulation challenges. *Compr. Rev. Food Sci. Food Saf.* **2020**, *19*, 574–594. [CrossRef] [PubMed]
45. Sharifi, N.; Tabrizi, R.; Moosazadeh, M.; Mirhosseini, N.; Lankarani, K.B.; Akbari, M.; Chamani, M.; Kolahdooz, F.; Asemi, Z. The effects of coenzyme q10 supplementation on lipid profiles among patients with metabolic diseases: A systematic review and meta-analysis of randomized controlled trials. *Curr. Pharmacol. Des.* **2018**, *24*, 2729–4272. [CrossRef] [PubMed]
46. Jorat, M.V.; Tabrizi, R.; Mirhosseini, N.; Lankarani, K.B.; Akbari, M.; Heydari, S.T.; Mottaghi, R.; Asemi, Z. The effects of coenzyme q10 supplementation on lipid profiles among patients with coronary artery disease: A systematic review and meta-analysis of randomized controlled trials. *Lipids Health Dis.* **2018**, *17*, 230. [CrossRef] [PubMed]
47. Coenzyme q10. Available online: https://www.cancer.gov/about-cancer/treatment/cam/hp/coenzyme-q10-pdq (accessed on 20 October 2022).
48. Vaisar, T.; Wang, S.; Omer, M.; Irwin, A.D.; Storey, C.; Tang, C.; den Hartigh, L.J. 10,12-conjugated linoleic acid supplementation improves hdl composition and function in mice. *J. Lipid Res.* **2022**, *63*, 100241. [CrossRef] [PubMed]
49. Derakhshande-Rishehri, S.M.; Mansourian, M.; Kelishadi, R.; Heidari-Beni, M. Association of foods enriched in conjugated linoleic acid (cla) and cla supplements with lipid profile in human studies: A systematic review and meta-analysis. *Public Health Nutr.* **2015**, *18*, 2041–2054. [CrossRef] [PubMed]

50. Joseph, S.V.; Jacques, H.; Plourde, M.; Mitchell, P.L.; McLeod, R.S.; Jones, P.J. Conjugated linoleic acid supplementation for 8 weeks does not affect body composition, lipid profile, or safety biomarkers in overweight, hyperlipidemic men. *J. Nutr.* **2011**, *141*, 1286–1291. [CrossRef]
51. Al, M.D.; van Houwelingen, A.C.; Badart-Smook, A.; Hornstra, G. Some aspects of neonatal essential fatty acid status are altered by linoleic acid supplementation of women during pregnancy. *J Nutr* **1995**, *125*, 2822–2830. [CrossRef] [PubMed]
52. Kumar, P.; Malhotra, P.; Ma, K.; Singla, A.; Hedroug, O.; Saksena, S.; Dudeja, P.K.; Gill, R.K.; Alrefai, W.A. Srebp2 mediates the modulation of intestinal npc1l1 expression by curcumin. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2011**, *301*, G148–G155. [CrossRef] [PubMed]
53. Tai, M.H.; Chen, P.K.; Chen, P.Y.; Wu, M.J.; Ho, C.T.; Yen, J.H. Curcumin enhances cell-surface ldlr level and promotes ldl uptake through downregulation of pcsk9 gene expression in hepg2 cells. *Mol. Nutr. Food Res.* **2014**, *58*, 2133–2145. [CrossRef] [PubMed]
54. Lin, X.L.; Liu, M.H.; Hu, H.J.; Feng, H.R.; Fan, X.J.; Zou, W.W.; Pan, Y.Q.; Hu, X.M.; Wang, Z. Curcumin enhanced cholesterol efflux by upregulating abca1 expression through ampk-sirt1-lxralpha signaling in thp-1 macrophage-derived foam cells. *DNA Cell Biol.* **2015**, *34*, 561–572. [CrossRef] [PubMed]
55. Sahebkar, A. A systematic review and meta-analysis of randomized controlled trials investigating the effects of curcumin on blood lipid levels. *Clin. Nutr.* **2014**, *33*, 406–414. [CrossRef] [PubMed]
56. Tumeric. NIH. Available online: https://www.nccih.nih.gov/health/turmeric (accessed on 11 November 2022).
57. Devaraj, R.D.; Reddy, C.K.; Xu, B. Health-promoting effects of konjac glucomannan and its practical applications: A critical review. *Int. J. Biol. Macromol.* **2019**, *126*, 273–281. [CrossRef] [PubMed]
58. Ho, H.V.T.; Jovanovski, E.; Zurbau, A.; Blanco Mejia, S.; Sievenpiper, J.L.; Au-Yeung, F.; Jenkins, A.L.; Duvnjak, L.; Leiter, L.; Vuksan, V. A systematic review and meta-analysis of randomized controlled trials of the effect of konjac glucomannan, a viscous soluble fiber, on ldl cholesterol and the new lipid targets non-hdl cholesterol and apolipoprotein b. *Am. J. Clin. Nutr.* **2017**, *105*, 1239–1247. [CrossRef]
59. Henrion, M.; Francey, C.; Le, K.A.; Lamothe, L. Cereal b-glucans: The impact of processing and how it affects physiological responses. *Nutrients* **2019**, *11*, 1729. [CrossRef] [PubMed]
60. Yu, J.; Xia, J.; Yang, C.; Pan, D.; Xu, D.; Sun, G.; Xia, H. Effects of oat beta-glucan intake on lipid profiles in hypercholesterolemic adults: A systematic review and meta-analysis of randomized controlled trials. *Nutrients* **2022**, *14*, 2043. [CrossRef]
61. Lin, J.; Sun, Y.; Santos, H.O.; Găman, M.A.; Bhat, L.T.; Cui, Y. Effects of guar gum supplementation on the lipid profile: A systematic review and meta-analysis of randomized controlled trials. *Nutr. Metab. Cardiovasc. Dis.* **2021**, *31*, 3271–3281. [CrossRef]
62. Gylling, H.; Riikonen, S.; Nikkilä, K.; Savonius, H.; Miettinen, T.A. Oral guar gum treatment of intrahepatic cholestasis and pruritus in pregnant women: Effects on serum cholestanol and other non-cholesterol sterols. *Eur. J. Clin. Investig.* **1998**, *28*, 359–363. [CrossRef]
63. Jovanovski, E.; Yashpal, S.; Komishon, A.; Zurbau, A.; Blanco Mejia, S.; Ho, H.V.T.; Li, D.; Sievenpiper, J.; Duvnjak, L.; Vuksan, V. Effect of psyllium (*Plantago ovata*) fiber on ldl cholesterol and alternative lipid targets, non-hdl cholesterol and apolipoprotein b: A systematic review and meta-analysis of randomized controlled trials. *Am. J. Clin. Nutr.* **2018**, *108*, 922–932. [CrossRef]
64. Chen, C.; Shang, C.; Xin, L.; Xiang, M.; Wang, Y.; Shen, Z.; Jiao, L.; Ding, F.; Cui, X. Beneficial effects of psyllium on the prevention and treatment of cardiometabolic diseases. *Food Funct.* **2022**, *13*, 7473–7486. [CrossRef]
65. Shirah, B.H.; Shirah, H.A.; Fallata, A.H.; Alobidy, S.N.; Al Hawsawi, M.M. Hemorrhoids during pregnancy: Sitz bath vs. Ano-rectal cream: A comparative prospective study of two conservative treatment protocols. *Women Birth* **2018**, *31*, e272–e277. [CrossRef]
66. Borlinghaus, J.; Albrecht, F.; Gruhlke, M.C.; Nwachukwu, I.D.; Slusarenko, A.J. Allicin: Chemistry and biological properties. *Molecules* **2014**, *19*, 12591–12618. [CrossRef] [PubMed]
67. Sun, Y.E.; Wang, W.; Qin, J. Anti-hyperlipidemia of garlic by reducing the level of total cholesterol and low-density lipoprotein: A meta-analysis. *Medicine* **2018**, *97*, e0255. [CrossRef] [PubMed]
68. Ried, K.; Toben, C.; Fakler, P. Effect of garlic on serum lipids: An updated meta-analysis. *Nutr. Rev.* **2013**, *71*, 282–299. [CrossRef] [PubMed]
69. Banach, M.; Patti, A.M.; Giglio, R.V.; Cicero, A.F.G.; Atanasov, A.G.; Bajraktari, G.; Bruckert, E.; Descamps, O.; Djuric, D.M.; Ezhov, M.; et al. The role of nutraceuticals in statin intolerant patients. *J. Am. Coll. Cardiol.* **2018**, *72*, 96–118. [CrossRef] [PubMed]
70. Huang, S.; Chen, H.; Teng, J.; Wu, Z.L.; Wei, L.; Xia, N. Antihyperlipidemic effect and increased antioxidant enzyme levels of aqueous extracts from liupao tea and green tea in vivo. *J. Food Sci.* **2022**, *87*, 4203–4220. [CrossRef] [PubMed]
71. Weng, X.; Odouli, R.; Li, D.K. Maternal caffeine consumption during pregnancy and the risk of miscarriage: A prospective cohort study. *Am. J. Obstet. Gynecol.* **2008**, *198*, 279.e1–279.e8. [CrossRef] [PubMed]
72. Erickson, N.; Zafron, M.; Harding, S.V.; Marinangeli, C.P.; Rideout, T.C. Evaluating the lipid-lowering effects of alpha-lipoic acid supplementation: A systematic review. *J. Diet. Suppl.* **2020**, *17*, 753–767. [CrossRef]
73. Mahmoudinezhad, M.; Farhangi, M.A. Alpha lipoic acid supplementation affects serum lipids in a dose and duration-dependent manner in different health status. *Int. J. Vitam. Nutr. Res.* **2021**. [CrossRef]
74. Najafi, N.; Mehri, S.; Ghasemzadeh Rahbardar, M.; Hosseinzadeh, H. Effects of alpha lipoic acid on metabolic syndrome: A comprehensive review. *Phytother. Res.* **2022**, *36*, 2300–2323. [CrossRef]

75. Lammi, C.; Fassi, E.M.A.; Li, J.; Bartolomei, M.; Benigno, G.; Roda, G.; Arnoldi, A.; Grazioso, G. Computational design and biological evaluation of analogs of lupin peptide p5 endowed with dual pcsk9/hmg-coar inhibiting activity. *Pharmaceutics* **2022**, *14*, 665. [CrossRef]
76. Lammi, C.; Bollati, C.; Lecca, D.; Abbracchio, M.P.; Arnoldi, A. Lupin peptide t9 (gqeqshqdegvivr) modulates the mutant pcsk9(d374y) pathway: In vitro characterization of its dual hypocholesterolemic behavior. *Nutrients* **2019**, *11*, 1665. [CrossRef] [PubMed]
77. Lammi, C.; Zanoni, C.; Scigliuolo, G.M.; D'Amato, A.; Arnoldi, A. Arnoldi. Lupin peptides lower low-density lipoprotein (ldl) cholesterol through an up-regulation of the ldl receptor/sterol regulatory element binding protein 2 (srebp2) pathway at hepg2 cell line. *J. Agric. Food Chem.* **2014**, *62*, 7151–7159. [CrossRef] [PubMed]
78. Bähr, M.; Fechner, A.; Krämer, J.; Kiehntopf, M.; Jahreis, G. Lupin protein positively affects plasma ldl cholesterol and ldl:Hdl cholesterol ratio in hypercholesterolemic adults after four weeks of supplementation: A randomized, controlled crossover study. *Nutr. J.* **2013**, *12*, 107. [CrossRef] [PubMed]
79. Zhang, Q.; Qian, Z.Y.; Zhou, P.H.; Zhou, X.L.; Zhang, D.L.; He, N.; Zhang, J.; Liu, Y.H.; Gu, Q. Effects of oral selenium and magnesium co-supplementation on lipid metabolism, antioxidative status, histopathological lesions, and related gene expression in rats fed a high-fat diet. *Lipids Health Dis.* **2018**, *17*, 165. [CrossRef]
80. Asbaghi, O.; Moradi, S.; Nezamoleslami, S.; Moosavian, S.P.; Hojjati Kermani, M.A.; Lazaridi, A.V.; Miraghajani, M. The effects of magnesium supplementation on lipid profile among type 2 diabetes patients: A systematic review and meta-analysis of randomized controlled trials. *Biol. Trace Elem. Res.* **2021**, *199*, 861–873. [CrossRef] [PubMed]
81. Simental-Mendia, L.E.; Simental-Mendia, M.; Sahebkar, A.; Rodriguez-Moran, M.; Guerrero-Romero, F. Effect of magnesium supplementation on lipid profile: A systematic review and meta-analysis of randomized controlled trials. *Eur. J. Clin. Pharmacol.* **2017**, *73*, 525–536. [CrossRef]
82. Liu, M.; Dudley, S.C., Jr. Magnesium, oxidative stress, inflammation, and cardiovascular disease. *Antioxidants* **2020**, *9*, 907. [CrossRef]
83. Van Laecke, S. Hypomagnesemia and hypermagnesemia. *Acta Clin. Belg.* **2019**, *74*, 41–47. [CrossRef]
84. Kamanna, V.S.; Kashyap, M.L. Mechanism of action of niacin. *Am. J. Cardiol.* **2008**, *101*, 20b–26b. [CrossRef]
85. HPS2-Thrive Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N. Engl. J. Med.* **2014**, *371*, 203–212. [CrossRef]
86. Aim-High Investigators. Niacin in patients with low hdl cholesterol levels receiving intensive statin therapy. *N. Engl. J. Med.* **2011**, *365*, 2255–2267. [CrossRef] [PubMed]
87. Palawaththa, S.; Islam, R.M.; Illic, D.; Rabel, K.; Lee, M.; Romero, L.; Leung, X.Y.; Karim, M.N. Effect of maternal dietary niacin intake on congenital anomalies: A systematic review and meta-analysis. *Eur. J. Nutr.* **2022**, *61*, 1133–1142. [CrossRef] [PubMed]
88. Niacin. Available online: https://ods.od.nih.gov/factsheets/Niacin-HealthProfessional/#h9 (accessed on 18 October 2022).
89. Asgary, S.; Sahebkar, A.; Goli-Malekabadi, N. Ameliorative effects of nigella sativa on dyslipidemia. *J. Endocrinol. Investig.* **2015**, *38*, 1039–1046. [CrossRef] [PubMed]
90. Hallajzadeh, J.; Milajerdi, A.; Mobini, M.; Amirani, E.; Azizi, S.; Nikkhah, E.; Bahadori, B.; Sheikhsoleimani, R.; Mirhashemi, S.M. Effects of nigella sativa on glycemic control, lipid profiles, and biomarkers of inflammatory and oxidative stress: A systematic review and meta-analysis of randomized controlled clinical trials. *Phytother. Res.* **2020**, *34*, 2586–2608. [CrossRef]
91. Jahan, S.; Mozumder, Z.M.; Shill, D.K. Use of herbal medicines during pregnancy in a group of bangladeshi women. *Heliyon* **2022**, *8*, e08854. [CrossRef]
92. Lockyer, S.; Yaqoob, P.; Spencer, J.P.E.; Rowland, I. Olive leaf phenolics and cardiovascular risk reduction: Physiological effects and mechanisms of action. *Nutr. Aging* **2012**, *1*, 125–140. [CrossRef]
93. Lockyer, S.; Rowland, I.; Spencer, J.P.E.; Yaqoob, P.; Stonehouse, W. Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: A randomised controlled trial. *Eur. J. Nutr.* **2017**, *56*, 1421–1432. [CrossRef]
94. Olive. Available online: https://medlineplus.gov/druginfo/natural/233.html (accessed on 18 October 2022).
95. Ramazani, E.; Akaberi, M.; Emami, S.A.; Tayarani-Najaran, Z. Biological and pharmacological effects of gamma-oryzanol: An updated review of the molecular mechanisms. *Curr. Pharm. Des.* **2021**, *27*, 2299–2316. [CrossRef]
96. Yan, S.; Chen, J.; Zhu, L.; Guo, T.; Qin, D.; Hu, Z.; Han, S.; Zhou, Y.; Akan, O.D.; Wang, J.; et al. Oryzanol attenuates high fat and cholesterol diet-induced hyperlipidemia by regulating the gut microbiome and amino acid metabolism. *J. Agric. Food Chem.* **2022**, *70*, 6429–6443. [CrossRef]
97. Pourrajab, B.; Sohouli, M.H.; Amirinejad, A.; Fatahi, S.; Gaman, M.A.; Shidfar, F. The impact of rice bran oil consumption on the serum lipid profile in adults: A systematic review and meta-analysis of randomized controlled trials. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 6005–6015. [CrossRef]
98. Evans, M.; Rumberger, J.A.; Azumano, I.; Napolitano, J.J.; Citrolo, D.; Kamiya, T. Pantethine, a derivative of vitamin b5, favorably alters total, ldl and non-hdl cholesterol in low to moderate cardiovascular risk subjects eligible for statin therapy: A triple-blinded placebo and diet-controlled investigation. *Vasc. Health Risk Manag.* **2014**, *10*, 89–100. [CrossRef] [PubMed]
99. Donati, C.; Barbi, G.; Cairo, G.; Prati, G.F.; Degli Esposti, E. Pantethine improves the lipid abnormalities of chronic hemodialysis patients: Results of a multicenter clinical trial. *Clin. Nephrol.* **1986**, *25*, 70–74. [PubMed]

100. Bertolini, S.; Donati, C.; Elicio, N.; Daga, A.; Cuzzolaro, S.; Marcenaro, A.; Saturnino, M.; Balestreri, R. Lipoprotein changes induced by pantethine in hyperlipoproteinemic patients: Adults and children. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **1986**, *24*, 630–637. [PubMed]
101. Harris, W.S.; Bulchandani, S. Why do omega-3 fatty acids lower serum triglycerides? *Curr. Opin. Lipidol.* **2006**, *17*, 387–393. [CrossRef]
102. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific opinion on the substantiation of health claims related to epa, dha, dpa and maintenance of normal blood pressure (id 502), maintenance of normal hdl-cholesterol concentrations (id 515), maintenance of normal (fasting) blood concentrations of triglycerides (ID 517), maintenance of normal LDL-cholesterol concentrations (ID 528, 698) and maintenance of joints (ID 503, 505, 507, 511, 518, 524, 526, 535, 537) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J.* **2009**, *7*, 1263. [CrossRef]
103. Nicholls, S.J.; Lincoff, A.M.; Garcia, M.; Bash, D.; Ballantyne, C.M.; Barter, P.J.; Davidson, M.H.; Kastelein, J.J.P.; Koenig, W.; McGuire, D.K.; et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: The strength randomized clinical trial. *JAMA* **2020**, *324*, 2268–2280. [CrossRef]
104. Zhang, H.J.; Gao, X.; Guo, X.F.; Li, K.L.; Li, S.; Sinclair, A.J.; Li, D. Effects of dietary eicosapentaenoic acid and docosahexaenoic acid supplementation on metabolic syndrome: A systematic review and meta-analysis of data from 33 randomized controlled trials. *Clin. Nutr.* **2021**, *40*, 4538–4550. [CrossRef]
105. Bhatt, D.L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Ketchum, S.B.; Doyle, R.T., Jr.; Juliano, R.A.; Jiao, L.; Granowitz, C.; et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N. Engl. J. Med.* **2019**, *380*, 11–22. [CrossRef]
106. Saha, S.; Saha, S. The effects of prenatal dietary supplements on blood glucose and lipid metabolism in gestational diabetes mellitus patients: A systematic review and network meta-analysis protocol of randomized controlled trials. *PLoS ONE* **2022**, *17*, e0267854. [CrossRef]
107. Brouns, F.; Theuwissen, E.; Adam, A.; Bell, M.; Berger, A.; Mensink, R.P. Cholesterol-lowering properties of different pectin types in mildly hyper-cholesterolemic men and women. *Eur. J. Clin. Nutr.* **2012**, *66*, 591–599. [CrossRef]
108. Hu, H.; Zhang, S.; Liu, F.; Zhang, P.; Muhammad, Z.; Pan, S. Role of the gut microbiota and their metabolites in modulating the cholesterol-lowering effects of citrus pectin oligosaccharides in c57bl/6 mice. *J. Agric. Food Chem.* **2019**, *67*, 11922–11930. [CrossRef] [PubMed]
109. Fermentable fibers and vitamin b12 dependency. *Nutr. Rev.* **1991**, *49*, 119–120. [CrossRef]
110. Shaghaghi, M.A.; Abumweis, S.S.; Jones, P.J. Cholesterol-lowering efficacy of plant sterols/stanols provided in capsule and tablet formats: Results of a systematic review and meta-analysis. *J. Acad. Nutr. Diet.* **2013**, *113*, 1494–14503. [CrossRef] [PubMed]
111. Sabeva, N.S.; McPhaul, C.M.; Li, X.; Cory, T.J.; Feola, D.J.; Graf, G.A. Phytosterols differentially influence abc transporter expression, cholesterol efflux and inflammatory cytokine secretion in macrophage foam cells. *J. Nutr. Biochem.* **2011**, *22*, 777–783. [CrossRef] [PubMed]
112. Ho, S.S.; Pal, S. Margarine phytosterols decrease the secretion of atherogenic lipoproteins from hepg2 liver and caco2 intestinal cells. *Atherosclerosis* **2005**, *182*, 29–36. [CrossRef] [PubMed]
113. Gao, F.; Wang, G.; Wang, L.; Guo, N. Phytosterol nutritional supplement improves pregnancy and neonatal complications of gestational diabetes mellitus in a double-blind and placebo-controlled clinical study. *Food Funct.* **2017**, *8*, 424–428. [CrossRef]
114. Singh, D.K.; Li, L.; Porter, T.D. Policosanol inhibits cholesterol synthesis in hepatoma cells by activation of amp-kinase. *J. Pharmacol Exp. Ther.* **2006**, *318*, 1020–1026. [CrossRef]
115. Zhai, Z.; Niu, K.M.; Liu, H.; Lin, C.; Tu, Y.; Liu, Y.; Cai, L.; Ouyang, K.; Liu, J. Policosanol alleviates hepatic lipid accumulation by regulating bile acids metabolism in c57bl6/mice through ampk-fxr-tgr5 cross-talk. *J. Food Sci.* **2021**, *86*, 5466–5478. [CrossRef]
116. Gong, J.; Qin, X.; Yuan, F.; Hu, M.; Chen, G.; Fang, K.; Wang, D.; Jiang, S.; Li, J.; Zhao, Y.; et al. Efficacy and safety of sugarcane policosanol on dyslipidemia: A meta-analysis of randomized controlled trials. *Mol. Nutr. Food Res.* **2018**, *62*, 1700280. [CrossRef]
117. Rodriguez, M.D.; Garcia, H. Evaluation of peri- and post-natal toxicity of policosanol in rats. *Teratog. Carcinog. Mutagen.* **1998**, *18*, 1–7. [CrossRef]
118. Rodríguez, M.D.; García, H. Teratogenic and reproductive studies of policosanol in the rat and rabbit. *Teratog. Carcinog. Mutagen.* **1994**, *14*, 107–113. [CrossRef] [PubMed]
119. Kim, G.B.; Yi, S.H.; Lee, B.H. Purification and characterization of three different types of bile salt hydrolases from bifidobacterium strains. *J. Dairy Sci.* **2004**, *87*, 258–266. [CrossRef] [PubMed]
120. Yoon, H.; Lee, Y.; Kang, H.J.; Ju, J.; Ji, Y.; Park, H.; Lee, H.; Holzapfel, W.H. Two putative probiotic strains improve diet-induced hypercholesterolemia through modulating intestinal cholesterol uptake and hepatic cholesterol efflux. *J. Appl. Microbiol.* **2022**, *132*, 562–570. [CrossRef] [PubMed]
121. Yang, M.; Zheng, J.; Zong, X.; Yang, X.; Zhang, Y.; Man, C.; Jiang, Y. Preventive effect and molecular mechanism of lactobacillus rhamnosus jl1 on food-borne obesity in mice. *Nutrients* **2021**, *13*, 3989. [CrossRef] [PubMed]
122. Sun, K.; Liu, Z.; Wang, H. The effect of probiotics on the serum lipid levels in non-obese healthy adults with hyperlipidemia: A systematic review and meta-analysis of randomized controlled trials. *Nutr. Hosp.* **2022**, *39*, 157–170. [CrossRef]
123. Probiotics Fact Sheet for Health Professionals. Available online: https://ods.od.nih.gov/factsheets/Probiotics-HealthProfessional/ (accessed on 9 December 2022).
124. Sirtori, C.R. The pharmacology of statins. *Pharmacol. Res.* **2014**, *88*, 3–11. [CrossRef]

125. *Statins: Drug Safety Communication–FDA Requests Removal of Strongest Warning Against Using Cholesterol-Lowering Statins during Pregnancy*; FDA: Silver Spring, MD, USA, 2021.
126. Banach, M.; Bruckert, E.; Descamps, O.S.; Ellegard, L.; Ezhov, M.; Foger, B.; Fras, Z.; Kovanen, P.T.; Latkovskis, G.; Marz, W.; et al. The role of red yeast rice (ryr) supplementation in plasma cholesterol control: A review and expert opinion. *Atheroscler. Suppl.* **2019**, *39*, e1–e8. [CrossRef]
127. Ahn, J.; Cho, I.; Kim, S.; Kwon, D.; Ha, T. Dietary resveratrol alters lipid metabolism-related gene expression of mice on an atherogenic diet. *J. Hepatol.* **2008**, *49*, 1019–1028. [CrossRef]
128. Dong, W.; Wang, X.; Bi, S.; Pan, Z.; Liu, S.; Yu, H.; Lu, H.; Lin, X.; Wang, X.; Ma, T.; et al. Inhibitory effects of resveratrol on foam cell formation are mediated through monocyte chemotactic protein-1 and lipid metabolism-related proteins. *Int. J. Mol. Med.* **2014**, *33*, 1161–1168. [CrossRef]
129. Resveratrol. Available online: https://medlineplus.gov/druginfo/natural/307.html (accessed on 18 October 2022).
130. Simental-Mendia, L.E.; Guerrero-Romero, F. Effect of resveratrol supplementation on lipid profile in subjects with dyslipidemia: A randomized double-blind, placebo-controlled trial. *Nutrition* **2019**, *58*, 7–10. [CrossRef]
131. Cao, X.; Liao, W.; Xia, H.; Wang, S.; Sun, G. The effect of resveratrol on blood lipid profile: A dose-response meta-analysis of randomized controlled trials. *Nutrients* **2022**, *14*, 3755. [CrossRef] [PubMed]
132. Xiao, P.T.; Liu, S.Y.; Kuang, Y.J.; Jiang, Z.M.; Lin, Y.; Xie, Z.S.; Liu, E.H. Network pharmacology analysis and experimental validation to explore the mechanism of sea buckthorn flavonoids on hyperlipidemia. *J. Ethnopharmacol.* **2022**, *264*, 113380. [CrossRef] [PubMed]
133. Geng, Y.; Wang, J.; Chen, K.; Li, Q.; Ping, Z.; Xue, R.; Zhang, S. Effects of sea buckthorn (*Hippophae rhamnoides* L.) on factors related to metabolic syndrome: A systematic review and meta-analysis of randomized controlled trial. *Phytother. Res.* **2022**, *36*, 4101–4114. [CrossRef] [PubMed]
134. Wen, P.; Zhao, P.; Qin, G.; Tang, S.; Li, B.; Zhang, J.; Peng, L. Genotoxicity and teratogenicity of seabuckthorn (*Hippophae rhamnoides* L.) berry oil. *Drug Chem. Toxicol.* **2020**, *43*, 391–397. [CrossRef]
135. Xiao, P.; Ji, H.; Ye, Y.; Zhang, B.; Chen, Y.; Tian, J.; Liu, P.; Chen, L.; Du, Z. Dietary silymarin supplementation promotes growth performance and improves lipid metabolism and health status in grass carp (*Ctenopharyngodon idellus*) fed diets with elevated lipid levels. *Fish Physiol. Biochem.* **2017**, *43*, 245–263. [CrossRef]
136. Wang, L.; Rotter, S.; Ladurner, A.; Heiss, E.H.; Oberlies, N.H.; Dirsch, V.M.; Atanasov, A.G. Silymarin constituents enhance abca1 expression in thp-1 macrophages. *Molecules* **2015**, *21*, 55. [CrossRef]
137. Soleymani, S.; Ayati, M.H.; Mansourzadeh, M.J.; Namazi, N.; Zargaran, A. The effects of silymarin on the features of cardiometabolic syndrome in adults: A systematic review and meta-analysis. *Phytother. Res.* **2022**, *36*, 842–856. [CrossRef]
138. Milk Thistle. August 2022. Available online: https://www.nccih.nih.gov/health/milk-thistle (accessed on 9 December 2022).
139. Li, T.T.; Tong, A.J.; Liu, Y.Y.; Huang, Z.R.; Wan, X.Z.; Pan, Y.Y.; Jia, R.B.; Liu, B.; Chen, X.H.; Zhao, C. Polyunsaturated fatty acids from microalgae spirulina platensis modulates lipid metabolism disorders and gut microbiota in high-fat diet rats. *Food Chem. Toxicol.* **2019**, *131*, 110558. [CrossRef]
140. Hatami, E.; Ghalishourani, S.S.; Najafgholizadeh, A.; Pourmasoumi, M.; Hadi, A.; Clark, C.C.; Assaroudi, M.; Salehi-Sahlabadi, A.; Joukar, F.; Mansour-Ghanaei, F. The effect of spirulina on type 2 diabetes: A systematic review and meta-analysis. *J. Diabetes Metab. Disord.* **2021**, *20*, 883–892. [CrossRef]
141. Macchi, C.; Greco, M.F.; Ferri, N.; Magni, P.; Arnoldi, A.; Corsini, A.; Sirtori, C.R.; Ruscica, M.; Lammi, C. Impact of soy beta-conglycinin peptides on pcsk9 protein expression in hepg2 cells. *Nutrients* **2021**, *14*, 193. [CrossRef]
142. Cho, S.J.; Juillerat, M.A.; Lee, C.H. Cholesterol lowering mechanism of soybean protein hydrolysate. *J. Agric. Food Chem.* **2007**, *55*, 10599–10604. [CrossRef] [PubMed]
143. Potter, S.M. Overview of proposed mechanisms for the hypocholesterolemic effect of soy. *J. Nutr.* **1995**, *125*, 606S–611S. [CrossRef] [PubMed]
144. Butteiger, D.N.; Hibberd, A.A.; McGraw, N.J.; Napawan, N.; Hall-Porter, J.M.; Krul, E.S. Soy protein compared with milk protein in a western diet increases gut microbial diversity and reduces serum lipids in golden syrian hamsters. *J. Nutr.* **2016**, *146*, 697–705. [CrossRef] [PubMed]
145. Napoli, C.; Leccese, M.; Palumbo, G.; De Nigris, F.; Chiariello, P.; Zuliani, P.; Somma, P.; Di Loreto, M.; De Matteis, C.; Cacciatore, F.; et al. Effects of vitamin e and hmg-coa reductase inhibition on cholesteryl ester transfer protein and lecithin-cholesterol acyltransferase in hypercholesterolemia. *Coron. Artery Dis.* **1998**, *9*, 257–264. [CrossRef]
146. Li, F.; Tan, W.; Kang, Z.; Wong, C.W. Tocotrienol enriched palm oil prevents atherosclerosis through modulating the activities of peroxisome proliferators-activated receptors. *Atherosclerosis* **2010**, *211*, 278–282. [CrossRef] [PubMed]
147. Traber, M.G.; Head, B. Vitamin e: How much is enough, too much and why! *Free Radic. Biol. Med.* **2021**, *177*, 212–225. [CrossRef]
148. Zuo, S.; Wang, G.; Han, Q.; Xiao, H.; Santos, H.O.; Rodriguez, D.A.; Khani, V.; Tang, J. The effects of tocotrienol supplementation on lipid profile: A meta-analysis of randomized controlled trials. *Complement Ther. Med.* **2020**, *52*, 102450. [CrossRef] [PubMed]
149. Saremi, A.; Arora, R. Vitamin e and cardiovascular disease. *Am. J. Ther.* **2010**, *17*, e56–e65. [CrossRef] [PubMed]
150. Yuan, R.; Yuan, Y.; Wang, L.; Xin, Q.; Wang, Y.; Shi, W.; Miao, Y.; Leng, S.X.; Chen, K.; Cong, W.; et al. Red yeast rice preparations reduce mortality, major cardiovascular adverse events, and risk factors for metabolic syndrome: A systematic review and meta-analysis. *Front. Pharmacol.* **2022**, *13*, 744928. [CrossRef] [PubMed]

151. Li, P.; Wang, Q.; Chen, K.; Zou, S.; Shu, S.; Lu, C.; Wang, S.; Jiang, Y.; Fan, C.; Luo, Y. Red yeast rice for hyperlipidemia: A meta-analysis of 15 high-quality randomized controlled trials. *Front. Pharmacol.* **2021**, *12*, 819482. [CrossRef]
152. Sungthong, B.; Yoothaekool, C.; Promphamorn, S.; Phimarn, W. Efficacy of red yeast rice extract on myocardial infarction patients with borderline hypercholesterolemia: A meta-analysis of randomized controlled trials. *Sci. Rep.* **2020**, *10*, 2769. [CrossRef] [PubMed]
153. Younes, M.; Aggett, P.; Aguilar, F.; Crebelli, R.; Dusemund, B.; Filipič, M.; Frutos, M.J.; Galtier, P.; Gott, D.; Gundert-Remy, U.; et al. Scientific opinion on the safety of monacolins in red yeast rice. *EFSA J.* **2018**, *16*, e05368. [CrossRef] [PubMed]
154. Visseren, F.L.J.; Mach, F.; Smulders, Y.M.; Carballo, D.; Koskinas, K.C.; Bäck, M.; Benetos, A.; Biffi, A.; Boavida, J.M.; Capodanno, D.; et al. 2021 esc guidelines on cardiovascular disease prevention in clinical practice. *Eur. J. Prev. Cardiol.* **2022**, *29*, 5–115. [CrossRef] [PubMed]
155. Sahebkar, A.; Serban, C.; Ursoniu, S.; Banach, M. Effect of garlic on plasma lipoprotein(a) concentrations: A systematic review and meta-analysis of randomized controlled clinical trials. *Nutrition* **2016**, *32*, 33–40. [CrossRef]
156. Matsumoto, S.; Nakanishi, R.; Li, D.; Alani, A.; Rezaeian, P.; Prabhu, S.; Abraham, J.; Fahmy, M.A.; Dailing, C.; Flores, F.; et al. Aged garlic extract reduces low attenuation plaque in coronary arteries of patients with metabolic syndrome in a prospective randomized double-blind study. *J. Nutr.* **2016**, *146*, 427S–432S. [CrossRef]
157. Shaikh, K.; Kinninger, A.; Cherukuri, L.; Birudaraju, D.; Nakanishi, R.; Almeida, S.; Jayawardena, E.; Shekar, C.; Flores, F.; Hamal, S.; et al. Aged garlic extract reduces low attenuation plaque in coronary arteries of patients with diabetes: A randomized, double-blind, placebo-controlled study. *Exp. Ther. Med.* **2020**, *19*, 1457–1461. [CrossRef]
158. Ben Salem, M.; Affes, H.; Ksouda, K.; Dhouibi, R.; Sahnoun, Z.; Hammami, S.; Zeghal, K.M. Pharmacological studies of artichoke leaf extract and their health benefits. *Plant Foods Hum. Nutr.* **2015**, *70*, 441–453. [CrossRef]
159. Henning, S.M.; Fajardo-Lira, C.; Lee, H.W.; Youssefian, A.A.; Go, V.L.; Heber, D. Catechin content of 18 teas and a green tea extract supplement correlates with the antioxidant capacity. *Nutr. Cancer* **2003**, *45*, 226–235. [CrossRef]
160. Busnelli, M.; Manzini, S.; Sirtori, C.R.; Chiesa, G.; Parolini, C. Effects of vegetable proteins on hypercholesterolemia and gut microbiota modulation. *Nutrients* **2018**, *10*, 1249. [CrossRef]
161. Blanco Mejia, S.; Messina, M.; Li, S.S.; Viguiliouk, E.; Chiavaroli, L.; Khan, T.A.; Srichaikul, K.; Mirrahimi, A.; Sievenpiper, J.L.; Kris-Etherton, P.; et al. A meta-analysis of 46 studies identified by the fda demonstrates that soy protein decreases circulating ldl and total cholesterol concentrations in adults. *J. Nutr.* **2019**, *149*, 968–981. [CrossRef]
162. Simental-Mendia, L.E.; Gotto, A.M., Jr.; Atkin, S.L.; Banach, M.; Pirro, M.; Sahebkar, A. Effect of soy isoflavone supplementation on plasma lipoprotein(a) concentrations: A meta-analysis. *J. Clin. Lipidol.* **2018**, *12*, 16–24. [CrossRef] [PubMed]
163. Ying, J.; Zhang, Y.; Yu, K. Phytosterol compositions of enriched products influence their cholesterol-lowering efficacy: A meta-analysis of randomized controlled trials. *Eur. J. Clin. Nutr.* **2019**, *73*, 1579–1593. [CrossRef] [PubMed]
164. Jacobson, T.A.; Maki, K.C.; Orringer, C.; Jones, E.P.; Kris-Etherton, H.P.; Sikand, G.; La Forge, R.; Daniels, S.R.; Wilson, D.P.; Morris, P.B.; et al. National lipid association recommendations for patient-centered management of dyslipidemia: Part 2. *J. Clin. Lipidol.* **2015**, *9* (Suppl. S6), S1-122.e1. [CrossRef] [PubMed]
165. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific opinion on the substantiation of health claims related to dietary fibre and maintenance of normal blood cholesterol concentrations (id 747, 750, 811) pursuant to article 13(1) of regulation (ec) no 1924/2006. *EFSA J.* **2015**, *7*, 1255. [CrossRef]
166. Soltani, M.D.; Meftahizadeh, H.; Barani, M.; Rahdar, A.; Hosseinikhah, S.M.; Hatami, M.; Ghorbanpour, M. Guar (*Cyamopsis tetragonoloba* L.) plant gum: From biological applications to advanced nanomedicine. *Int. J. Biol. Macromol.* **2021**, *193*, 1972–1985. [CrossRef]
167. Packer, L.; Witt, E.H.; Tritschler, H.J. Alpha-lipoic acid as a biological antioxidant. *Free Radic. Biol. Med.* **1995**, *19*, 227–250. [CrossRef]
168. Budoff, M.J.; Bhatt, D.L.; Kinninger, A.; Lakshmanan, S.; Muhlestein, J.B.; Le, V.T.; May, H.T.; Shaikh, K.; Shekar, C.; Roy, S.K.; et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: Final results of the evaporate trial. *Eur. Heart J.* **2020**, *41*, 3925–3932. [CrossRef]
169. Xiao, Y.; Zhang, Q.; Liao, X.; Elbelt, U.; Weylandt, K.H. The effects of omega-3 fatty acids in type 2 diabetes: A systematic review and meta-analysis. *Prostaglandins Leukot. Essent. Fat. Acids* **2022**, *182*, 102456. [CrossRef]
170. Saito, Y.; Yokoyama, M.; Origasa, H.; Matsuzaki, M.; Matsuzawa, Y.; Ishikawa, Y.; Oikawa, S.; Sasaki, J.; Hishida, H.; Itakura, H.; et al. Effects of epa on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the japan epa lipid intervention study (jelis). *Atherosclerosis* **2008**, *200*, 135–140. [CrossRef]
171. D'Andrea, E.; Hey, S.P.; Ramirez, C.L.; Kesselheim, A.S. Assessment of the role of niacin in managing cardiovascular disease outcomes: A systematic review and meta-analysis. *JAMA Netw. Open* **2019**, *2*, e192224. [CrossRef]
172. Sahebkar, A.; Reiner, Ž.; Simental-Mendia, L.E.; Ferretti, G.; Cicero, A.F. Effect of extended-release niacin on plasma lipoprotein(a) levels: A systematic review and meta-analysis of randomized placebo-controlled trials. *Metabolism* **2016**, *65*, 1664–1678. [CrossRef] [PubMed]
173. Food and Drug Administration. Withdrawal of approval of indications related to the coadministration with statins in applications for niacin extended-release tablets and fenofibric acid delayed-release capsules. *Fed. Regist.* **2016**, *81*, 22612–22613.

174. European Medicines Agency Confirms Recommendation to Suspend Tredaptive, Pelzont and Trevaclyn. 2013. Available online: https://www.ema.europa.eu/en/news/european-medicines-agency-confirms-recommendation-suspend-tredaptive-pelzont-trevaclyn (accessed on 12 December 2022).
175. DiNicolantonio, J.J. Coq10 and l-carnitine for statin myalgia? *Expert. Rev. Cardiovasc. Ther.* **2012**, *10*, 1329–1333. [CrossRef] [PubMed]
176. Serban, M.C.; Sahebkar, A.; Mikhailidis, D.P.; Toth, P.P.; Jones, S.R.; Muntner, P.; Blaha, M.J.; Andrica, F.; Martin, S.S.; Borza, C.; et al. Impact of l-carnitine on plasma lipoprotein(a) concentrations: A systematic review and meta-analysis of randomized controlled trials. *Sci. Rep.* **2016**, *6*, 19188. [CrossRef]
177. Salonen, R.M.; Nyyssönen, K.; Kaikkonen, J.; Porkkala-Sarataho, E.; Voutilainen, S.; Rissanen, T.H.; Tuomainen, T.P.; Valkonen, V.P.; Ristonmaa, U.; Lakka, H.M.; et al. Six-year effect of combined vitamin c and e supplementation on atherosclerotic progression: The antioxidant supplementation in atherosclerosis prevention (asap) study. *Circulation* **2003**, *107*, 947–953. [CrossRef]
178. Akbari, M.; Tamtaji, O.R.; Lankarani, K.B.; Tabrizi, R.; Dadgostar, E.; Haghighat, N.; Kolahdooz, F.; Ghaderi, A.; Mansournia, M.A.; Asemi, Z. The effects of resveratrol on lipid profiles and liver enzymes in patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. *Lipids Health Dis.* **2020**, *19*, 25. [CrossRef]
179. Khalili, L.; Nammi, S. The effects of curcumin supplementation on metabolic biomarkers and body mass index in patients with nonalcoholic fatty liver disease: A systematic review and meta-analysis of randomized controlled trials. *Curr. Pharmacol. Des.* **2022**, *28*, 1911–1925. [CrossRef]
180. Altobelli, E.; Angeletti, P.M.; Marziliano, C.; Mastrodomenico, M.; Giuliani, A.R.; Petrocelli, R. Potential therapeutic effects of curcumin on glycemic and lipid profile in uncomplicated type 2 diabetes-a meta-analysis of randomized controlled trial. *Nutrients* **2021**, *13*, 404. [CrossRef]
181. Mahdi, G.S. Chromium deficiency might contribute to insulin resistance, type 2 diabetes mellitus, dyslipidaemia, and atherosclerosis. *Diabet. Med.* **1996**, *13*, 389–390.
182. Warden, B.A.; Guyton, J.R.; Kovacs, A.C.; Durham, J.A.; Jones, L.K.; Dixon, D.L.; Jacobson, T.A.; Duell, P.B. Assessment and management of statin-associated muscle symptoms (sams): A clinical perspective from the national lipid association. *J. Clin. Lipidol.* **2022**, *17*, 19–39. [CrossRef]
183. Alehagen, U.; Aaseth, J.; Alexander, J.; Johansson, P. Still reduced cardiovascular mortality 12 years after supplementation with selenium and coenzyme q10 for four years: A validation of previous 10-year follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly. *PLoS ONE* **2018**, *13*, e0193120. [CrossRef] [PubMed]
184. Alehagen, U.; Johansson, P.; Björnstedt, M.; Rosén, A.; Dahlström, U. Cardiovascular mortality and n-terminal-probnp reduced after combined selenium and coenzyme q10 supplementation: A 5-year prospective randomized double-blind placebo-controlled trial among elderly swedish citizens. *Int. J. Cardiol.* **2013**, *167*, 1860–1866. [CrossRef] [PubMed]
185. AHA eStaff. What is the Mediterranean Diet? 2020. Available online: https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/mediterranean-diet#:~:text=A%20Mediterranean-style%20diet%20typically%20includes%3A%201%20plenty%20of,fish%20and%20poultry%20in%20low%20to%20moderate%20amounts (accessed on 1 February 2023).
186. Arnett, D.K.; Blumenthal, R.S.; Albert, M.A.; Buroker, A.B.; Goldberger, Z.D.; Hahn, E.J.; Himmelfarb, C.D.; Khera, A.; Lloyd-Jones, D.; McEvoy, J.W.; et al. 2019 acc/aha guideline on the primary prevention of cardiovascular disease: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Circulation* **2019**, *140*, e596–e646. [CrossRef]
187. Papadaki, A.; Nolen-Doerr, E.; Mantzoros, C.S. The effect of the mediterranean diet on metabolic health: A systematic review and meta-analysis of controlled trials in adults. *Nutrients* **2020**, *12*, 3342. [CrossRef] [PubMed]
188. Estruch, R.; Ros, E.; Salas-Salvadó, J.; Covas, M.I.; Corella, D.; Arós, F.; Gómez-Gracia, E.; Ruiz-Gutiérrez, V.; Fiol, M.; Lapetra, J.; et al. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. *N. Engl. J. Med.* **2018**, *378*, e34. [CrossRef] [PubMed]
189. Martínez-González, M.A.; Sánchez-Tainta, A.; Corella, D.; Salas-Salvado, J.; Ros, E.; Arós, F.; Gómez-Gracia, E.; Fiol, M.; Lamuela-Raventós, R.M.; Schröder, H.; et al. A provegetarian food pattern and reduction in total mortality in the prevención con dieta mediterránea (predimed) study. *Am. J. Clin. Nutr.* **2014**, *100*, 320s–328s. [CrossRef]
190. Tang, C.; Wang, X.; Qin, L.Q.; Dong, J.Y. Mediterranean diet and mortality in people with cardiovascular disease: A meta-analysis of prospective cohort studies. *Nutrients* **2021**, *13*, 2623. [CrossRef] [PubMed]
191. Leucht, S.; Chaimani, A.; Cipriani, A.S.; Davis, J.M.; Furukawa, T.A.; Salanti, G. Network meta-analyses should be the highest level of evidence in treatment guidelines. *Eur. Arch. Psychiatry Clin. Neurosci.* **2016**, *266*, 477–480. [CrossRef]
192. Laffin, L.J.; Bruemmer, D.; Garcia, M.; Brennan, D.M.; McErlean, E.; Jacoby, D.S.; Michos, E.D.; Ridker, P.M.; Wang, T.Y.; Watson, K.E.; et al. Comparative effects of low-dose rosuvastatin, placebo and dietary supplements on lipids and inflammatory biomarkers. *J. Am. Coll. Cardiol.* **2022**, *81*, 1–12. [CrossRef]

Journal of
Clinical Medicine

MDPI

Review

Evolution of More Aggressive LDL-Cholesterol Targets and Therapies for Cardiovascular Disease Prevention

Jeffrey E. Jones †, Kevin S. Tang †, Ailin Barseghian and Nathan D. Wong *

Heart Disease Prevention Program, C240 Medical Sciences, Division of Cardiology, Department of Medicine, University of California, Irvine, CA 92697, USA; jeffreej@hs.uci.edu (J.E.J.); ktang16@hs.uci.edu (K.S.T.); barsegha@hs.uci.edu (A.B.)

* Correspondence: ndwong@hs.uci.edu

† These authors contributed equally to this work.

Abstract: Over the last half-century, discussions on the exact targets for low-density lipoprotein cholesterol (LDL-C) reduction have evolved towards a more aggressive approach with lower LDL-C targets, particularly for high-risk patients with pre-existing atherosclerotic cardiovascular disease (ASCVD). A wealth of cardiovascular outcome trials have shown the efficacy of statin therapy in general, as well as the incremental impact of high-intensity statin therapy in particular. More recent trials have further demonstrated the impact of non-statin therapies, including ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, and, most recently, bempedoic acid, on reducing ASCVD outcomes. The availability of these and other newer therapies has prompted clinicians to strive for lower LDL-C targets to address residual ASCVD risk after statin therapy. This paper will provide an overview of the historical trends in lipid management and therapeutics and review the current state of evidence for lower LDL-C targets in clinical guidelines and recommendations.

Keywords: dyslipidemia; low density lipoprotein cholesterol; guidelines; cardiovascular disease

Citation: Jones, J.E.; Tang, K.S.; Barseghian, A.; Wong, N.D. Evolution of More Aggressive LDL-Cholesterol Targets and Therapies for Cardiovascular Disease Prevention. *J. Clin. Med.* **2023**, *12*, 7432. https://doi.org/10.3390/jcm12237432

Academic Editor: Alessandro Di Minno

Received: 2 November 2023
Revised: 22 November 2023
Accepted: 27 November 2023
Published: 30 November 2023

1. Background

Cardiovascular disease (CVD) continues to be the leading cause of mortality in the United States and globally, accounting for about one-fourth of all deaths [1,2]. Whereas age, sex, family history, and genotype are fixed risk factors for cardiovascular disease, modifiable predictors of CVD include an unhealthy diet, hypertension, obesity, type 2 diabetes mellitus, and dyslipidemia—defined as the imbalance of lipids such as triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) [1–6].

Compelling data indicate that aggressive lipid-lowering therapy further reduces the risk of atherosclerotic cardiovascular disease (ASCVD) events, especially among individuals with established CVD [7]. The Cholesterol Treatment Trialists Collaboration has shown an approximately 20% reduction in the risk for cardiovascular disease events for every 1 mmol/L (approximately 40 mg/dL) reduction in LDL-C [8]. Moreover, lipid-lowering therapy is associated with reductions in cardiovascular events in populations with a high coronary event risk (≥30% risk: 22% reduction in major coronary events per mmol/L reduction in LDL-C) and individuals with diabetes mellitus (21% reduction in major vascular events per mmol/L reducing in LDL-C) [8–10]. Since 1988 and beginning with the Third Adult Treatment Panel of the National Cholesterol Education Program (ATP-III), there has been an evolution in guidelines calling for lower LDL-C targets, especially in higher-risk populations, which has corresponded with the publication of key clinical trials of both statin and non-statin therapies. The goal of this review is to synthesize this evolution of evidence and guidelines over the last several decades and provide a summary of the latest recommendations for aggressive lipid control in cardiovascular disease risk reduction.

2. LDL-C as a Predictor of CVD

The relationship between cholesterol and CVD was first elucidated as early as the mid-20th century. In 1939, Carl Muller observed that individuals with familial hypercholesterolemia had extreme arterial plaque deposition and faced a very high risk for cardiovascular death [11,12]. In 1952, John Gofman discovered that patients with a history of myocardial infarction (MI) have higher levels of low-density serum cholesterol than healthy individuals [13]. By 1977, the Framingham Heart Study had established serum LDL-C as an independent risk factor for ASCVD [14].

Cholesterol and triglycerides are insoluble molecules that must be complexed with proteins to be transported within circulation. Lipoproteins have a hydrophobic core of cholesterol and triglycerides surrounded by a hydrophilic membrane consisting of free cholesterol, phospholipids, and apolipoproteins. Plasma lipoproteins are grouped into categories based on size, lipid composition, and associated apolipoproteins. Chylomicrons, the largest lipoproteins, are formed from dietary triglycerides and metabolized by muscle and adipose tissue into chylomicron remnants which are absorbed by the liver. The liver's endogenous pathway of cholesterol metabolism begins with the formation of very low-density lipoproteins (VLDL) which are subsequently metabolized into indeterminate-density lipoproteins (IDL) and further catabolized into LDL-C [15].

Biochemical studies link LDL-C and atherosclerosis via cholesterol penetration and retention in the arterial endothelium. LDL-C is oxidized and subsequently targeted by scavenger macrophages that become cytokine-secreting foam cells. Inflammation and atherosclerotic progression lead to the formation of intravascular plaque, which can cause myocardial ischemia and infarction [16–18].

The liver can initiate reverse cholesterol transport via the release of high-density lipoprotein (HDL) particles that acquire cholesterol from circulation. By absorbing excess cholesterol and returning it back to the liver, this mechanism reduces and inhibits the formation of atherosclerotic plaques [19]. Low serum HDL-C is associated with a higher risk for ASCVD; however, a very high HDL-C has not been shown to be protective against ASCVD [20–22].

Familial hypercholesterolemia (FH) is an autosomal dominant condition characterized by high serum cholesterol and as much as a 20-fold increased risk of ASCVD. Deleterious mutations in the LDL-C receptor itself or apolipoprotein B (apoB), the major ligand between LDL-C particles and their receptor, can predispose individuals to extremely high serum LDL-C. Additionally, gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme that mediates LDL-C receptor degradation, resulting in very high LDL-C levels, are also an etiology for FH [23]. Patients with heterozygous FH tend to have LDL-C $\geq$ 190 mg/dL in adults or $\geq$160 mg/dL in children while homozygous FH often presents with LDL-C $\geq$ 400 mg/dL [24–27]. Heterozygous FH is relatively common in the general population (approximately 1 in 250–300) while homozygous FH is found in approximately 1 in 250,000–300,000 [24,28,29]. The ASCVD risk in individuals with FH is proportionate to the cumulative LDL-C burden, and treatment options consist of lipid-lowering pharmacotherapies, including statins and non-statin therapies (e.g., ezetimibe, PCSK9 inhibitors, inclisiran, and evinacumab), as well as plasma apheresis [30–32].

Serum LDL-C levels in many adults are influenced by diet, and a diet low in fat and cholesterol is the foundation of treatment for dyslipidemia. The average American serum LDL-C in 2000 was 127.9 mg/dL and has progressively decreased to 110.5 mg/dL in 2020 [33]. Though the decrease over time is encouraging, this may reflect the better treatment of dyslipidemia rather than prevention. Studies in different human populations demonstrate that the average American LDL-C is far from optimal. Cholesterol panels of hunter–gatherer populations, such as the Hadza of Tanzania and Pacific Islanders of Pukapuka and Tokelau, show that these groups have significantly lower serum cholesterol and a lower prevalence of cardiovascular disease compared to the US population [34–36]. A survey of the Tsimane of Bolivia, a population with the lowest documented prevalence of atherosclerosis, revealed that individuals have an average LDL-C of 72 mg/dL [37,38].

3. LDL-Cholesterol-Lowering Pharmacotherapy and Cardiovascular Outcomes Benefit

Diet and lifestyle modification can often sufficiently mitigate risk in individuals at a low risk for CVD, but higher-risk individuals and those with existing ASCVD often need pharmacologic treatment [39–41]. There has been a wealth of pharmacologic therapies addressing reductions in total and LDL-C, now spanning nearly 75 years (Table 1). As early as the mid-1950s, the water-soluble vitamin niacin (nicotinic acid) was identified as a pharmacologic therapy for lowering cholesterol [42–44]. Around the same time, the bile acid sequestrant cholestyramine was developed as another LDL-C-lowering strategy, showing significant reductions in both LDL-C and cardiovascular mortality in the Lipid Research Clinics Coronary Primary Prevention Trial [45]. Fibrates such as gemfibrozil showed early promise as an additional therapy in the Helsinki Heart Study, demonstrating a significant reduction in coronary heart disease [46]. However, these results were later complicated by the FIELD and ACCORD studies, and more recently by the PROMINENT trial, which did not show the benefit of fibrate therapy alone or when added to statin therapy [47–49].

Table 1. LDL-lowering Pharmacotherapies.

Drug	Year of FDA Approval	Mechanism of Action	Major Randomized Controlled Trials
Nicotinic acid (Niacin)	1950s *	Mechanism not well defined	**Coronary Drug Project**: Patients with a history of myocardial infarction on nicotinic acid had an 11% lower mortality compared to those on placebo [50]. **Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) and Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)** did not demonstrate reductions in vascular events compared to statin monotherapy [51,52].
Bile acid sequestrants (Cholestyramine, Colesevelam, Colestipol)	1970s *	Increased cholesterol metabolism via bile excretion	**Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)**: Colestipol reduced the risk of coronary heart disease mortality by 24% in middle-aged men with primary hypercholesterolemia [45].
Fibrates (Gemfibrozil, Fenofibrate)	1970s *	Promote receptor-mediated LDL-C clearance and increased catabolism of LDL-C	**Helsinki Heart Study**: Gemfibrozil was associated with a 34% reduction in incident coronary heart disease in middle-aged men with dyslipidemia [46]. **FIELD (Fenofibrate Event Lowering and Intervention in Diabetes) and ACCORD (Action to Control Cardiovascular Risk in Diabetes)** did not show significant reductions in cardiovascular events with fenofibrate monotherapy or in combination with other lipid-lowering medications [47,48].
Lovastatin	1987	Competitive inhibitor of HMG-CoA reductase	**Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS):** Lovastatin reduced the risk of major coronary events by 37% in patients with moderately elevated cholesterol [53].
Pravastatin	1991	Competitive inhibitor of HMG-CoA reductase	**Cholesterol and Recurrent Events (CARE):** Pravastatin decreased the incidence of fatal coronary events or nonfatal myocardial infarction by 24% in patients with myocardial infarction who had plasma total cholesterol levels below 240 mg/dL [54].

Table 1. *Cont.*

Drug	Year of FDA Approval	Mechanism of Action	Major Randomized Controlled Trials
Atorvastatin	1996	Competitive inhibitor of HMG-CoA reductase	**Treating to New Targets (TNT)**: Intense lipid lowering with 80 mg/day atorvastatin showed a 22% relative risk reduction in cardiovascular events over treatment with 10 mg/day in patients with stable coronary heart disease [55].
Simvastatin	1998	Competitive inhibitor of HMG-CoA reductase	**Scandinavian Simvastatin Survival Study (4S)**: Simvastatin treatment was associated with a 30% reduction in death in patients with coronary heart disease [56].
Rosuvastatin	2003	Competitive inhibitor of HMG-CoA reductase	**Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER):** Rosuvastatin decreased cardiovascular events by 44% in patients with LDL-C < 130 mg/dL but elevated C-reactive protein [57].
Ezetimibe	2004	Inhibitor of the NPC1L1 cholesterol transporter	**Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)**: Ezetimibe-simvastatin therapy provided reduction in LDL-C, with a 6% relative risk reduction in adverse cardiovascular outcomes compared to statin monotherapy [58].
Lomitapide	2012	Microsomal triglyceride transfer protein inhibitor	Phase III trials in patients with homozygous familial hypercholesterolemia on current lipid-lowering therapy demonstrate a 50% LDL-C reduction (8.7 mmol/L to 4.3 mmol/L) at 26 weeks [59].
Mipomersen	2013	Small interfering RNA inhibitor of apolipoprotein B	A randomized controlled trial of individuals with familial hypercholesterolemia on lipid-lowering therapy showed a 36% reduction in LDL-C and significant reductions in apolipoprotein B [60].
Alirocumab	2015	Monoclonal antibody inhibitor of PCSK9	**Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES)**: Alirocumab treatment resulted in a relative risk reduction of 15% for ASCVD events compared to the placebo in acute coronary syndrome patients on statin therapy [61].
Evolocumab	2015	Monoclonal antibody inhibitor of PCSK9	**Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)**: Evolocumab treatment was associated with a relative risk reduction of 15% for ASCVD events in patients with ASCVD on statin therapy [62].
Bempedoic Acid	2020	Adenosine triphosphate-citrate lyase inhibitor	**Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR OUTCOMES)**: Bempedoic acid compared to placebo given to patients with statin intolerance showed a reduction in the primary endpoint of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization of 13% [63].
Evinacumab	2021	Monoclonal antibody inhibitor of angiopoietin-like protein 3	**Evinacumab for Homozygous Familial Hypercholesterolemia (ELIPSE HoFH):** Evinacumab decreases LDL-C by 49% in patients with homozygous familial hypercholesterolemia (average LDL-C 255.1 mg/dL) on a maximum background lipid-lowering therapy [64].

Table 1. *Cont.*

Drug	Year of FDA Approval	Mechanism of Action	Major Randomized Controlled Trials
Inclisiran	2021	Small interfering RNA inhibitor of PCSK9	**Inclisiran for Participants with Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10 and 11)**: Inclisiran reduces LDL-C by 50% in ASCVD patients on maximally tolerated statin [65]. Cardiovascular outcomes trials are ongoing.

* Date reflects approximate period of significant adoption. HMG-CoA reductase, Hydroxymethylglutaryl coenzyme A reductase; PCSK9, Proprotein convertase subtilisin/kexin type 9.

The advent of statins, competitive inhibitors of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, revolutionized how clinicians treat elevated LDL-C and reduce ASCVD risk and spurred the growth of clinical lipidology. In 1987, lovastatin became the first statin approved for human use. Statin therapy quickly became the cornerstone of lipid management, and other pharmaceuticals have been approved for further reducing LDL-C. The 1994 Scandinavian Simvastatin Survival Study (4S) demonstrated a dramatic 30% mortality reduction and a 42% reduction in major coronary events from simvastatin treatment in patients with coronary heart disease [56]. Similarly, the 1996 Cholesterol and Recurrent Events (CARE) trial of secondary prevention with pravastatin found a 24% reduction in recurrent cardiovascular events in patients who had experienced a prior MI [54]. In 1998, the AFCAPS/TEXCAPS study, a primary prevention trial, showed a 37% reduction in major coronary events from lovastatin treatment in patients with average to moderately elevated LDL-C [53]. In 2001, the MIRACL study showed that more intensive statin therapy with atorvastatin (compared to pravastatin) resulted in a further reduction in cardiovascular risk, although the endpoint was highly impacted by the reduction in hospitalization for unstable angina [66]. The Treating to New Targets (TNT) trial compared high-intensity statin therapy (atorvastatin 80 mg) to moderate-intensity therapy (atorvastatin 10 mg) in patients at a high risk for ASCVD, finding that high-intensity statin therapy further reduced cardiovascular events by 22% compared to moderate-intensity therapy [55]. The 2008 JUPITER trial investigated the use of rosuvastatin in individuals with LDL-C < 130 mg/dL but elevated C-reactive protein levels (>2 mg/L) as a measure of systemic inflammation, finding a 44% reduction in vascular events and a 54% reduction in MI compared to the control [57]. The Cholesterol Treatment Trialists' meta-analysis of 27 randomized controlled trials of statin therapy further supported the value of statin therapy in safely reducing the risk of MI, coronary death, ischemic stroke, and coronary revascularization in a wide range of patients [8].

Ezetimibe, an inhibitor of the NPC1L1 cholesterol transporter, was approved by the FDA in 2004 as another agent for dyslipidemia. The IMPROVE-IT trial demonstrated that ezetimibe-simvastatin therapy further reduces LDL-C and adverse cardiovascular outcomes compared to statin monotherapy [58]. However, this trial was carried out in select very-high-risk ASCVD patients with an acute coronary syndrome (ACS) in the past 10 days and took 7 years to show only a modest (despite being statistically significant) benefit of a 6% relative risk reduction in the primary endpoint [58].

The advent of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has dramatically impacted the lipid therapy landscape in recent years. They provide an additional 50–60% LDL-C reduction beyond statin therapy, allowing for the achievement of LDL-C levels often below 30 mg/dL and, in some patients, below 10 mg/dL, lower than what has previously been seen from existing therapies. In 2015, alirocumab, the first FDA-approved monoclonal antibody inhibitor of PCSK9, was approved as another treatment for hyperlipidemia [61,67]. This was followed by the approval of evolocumab, whose effects on atherosclerosis were first demonstrated by the GLAGOV trial, showing that, in patients with angiographic coronary disease treated with statins, individuals taking

the PCSK9 inhibitor evolocumab had significantly decreased LDL-C and a reduction in plaque atheroma volume compared to those on the placebo [68]. A reduction in ASCVD outcomes from PCSK9 inhibitor therapy was first demonstrated by the FOURIER trial, showing a 15% relative risk reduction with evolocumab-treated patients achieving median LDL-C levels of 30 mg/dL [62]. This was then followed by the ODYSSEY Outcomes trial, also showing a 15% risk reduction from treatment with alirocumab.

In 2020, bempedoic acid, an inhibitor of adenosine triphosphate citrate lyase, received approval as another lipid-lowering drug. This therapy lowers LDL-C by 15–20% as a monotherapy and by approximately 35% in a fixed-dose combination therapy with ezetimibe. In the recently reported CLEAR OUTCOMES trial, bempedoic acid reduced LDL-C by an average of 21.1% compared to the placebo in patients who were unable or unwilling to take statins owing to unacceptable adverse effects. The trial demonstrated a relative risk reduction of 13% in the primary endpoint (death from cardiovascular causes, nonfatal MI, nonfatal stroke, or coronary revascularization) in those taking bempedoic acid compared to the placebo in the overall trial population, but with a more striking 30% reduction in risk demonstrated among the primary prevention subgroup [63,69].

One year later, the small-interfering RNA inclisiran was approved for individuals who require additional LDL-C lowering. In Phase 3 clinical trials, inclisiran was associated with an approximately 50% time-averaged reduction in LDL-C [65]. Of interest, a recent analysis of 3655 patients followed for 18 months in a phase III trial of incisliran showed the therapy to be associated with a 26% risk reduction in major adverse cardiovascular events [70]. Ongoing cardiovascular outcome trials of inclisiran in both the high-risk primary and secondary prevention populations will be important for demonstrating the clinical benefit of this therapy beyond statin therapy.

4. Early Years of Cholesterol Treatment Guidelines

The first set of cholesterol treatment guidelines from the National Cholesterol Education Program was released in 1988. The Adult Treatment Panel (ATP) I guidelines focused on adults aged 20 years and over. Individuals with high ($\geq$240 mg/dL) or borderline-high (200–239 mg/dL) total cholesterol with definite coronary heart disease (CHD) or at least two risk factors (male sex, family history of premature CHD, cigarette smoking, hypertension, low HDL-C, diabetes mellitus, definite cerebrovascular or peripheral vascular disease, or severe obesity) were recommended to undergo lipoprotein analysis that included LDL-C calculation [71]. At the time, primary prevention solely involved dietary therapy. If individuals continued to have LDL-C $\geq$ 130 mg/dL after 6 months, pharmacologic intervention with bile acid sequestrants and/or nicotinic acid was recommended. Statins were not yet recommended since their impact on CV death and the long-term safety profile had not yet been established.

The 1993 ATP II recommendations suggested HDL-C screening in all individuals, not just those with high total cholesterol. Like ATP I, these guidelines stratified patients based on total cholesterol and LDL-C. However, the LDL-C treatment goal in those with CHD was decreased from <130 mg/dL to <100 mg/dL. The risk factors for CHD were slightly changed to include men > 45 years, women > 55 years, women who had undergone premature menopause without estrogen replacement therapy, and HDL-C < 35 mg/dL. Statins (lovastatin, pravastatin, simvastatin, atorvastatin, rosuvastatin, and pitavastatin) were finally added to the list of effective pharmacologic treatments, but caution in young individuals was recommended due to the lack of long-term safety data [72].

The 2001 ATP III guidelines recommended that clinicians focus on LDL-C as the primary target for therapy [73]. These new guidelines used Framingham algorithms for the prediction of 10-year absolute CHD risk to stratify patients for treatment goals and recommended a full lipid panel be performed instead of just total cholesterol and HDL-C. The LDL-C treatment target for individuals with CHD was maintained at <100 mg/dL, but individuals with diabetes, peripheral artery disease, or a $\geq$20% 10-year risk of CHD were also recommended for treatment. These guidelines also recognized statins for dyslipidemia

treatment given their growing evidence of benefit. The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) released similar guidelines in 2003, recommending a treatment target of <100 mg/dL for patients with clinically established CVD [74]. In 2004, the ATP III guidelines were updated after numerous statin trials solidified statins as an effective treatment for dyslipidemia [75]. In addition to the <100 mg/dL treatment target, an optional treatment goal of LDL-C < 70 mg/dL was added for individuals with CHD plus multiple major or poorly controlled risk factors (especially diabetes) or ACS. This target of <70 mg/dL remained the clinical standard for over a decade.

The 2006 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines similarly adopted an LDL-C treatment goal of <100 mg/dL for all individuals on lipid-lowering pharmacotherapy (a Class I recommendation) and an optional target of <70 mg/dL for individuals with CHD and other clinical forms of atherosclerotic disease [76]. The 2007 ESC/EAS guidelines similarly continued the LDL-C treatment target of <100 mg/dL but added an optional treatment target of <80 mg/dL, if feasible [77]. The 2011 update to these guidelines based treatment recommendations on the 10-year predicted risk from the SCORE algorithm and recommended an LDL-C treatment target of <70 mg/dL in those at the highest risk [78]. This recommendation was unchanged in the 2016 update [79].

LDL-C reduction is a key strategy in secondary ASCVD prevention [80–82]. While statins are the first-line pharmacotherapy in LDL-C management, many patients at risk for ASCVD who have been prescribed statin therapy have not achieved appropriate LDL-C lowering. An earlier reduction in LDL-C in patients with ACS could be an important aspect of secondary prevention, especially considering that the greatest risk for recurrent events occurs during the month following the initial event [83,84]. Studies have demonstrated that a combination therapy of a statin plus an additional lipid-lowering agent can produce immense reductions in LDL-C and longer survival for individuals at a high risk for ASCVD. The EVOPACS study demonstrated that in patients previously hospitalized for ACS with elevated LDL-C, PCSK9 inhibitor therapy evolocumab enabled 95.7% of patients to achieve the 70 mg/dL target, compared to 37.6% of placebo group patients [85]. While the study did not identify a decrease in ACS events over the 8-week timeframe, some organizations such as the Lipid Association of India (LAI) have released recommendations for intense LDL-C lowering in patients who have experienced ACS, using ezetimibe and PCSK9 inhibitors to reach the target LDL-C of 30 mg/dL [86]. The ongoing EVOLVE-MI trial of evolocumab is testing the efficacy of evolocumab if given within 10 days of hospitalization for ACS for reducing subsequent ASCVD events.

5. Lower and More Aggressive LDL-Cholesterol Targets

Over the last decade, treatment targets have shifted to lower treatment and greater reduction targets for lipid-lowering therapy (Figure 1). While the 2013 ACC/AHA guideline recognized that most clinicians used LDL-C targets of <100 mg/dL and <70 mg/dL for the primary and secondary prevention of ASCVD, respectively, the guideline removed specific targets due to the lack of clinical trials testing specific LDL-C targets and focused instead on statin intensity, which prior clinical trials utilized in their design, showing the superiority of high-intensity statin over lower intensities. Higher-risk persons such as those with ASCVD, LDL-C $\geq$ 190, diabetes, and multiple risk factors, or those with >20% 10-year ASCVD risk, were recommended high-intensity statin to reduce LDL-C by at least 50%, with those of an intermediate risk or diabetes without multiple risk factors recommended moderate-intensity statin designed to lower LDL-C 30–49% [87].

In 2017, the American Association of Clinical Endocrinologists and American College of Endocrinology released dyslipidemia guidelines advising that individuals at an extreme risk for ASCVD should have an LDL-C goal of <55 mg/dL [88].

In 2018, the ACC/AHA/Multispecialty cholesterol guidelines did not specify target LDL-C values for the same reasons as the 2013 guidelines but instead recommended moderate-intensity statin treatment for those of borderline (5- < 7.5%) and intermediate (7.5- < 20%) 10-year ASCVD risk (especially in the presence of additional risk enhancing fac-

tors such as a premature family history of ASCVD, persistently elevated LDL-C, metabolic syndrome, chronic kidney disease, chronic inflammatory conditions, female-specific risk enhancers such as premature menopause or pre-eclampsia, high risk race/ethnicities, or elevated lipid or other biomarkers) and high intensity statin for higher-risk primary prevention and all those with ASCVD. The "threshold" concept was also introduced as an alternative to using targets, where if the LDL-C was still at or above 70 mg/dL despite maximally tolerated statin therapy, further non-statin therapy was recommended [80]. This guideline also proposed further risk stratification of those with ASCVD into those at a very high risk (based on the presence of two or more ASCVD events or one event and multiple high-risk conditions) or not at very high risk. A more recent 2022 ACC Expert Consensus Report further reduced this threshold for the consideration of non-statin therapy to 55 mg/dL for patients with clinical ASCVD at a very high risk [82]. It recommended that ezetimibe or a PCSK9 inhibitor be considered first (because of the already published clinical outcome data at the time of writing), followed by bempedoic acid or inclisiran.

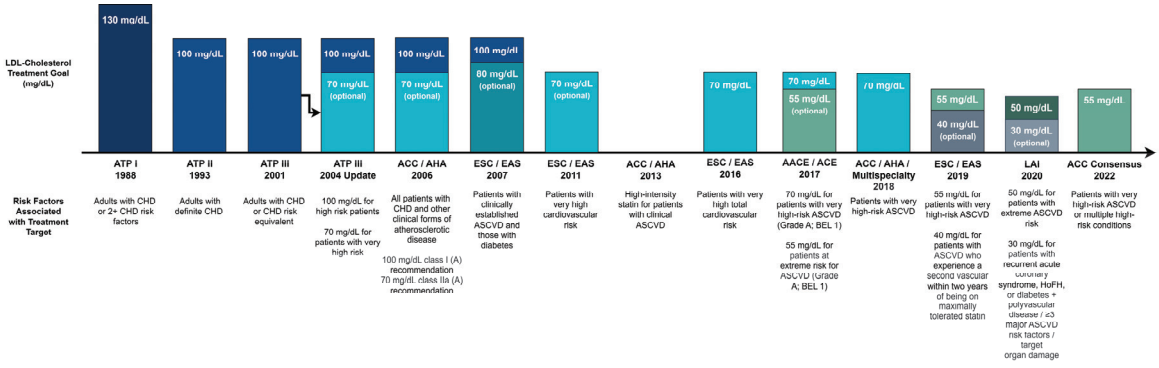

Figure 1. History of Cholesterol Guidelines and LDL-Cholesterol Treatment Targets. CHD, coronary heart disease; ASCVD, atherosclerotic cardiovascular disease; BEL, best evidence level; HoFH, Homozygous Familial Hypercholesterolemia; ATP, Adult Treatment Panel; ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; EAS, European Atherosclerosis Society; AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; LAI, Lipid Association of India.

The 2019 ESC/EAS guidelines similarly recommended an LDL-C treatment goal of <55 mg/dL for very-high-risk individuals (a Class I recommendation) but lowered this even further to <40 mg/dL in patients with ASCVD who experience a second vascular event within two years (not necessarily of the same type, such as a stroke) (a Class IIb recommendation) [89].

The 2020 LAI guidelines for dyslipidemia recommended LDL-C treatment targets based upon an individual's risk group. A treatment target of 100 mg/dL was suggested for individuals with a low or intermediate risk, and one of 70 mg/dL was suggested for individuals with a high risk. A target of 50 mg/dL was recommended for individuals at a 'very high risk', defined as pre-existing ASCVD, diabetes with two or more risk factors/target organ damage, or homozygous FH. For individuals with an extreme risk—those with CAD and one or more feature of a high-risk group (i.e., diabetes mellitus with zero to one other major ASCVD risk factors, CKD stage 3B or 4, coronary calcium score > 300 HU, lipoprotein (a) $\geq$ 50 mg/dL or 125 nmol/L, etc.)—a treatment target of 50 mg/dL was recommended, with an optional goal of 30 mg/dL. Individuals at an extreme risk with recurrent ACS, polyvascular disease, or an additional 'very high risk' factor were recommended the most intense treatment target of 30 mg/dL [90].

6. Benefits and Risks of Very Low LDL-Cholesterol

There have been previously reported observational data suggesting an increased risk of coronary heart disease (CHD) and stroke mortality with low LDL-C levels. A recent study published in the Journal of the American Heart Association examined over fourteen thousand participants in the National Health and Nutrition Examination Survey (NHANES) over 20 years and found an increased risk of all-cause mortality (HR 1.45, 95% CI 1.10–1.93) in those with LDL-C < 70 mg/dL compared to those with LDL-C 100–129.9 mg/dL, controlling for demographic factors and comorbidities [91]. However, this observed relationship could be confounded by subclinical comorbidities not adjusted for. Moreover, clinical trials achieving low LDL-C levels, as described earlier, have not corroborated these results. However, some have shown such an association to occur in those who also have elevated high-sensitivity CRP levels > 2 mg/dL [92,93]. An earlier analysis also warned of a potential association between LDL-C < 70 mg/dL and the incidence of intracranial hemorrhage (ICH) stroke [94]; this association persists whether using LDL-C 70–99.9 mg/dL or LDL-C 100–129.9 mg/dL as the reference mark [95,96].

Notably, this association of very low LDL-C with higher rates of adverse events has not been corroborated by contemporary clinical trials. For example, the EBBINGHAUS study demonstrated no difference in effects on cognitive function with increased lipid lowering using evolocumab [97,98]; however, it is realized that we do not have such data from a longer-term follow-up. Furthermore, there are competing data suggesting that there are further cardiovascular and mortality benefits conferred with aggressive LDL-C reduction. Although the IMPROVE-IT trial found a non-significant trend towards increased hemorrhagic stroke in those treated to a lower LDL-C goal with ezetimibe and simvastatin, a subsequent 2017 analysis showed significant reductions in major adverse cardiovascular events (MACE) with LDL-C < 30 mg/dL compared to $\geq$70 mg/dL, without a concomitant increase in rates of neurocognitive events, hemorrhagic stroke, or non-CVD deaths [58,99]. The American Heart Association recently published a scientific statement on LDL-C lowering and the risk for dementia and hemorrhagic stroke, stating that achieving very low LDL-C does not increase the risk for hemorrhagic stroke and that the risk of a hemorrhagic stroke associated with statin therapy in patients without a history of cerebrovascular disease is small and consistently nonsignificant [100].

Notably, with lower LDL-C levels achieved in more recent trials, further benefits in ASCVD risk reduction have also been observed, further solidifying the LDL-C hypothesis. A subgroup analysis of the 2004 PROVE-IT TIMI 22 study showed that individuals who achieved LDL-C $\leq$ 40 mg/dL had an even greater benefit for ASCVD risk reduction (HR 0.61 compared to individuals with LDL-C 80–100 mg/dL) than those who achieved LDL-C 40–60 mg/dL (HR 0.67) [101]. The ODYSSEY OUTCOMES trial used alirocumab for extreme lipid lowering and demonstrated a 15% reduction in ASCVD events in those with a target LDL-C of 25–50 mg/dL. [61] The GLAGOV trial [68] showed greater reduction in plaque atheroma volume (regression of atherosclerosis) with the lower the LDL-C achieved down to 20 mg/dL with no evidence of a threshold effect. The FOURIER Trial compared the addition of PCSK9 inhibition with evolocumab to statin therapy with a placebo and found that the additional lowering of LDL-C to a median of 30 mg/dL resulted in a 15% reduction in the primary composite endpoint of cardiovascular death, MI, hospitalization for ACS, and coronary revascularization without a significant increase in adverse events; further reductions in cardiovascular risk were also demonstrated in this study, achieving LDL-C levels of <10 mg/dL, with no evidence of a threshold below which there was no further benefit [62]. These outcomes provide foundational evidence for the more aggressive LDL-C targets in recent international guidelines; however, more research is needed to evaluate and quantify the risks of very low LDL-C.

7. Non-HDL Cholesterol and Apolipoprotein B as Secondary Treatment Targets

Statins and other lipid-lowering therapies are effective in lowering LDL-C, as well as apolipoprotein B (apoB) and non-HDL cholesterol; however, clinical trials (and thus

guidelines) have all focused on LDL-C as the primary efficacy endpoint. Serum apoB correlates with the amount of circulating LDL but can also carry other atherogenic lipid particles not reflected when measuring LDL-C. Similarly, non-HDL cholesterol is a more inclusive measurement of atherogenic lipids compared to LDL-C. Analyses of major statin trials report significant decreases in apoB and non-HDL with statin use, though some suggest that statin treatments reduce LDL-C by a greater percentage than apoB and non-HDL [102,103].

Recent data have indicated that apoB and non-HDL cholesterol may be more accurate predictors of ASCVD risk compared to LDL-C in statin-treated patients [104]. One meta-analysis predicts that ASCVD risk assessment strategies centered on non-HDL cholesterol and apoB would prevent 300,000 to 500,000 more ischemic cardiac events over 10 years compared to assessment based on LDL-C [105]. The ACC, AHA, ESC, and National Lipid Association (NLA) already recognize apoB and non-HDL as risk-enhancing factors for ASCVD [78,89,90,106]. In 2015, the NLA released dyslipidemia guidelines specifying both LDL-C and non-HDL cholesterol as primary treatment targets and recommended a treatment goal of <100 mg/dL for non-HDL cholesterol, one of <70 mg/dL for LDL-C, and a secondary optional apoB target of <80 mg/dL for individuals with a very high ASCVD risk [106]. The 2016 ESC/EAS dyslipidemia guidelines similarly specified a treatment target of <100 mg/dL non-HDL cholesterol and <80 mg/dL apoB for patients with a high total cardiovascular risk as a Class IIa recommendation [79]. The 2022 ACC Expert Consensus decision pathway recommended the consideration of nonstatin therapy if non-HDL cholesterol exceeds the LDL-C treatment target by 30 mg/dL (non-HDL cholesterol $\geq$ 85 mg/dL for adults with clinical ASCVD at a very high risk) [82]. Whether non-HDL cholesterol or apoB eventually will replace LDL-C as the primary lipid measure for ASCVD risk remains to be seen and will depend on more robust data and the consideration of testing costs.

8. Conclusions

While the pathophysiology of atherosclerotic plaque formation and its relation to serum levels of LDL-C have long been known, the optimal degree of LDL-C reduction remains an important topic of consideration. While some studies have suggested an increased risk of adverse events, particularly hemorrhagic stroke with aggressive LDL-C reduction, this association has not been consistently demonstrated. Updates to several international guidelines have sourced data from numerous large trials in the last decade to inform new recommendations for lower LDL-C targets that have been demonstrated to confer a further reduction in cardiovascular morbidity and mortality. Guidelines are by nature destined for obsolescence, and emerging evidence aiding in the quantification of ideal LDL-C targets for moderate- and high-risk patients will have important clinical practice implications for years to come.

Author Contributions: J.E.J., K.S.T., A.B. and N.D.W. wrote, reviewed, and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: This review paper did not involve creation or analysis of new data.

Conflicts of Interest: Wong receives research funding through the University of California, Irvine from Novartis, Regeneron, Novo Nordisk, and Lilly and has received consulting fees from Novartis, Kaneka, and Ionis. Barseghian receives research funding through the University of California, Irvine from Novartis and Amgen. The other authors have no relationships to disclose.

References

1. Tsao, C.W.; Aday, A.W.; Almarzooq, Z.I.; Anderson, C.A.M.; Arora, P.; Avery, C.L.; Baker-Smith, C.M.; Beaton, A.Z.; Boehme, A.K.; Buxton, A.E.; et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation* **2023**, *147*, e93–e621. [CrossRef] [PubMed]
2. Vaduganathan, M.; Mensah, G.A.; Turco, J.V.; Fuster, V.; Roth, G.A. The Global Burden of Cardiovascular Diseases and Risk: A Compass for Future Health. *J. Am. Coll. Cardiol.* **2022**, *80*, 2361–2371. [CrossRef] [PubMed]
3. Yusuf, S.; Joseph, P.; Rangarajan, S.; Islam, S.; Mente, A.; Hystad, P.; Brauer, M.; Kutty, V.R.; Gupta, R.; Wielgosz, A.; et al. Modifiable Risk Factors, Cardiovascular Disease, and Mortality in 155,722 Individuals from 21 High-Income, Middle-Income, and Low-Income Countries (PURE): A Prospective Cohort Study. *Lancet Lond. Engl.* **2020**, *395*, 795–808. [CrossRef] [PubMed]
4. Kathiresan, S.; Srivastava, D. Genetics of Human Cardiovascular Disease. *Cell* **2012**, *148*, 1242–1257. [CrossRef] [PubMed]
5. Li, S.; Liu, Z.; Joseph, P.; Hu, B.; Yin, L.; Tse, L.A.; Rangarajan, S.; Wang, C.; Wang, Y.; Islam, S.; et al. Modifiable Risk Factors Associated with Cardiovascular Disease and Mortality in China: A PURE Substudy. *Eur. Heart J.* **2022**, *43*, 2852–2863. [CrossRef] [PubMed]
6. Global Cardiovascular Risk Consortium; Magnussen, C.; Ojeda, F.M.; Leong, D.P.; Alegre-Diaz, J.; Amouyel, P.; Aviles-Santa, L.; De Bacquer, D.; Ballantyne, C.M.; Bernabé-Ortiz, A.; et al. Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality. *N. Engl. J. Med.* **2023**, *389*, 1273–1285. [CrossRef] [PubMed]
7. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group Prevention of Cardiovascular Events and Death with Pravastatin in Patients with Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels. *N. Engl. J. Med.* **1998**, *339*, 1349–1357. [CrossRef]
8. Cholesterol Treatment Trialists' (CTT) Collaborators; Mihaylova, B.; Emberson, J.; Blackwell, L.; Keech, A.; Simes, J.; Barnes, E.H.; Voysey, M.; Gray, A.; Collins, R.; et al. The Effects of Lowering LDL Cholesterol with Statin Therapy in People at Low Risk of Vascular Disease: Meta-Analysis of Individual Data from 27 Randomised Trials. *Lancet Lond. Engl.* **2012**, *380*, 581–590. [CrossRef]
9. Cholesterol Treatment Trialists' (CTT) Collaborators; Kearney, P.M.; Blackwell, L.; Collins, R.; Keech, A.; Simes, J.; Peto, R.; Armitage, J.; Baigent, C. Efficacy of Cholesterol-Lowering Therapy in 18,686 People with Diabetes in 14 Randomised Trials of Statins: A Meta-Analysis. *Lancet Lond. Engl.* **2008**, *371*, 117–125. [CrossRef]
10. Fox, C.S.; Pencina, M.J.; Wilson, P.W.F.; Paynter, N.P.; Vasan, R.S.; D'Agostino, R.B. Lifetime Risk of Cardiovascular Disease among Individuals with and without Diabetes Stratified by Obesity Status in the Framingham Heart Study. *Diabetes Care* **2008**, *31*, 1582–1584. [CrossRef]
11. Kuijpers, P.M.J.C. History in Medicine: The Story of Cholesterol, Lipids and Cardiology. Available online: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-19/history-in-medicine-the-story-of-cholesterol-lipids-and-cardiology (accessed on 4 September 2023).
12. Endo, A. A Historical Perspective on the Discovery of Statins. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* **2010**, *86*, 484–493. [CrossRef]
13. Gofman, J.W. Diet and Lipotrophic Agents in Atherosclerosis. *Bull. N. Y. Acad. Med.* **1952**, *28*, 279–293. [PubMed]
14. Gordon, T.; Castelli, W.P.; Hjortland, M.C.; Kannel, W.B.; Dawber, T.R. High Density Lipoprotein as a Protective Factor against Coronary Heart Disease. The Framingham Study. *Am. J. Med.* **1977**, *62*, 707–714. [CrossRef] [PubMed]
15. Kwiterovich, P.O. The Metabolic Pathways of High-Density Lipoprotein, Low-Density Lipoprotein, and Triglycerides: A Current Review. *Am. J. Cardiol.* **2000**, *86*, 5L–10L. [CrossRef] [PubMed]
16. Low-Density Lipoproteins Cause Atherosclerotic Cardiovascular Disease: Pathophysiological, Genetic, and Therapeutic Insights: A Consensus Statement from the European Atherosclerosis Society Consensus Panel | European Heart Journal | Oxford Academic. Available online: https://academic.oup.com/eurheartj/article/41/24/2313/5735221 (accessed on 4 September 2023).
17. Moore, K.; Sheedy, F.; Fisher, E. Macrophages in Atherosclerosis: A Dynamic Balance. *Nat. Rev. Immunol.* **2013**, *13*, 709–721. [CrossRef]
18. Bentzon, J.F.; Otsuka, F.; Virmani, R.; Falk, E. Mechanisms of Plaque Formation and Rupture. *Circ. Res.* **2014**, *114*, 1852–1866. [CrossRef] [PubMed]
19. Glomset, J.A.; Janssen, E.T.; Kennedy, R.; Dobbins, J. Role of Plasma Lecithin:Cholesterol Acyltransferase in the Metabolism of High Density Lipoproteins. *J. Lipid Res.* **1966**, *7*, 638–648. [CrossRef] [PubMed]
20. Wilson, P.W.; Abbott, R.D.; Castelli, W.P. High Density Lipoprotein Cholesterol and Mortality. The Framingham Heart Study. *Arteriosclerosis* **1988**, *8*, 737–741. [CrossRef]
21. Gordon, D.J.; Probstfield, J.L.; Garrison, R.J.; Neaton, J.D.; Castelli, W.P.; Knoke, J.D.; Jacobs, D.R.; Bangdiwala, S.; Tyroler, H.A. High-Density Lipoprotein Cholesterol and Cardiovascular Disease. Four Prospective American Studies. *Circulation* **1989**, *79*, 8–15. [CrossRef]
22. Liu, C.; Dhindsa, D.; Almuwaqqat, Z.; Ko, Y.-A.; Mehta, A.; Alkhoder, A.A.; Alras, Z.; Desai, S.R.; Patel, K.J.; Hooda, A.; et al. Association Between High-Density Lipoprotein Cholesterol Levels and Adverse Cardiovascular Outcomes in High-Risk Populations. *JAMA Cardiol.* **2022**, *7*, 672–680. [CrossRef]
23. Soutar, A.K.; Naoumova, R.P. Mechanisms of Disease: Genetic Causes of Familial Hypercholesterolemia. *Nat. Clin. Pract. Cardiovasc. Med.* **2007**, *4*, 214–225. [CrossRef] [PubMed]

24. Cuchel, M.; Bruckert, E.; Ginsberg, H.N.; Raal, F.J.; Santos, R.D.; Hegele, R.A.; Kuivenhoven, J.A.; Nordestgaard, B.G.; Descamps, O.S.; Steinhagen-Thiessen, E.; et al. Homozygous Familial Hypercholesterolaemia: New Insights and Guidance for Clinicians to Improve Detection and Clinical Management. A Position Paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur. Heart J.* **2014**, *35*, 2146–2157. [CrossRef] [PubMed]
25. Alonso, R.; Mata, P.; Zambón, D.; Mata, N.; Fuentes-Jiménez, F. Early Diagnosis and Treatment of Familial Hypercholesterolemia: Improving Patient Outcomes. *Expert Rev. Cardiovasc. Ther.* **2013**, *11*, 327–342. [CrossRef] [PubMed]
26. Nordestgaard, B.G.; Chapman, M.J.; Humphries, S.E.; Ginsberg, H.N.; Masana, L.; Descamps, O.S.; Wiklund, O.; Hegele, R.A.; Raal, F.J.; Defesche, J.C.; et al. Familial Hypercholesterolaemia Is Underdiagnosed and Undertreated in the General Population: Guidance for Clinicians to Prevent Coronary Heart Disease: Consensus Statement of the European Atherosclerosis Society. *Eur. Heart J.* **2013**, *34*, 3478–3490. [CrossRef] [PubMed]
27. Onorato, A.; Sturm, A.C. Heterozygous Familial Hypercholesterolemia. *Circulation* **2016**, *133*, e587–e589. [CrossRef] [PubMed]
28. Sjouke, B.; Kusters, D.M.; Kindt, I.; Besseling, J.; Defesche, J.C.; Sijbrands, E.J.G.; Roeters van Lennep, J.E.; Stalenhoef, A.F.H.; Wiegman, A.; de Graaf, J.; et al. Homozygous Autosomal Dominant Hypercholesterolaemia in the Netherlands: Prevalence, Genotype–Phenotype Relationship, and Clinical Outcome. *Eur. Heart J.* **2015**, *36*, 560–565. [CrossRef] [PubMed]
29. Akioyamen, L.E.; Genest, J.; Shan, S.D.; Reel, R.L.; Albaum, J.M.; Chu, A.; Tu, J.V. Estimating the Prevalence of Heterozygous Familial Hypercholesterolaemia: A Systematic Review and Meta-Analysis. *BMJ Open* **2017**, *7*, e016461. [CrossRef]
30. Raal, F.J.; Hovingh, G.K.; Blom, D.; Santos, R.D.; Harada-Shiba, M.; Bruckert, E.; Couture, P.; Soran, H.; Watts, G.F.; Kurtz, C.; et al. Long-Term Treatment with Evolocumab Added to Conventional Drug Therapy, with or without Apheresis, in Patients with Homozygous Familial Hypercholesterolaemia: An Interim Subset Analysis of the Open-Label TAUSSIG Study. *Lancet Diabetes Endocrinol.* **2017**, *5*, 280–290. [CrossRef]
31. Wang, A.; Richhariya, A.; Gandra, S.R.; Calimlim, B.; Kim, L.; Quek, R.G.W.; Nordyke, R.J.; Toth, P.P. Systematic Review of Low-Density Lipoprotein Cholesterol Apheresis for the Treatment of Familial Hypercholesterolemia. *J. Am. Heart Assoc.* **2016**, *5*, e003294. [CrossRef]
32. Moriarty, P.M.; Parhofer, K.G.; Babirak, S.P.; Cornier, M.-A.; Duell, P.B.; Hohenstein, B.; Leebmann, J.; Ramlow, W.; Schettler, V.; Simha, V.; et al. Alirocumab in Patients with Heterozygous Familial Hypercholesterolaemia Undergoing Lipoprotein Apheresis: The ODYSSEY ESCAPE Trial. *Eur. Heart J.* **2016**, *37*, 3588–3595. [CrossRef]
33. Gao, Y.; Shah, L.M.; Ding, J.; Martin, S.S. US Trends in Cholesterol Screening, Lipid Levels, and Lipid-Lowering Medication Use in US Adults, 1999 to 2018. *J. Am. Heart Assoc.* **2023**, *12*, e028205. [CrossRef] [PubMed]
34. Prior, I.A.; Davidson, F.; Salmond, C.E.; Czochanska, Z. Cholesterol, Coconuts, and Diet on Polynesian Atolls: A Natural Experiment: The Pukapuka and Tokelau Island Studies. *Am. J. Clin. Nutr.* **1981**, *34*, 1552–1561. [CrossRef] [PubMed]
35. Raichlen, D.A.; Pontzer, H.; Harris, J.A.; Mabulla, A.Z.P.; Marlowe, F.W.; Josh Snodgrass, J.; Eick, G.; Colette Berbesque, J.; Sancilio, A.; Wood, B.M. Physical Activity Patterns and Biomarkers of Cardiovascular Disease Risk in Hunter-Gatherers. *Am. J. Hum. Biol. Off. J. Hum. Biol. Counc.* **2017**, *29*, e22919. [CrossRef] [PubMed]
36. Barnicot, N.A.; Bennett, F.J.; Woodburn, J.C.; Pilkington, T.R.; Antonis, A. Blood Pressure and Serum Cholesterol in the Hadza of Tanzania. *Hum. Biol.* **1972**, *44*, 87–116. [PubMed]
37. Kaplan, H.; Thompson, R.C.; Trumble, B.C.; Wann, L.S.; Allam, A.H.; Beheim, B.; Frohlich, B.; Sutherland, M.L.; Sutherland, J.D.; Stieglitz, J.; et al. Coronary Atherosclerosis in Indigenous South American Tsimane: A Cross-Sectional Cohort Study. *Lancet* **2017**, *389*, 1730–1739. [CrossRef] [PubMed]
38. Vasunilashorn, S.; Crimmins, E.M.; Kim, J.K.; Winking, J.; Gurven, M.; Kaplan, H.; Finch, C.E. Blood Lipids, Infection, and Inflammatory Markers in the Tsimane of Bolivia. *Am. J. Hum. Biol. Off. J. Hum. Biol. Counc.* **2010**, *22*, 731–740. [CrossRef] [PubMed]
39. Sikand, G.; Handu, D.; Rozga, M.; de Waal, D.; Wong, N.D. Medical Nutrition Therapy Provided by Dietitians Is Effective and Saves Healthcare Costs in the Management of Adults with Dyslipidemia. *Curr. Atheroscler. Rep.* **2023**, *25*, 331–342. [CrossRef]
40. Carson, J.A.S.; Lichtenstein, A.H.; Anderson, C.A.M.; Appel, L.J.; Kris-Etherton, P.M.; Meyer, K.A.; Petersen, K.; Polonsky, T.; Van Horn, L. Dietary Cholesterol and Cardiovascular Risk: A Science Advisory From the American Heart Association. *Circulation* **2020**, *141*, e39–e53. [CrossRef]
41. Schoeneck, M.; Iggman, D. The Effects of Foods on LDL Cholesterol Levels: A Systematic Review of the Accumulated Evidence from Systematic Reviews and Meta-Analyses of Randomized Controlled Trials. *Nutr. Metab. Cardiovasc. Dis. NMCD* **2021**, *31*, 1325–1338. [CrossRef]
42. Altschul, R.; Herman, I.H. Influence of Oxygen Inhalation on Cholesterol Metabolism. *Arch. Biochem. Biophys.* **1954**, *51*, 308–309. [CrossRef]
43. Altschul, R.; Hoffer, A.; Stephen, J.D. Influence of Nicotinic Acid on Serum Cholesterol in Man. *Arch. Biochem. Biophys.* **1955**, *54*, 558–559. [CrossRef] [PubMed]
44. Parsons, W.B.; Achor, R.W.; Berge, K.G.; Mckenzie, B.F.; Barker, N.W. Changes in Concentration of Blood Lipids Following Prolonged Administration of Large Doses of Nicotinic Acid to Persons with Hypercholesterolemia: Preliminary Observations. *Proc. Staff Meet. Mayo Clin.* **1956**, *31*, 377–390. [PubMed]

45. The Lipid Research Clinics Coronary Primary Prevention Trial Results. I. Reduction in Incidence of Coronary Heart Disease. *JAMA* **1984**, *251*, 351–364. [CrossRef] [PubMed]
46. Frick, M.H.; Elo, O.; Haapa, K.; Heinonen, O.P.; Heinsalmi, P.; Helo, P.; Huttunen, J.K.; Kaitaniemi, P.; Koskinen, P.; Manninen, V. Helsinki Heart Study: Primary-Prevention Trial with Gemfibrozil in Middle-Aged Men with Dyslipidemia. Safety of Treatment, Changes in Risk Factors, and Incidence of Coronary Heart Disease. *N. Engl. J. Med.* **1987**, *317*, 1237–1245. [CrossRef]
47. FIELD Study Investigators. Effects of Long-Term Fenofibrate Therapy on Cardiovascular Events in 9795 People with Type 2 Diabetes Mellitus (the FIELD Study): Randomised Controlled Trial. *Lancet* **2005**, *366*, 1849–1861. [CrossRef] [PubMed]
48. ACCORD Study Group. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. *N. Engl. J. Med.* **2010**, *362*, 1563–1574. [CrossRef] [PubMed]
49. Das Pradhan, A.; Glynn, R.J.; Fruchart, J.-C.; MacFadyen, J.G.; Zaharris, E.S.; Everett, B.M.; Campbell, S.E.; Oshima, R.; Amarenco, P.; Blom, D.J.; et al. Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. *N. Engl. J. Med.* **2022**, *387*, 1923–1934. [CrossRef]
50. Canner, P.L.; Berge, K.G.; Wenger, N.K.; Stamler, J.; Friedman, L.; Prineas, R.J.; Friedewald, W. Fifteen Year Mortality in Coronary Drug Project Patients: Long-Term Benefit with Niacin. *J. Am. Coll. Cardiol.* **1986**, *8*, 1245–1255. [CrossRef]
51. Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy. *N. Engl. J. Med.* **2011**, *365*, 2255–2267. [CrossRef]
52. HPS2-THRIVE Collaborative Group; Landray, M.J.; Haynes, R.; Hopewell, J.C.; Parish, S.; Aung, T.; Tomson, J.; Wallendszus, K.; Craig, M.; Jiang, L.; et al. Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients. *N. Engl. J. Med.* **2014**, *371*, 203–212. [CrossRef]
53. Downs, J.R.; Clearfield, M.; Weis, S.; Whitney, E.; Shapiro, D.R.; Beere, P.A.; Langendorfer, A.; Stein, E.A.; Kruyer, W.; Gotto, J.; et al. Primary Prevention of Acute Coronary Events With Lovastatin in Men and Women With Average Cholesterol LevelsResults of AFCAPS/TexCAPS. *JAMA* **1998**, *279*, 1615–1622. [CrossRef]
54. Sacks, F.M.; Pfeffer, M.A.; Moye, L.A.; Rouleau, J.L.; Rutherford, J.D.; Cole, T.G.; Brown, L.; Warnica, J.W.; Arnold, J.M.O.; Wun, C.-C.; et al. The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels | NEJM. Available online: https://www.nejm.org/doi/full/10.1056/nejm199610033351401 (accessed on 5 October 2023).
55. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease | NEJM. Available online: https://www.nejm.org/doi/full/10.1056/NEJMoa050461 (accessed on 5 October 2023).
56. Scandinavian Simvastatin Survival Study Group. Randomised Trial of Cholesterol Lowering in 4444 Patients with Coronary Heart Disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* **1994**, *344*, 1383–1389. [CrossRef]
57. Ridker, P.M.; Danielson, E.; Fonseca, F.A.H.; Genest, J.; Gotto, A.M.; Kastelein, J.J.P.; Koenig, W.; Libby, P.; Lorenzatti, A.J.; MacFadyen, J.G.; et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *N. Engl. J. Med.* **2008**, *359*, 2195–2207. [CrossRef] [PubMed]
58. Cannon, C.P.; Blazing, M.A.; Giugliano, R.P.; McCagg, A.; White, J.A.; Theroux, P.; Darius, H.; Lewis, B.S.; Ophuis, T.O.; Jukema, J.W.; et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N. Engl. J. Med.* **2015**, *372*, 2387–2397. [CrossRef]
59. Cuchel, M.; Meagher, E.A.; Theron, H.; du, T.; Blom, D.J.; Marais, A.D.; Hegele, R.A.; Averna, M.R.; Sirtori, C.R.; Shah, P.K.; et al. Efficacy and Safety of a Microsomal Triglyceride Transfer Protein Inhibitor in Patients with Homozygous Familial Hypercholesterolaemia: A Single-Arm, Open-Label, Phase 3 Study. *Lancet* **2013**, *381*, 40–46. [CrossRef] [PubMed]
60. McGowan, M.P.; Tardif, J.-C.; Ceska, R.; Burgess, L.J.; Soran, H.; Gouni-Berthold, I.; Wagener, G.; Chasan-Taber, S. Randomized, Placebo-Controlled Trial of Mipomersen in Patients with Severe Hypercholesterolemia Receiving Maximally Tolerated Lipid-Lowering Therapy. *PLoS ONE* **2012**, *7*, e49006. [CrossRef] [PubMed]
61. Schwartz, G.G.; Steg, P.G.; Szarek, M.; Bhatt, D.L.; Bittner, V.A.; Diaz, R.; Edelberg, J.M.; Goodman, S.G.; Hanotin, C.; Harrington, R.A.; et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N. Engl. J. Med.* **2018**, *379*, 2097–2107. [CrossRef] [PubMed]
62. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease | NEJM. Available online: https://www.nejm.org/doi/full/10.1056/nejmoa1615664 (accessed on 5 September 2023).
63. Nissen, S.E.; Lincoff, A.M.; Brennan, D.; Ray, K.K.; Mason, D.; Kastelein, J.J.P.; Thompson, P.D.; Libby, P.; Cho, L.; Plutzky, J.; et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N. Engl. J. Med.* **2023**, *388*, 1353–1364. [CrossRef]
64. Raal, F.J.; Rosenson, R.S.; Reeskamp, L.F.; Hovingh, G.K.; Kastelein, J.J.P.; Rubba, P.; Ali, S.; Banerjee, P.; Chan, K.-C.; Gipe, D.A.; et al. Evinacumab for Homozygous Familial Hypercholesterolemia. *N. Engl. J. Med.* **2020**, *383*, 711–720. [CrossRef]
65. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol | NEJM. Available online: https://www.nejm.org/doi/full/10.1056/NEJMoa1912387 (accessed on 5 September 2023).
66. Schwartz, G.G.; Olsson, A.G.; Ezekowitz, M.D.; Ganz, P.; Oliver, M.F.; Waters, D.; Zeiher, A.; Chaitman, B.R.; Leslie, S.; Stern, T.; et al. Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary SyndromesThe MIRACL Study: A Randomized Controlled Trial. *JAMA* **2001**, *285*, 1711–1718. [CrossRef]
67. Robinson, J.G.; Farnier, M.; Krempf, M.; Bergeron, J.; Luc, G.; Averna, M.; Stroes, E.S.; Langslet, G.; Raal, F.J.; El Shahawy, M.; et al. Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events. *N. Engl. J. Med.* **2015**, *372*, 1489–1499. [CrossRef] [PubMed]

68. Nicholls, S.J.; Puri, R.; Anderson, T.; Ballantyne, C.M.; Cho, L.; Kastelein, J.J.P.; Koenig, W.; Somaratne, R.; Kassahun, H.; Yang, J.; et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA* **2016**, *316*, 2373–2384. [CrossRef] [PubMed]
69. Nissen, S.E.; Menon, V.; Nicholls, S.J.; Brennan, D.; Laffin, L.; Ridker, P.; Ray, K.K.; Mason, D.; Kastelein, J.J.P.; Cho, L.; et al. Bempedoic Acid for Primary Prevention of Cardiovascular Events in Statin-Intolerant Patients. *JAMA* **2023**, *330*, 131–140. [CrossRef] [PubMed]
70. Ray, K.K.; Raal, F.J.; Kallend, D.G.; Jaros, M.J.; Koenig, W.; Leiter, L.A.; Landmesser, U.; Schwartz, G.G.; Lawrence, D.; Friedman, A.; et al. Inclisiran and Cardiovascular Events: A Patient-Level Analysis of Phase III Trials. *Eur. Heart J.* **2023**, *44*, 129–138. [CrossRef] [PubMed]
71. Ernst, N.D.; Cleeman, J.; Mullis, R.; Sooter-Bochenek, J.; Horn, L.V. The National Cholesterol Education Program: Implications for Dietetic Practitioners from the Adult Treatment Panel Recommendations. *J. Am. Diet. Assoc.* **1988**, *88*, 1401–1409. [CrossRef]
72. Grundy, S.M.; Bilheimer, D.; Chait, A.; Clark, L.T.; Denke, M.; Havel, R.J.; Hazzard, W.R.; Hulley, S.B.; Hunninghake, D.B.; Kreisberg, R.A.; et al. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* **1993**, *269*, 3015–3023. [CrossRef]
73. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* **2001**, *285*, 2486–2497. [CrossRef]
74. De Backer, G.; Ambrosioni, E.; Borch-Johnsen, K.; Brotons, C.; Cifkova, R.; Dallongeville, J.; Ebrahim, S.; Faergeman, O.; Graham, I.; Mancia, G.; et al. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur. Heart J.* **2003**, *24*, 1601–1610. [CrossRef]
75. Grundy, S.M.; Cleeman, J.I.; Merz, C.N.B.; Brewer, H.B.; Clark, L.T.; Hunninghake, D.B.; Pasternak, R.C.; Smith, S.C.; Stone, N.J. Coordinating Committee of the National Cholesterol Education Program Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J. Am. Coll. Cardiol.* **2004**, *44*, 720–732. [CrossRef]
76. AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update|Circulation. Available online: https://www.ahajournals.org/doi/full/10.1161/circulationaha.106.174516 (accessed on 5 September 2023).
77. Graham, I.; Atar, D.; Borch-Johnsen, K.; Boysen, G.; Burell, G.; Cifkova, R.; Dallongeville, J.; De Backer, G.; Ebrahim, S.; Gjelsvik, B.; et al. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: Executive Summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by Representatives of Nine Societies and by Invited Experts). *Eur. Heart J.* **2007**, *28*, 2375–2414. [CrossRef]
78. European Association for Cardiovascular Prevention & Rehabilitation; Reiner, Z.; Catapano, A.L.; De Backer, G.; Graham, I.; Taskinen, M.-R.; Wiklund, O.; Agewall, S.; Alegria, E.; Chapman, M.J.; et al. ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur. Heart J.* **2011**, *32*, 1769–1818. [CrossRef] [PubMed]
79. Catapano, A.L.; Graham, I.; De Backer, G.; Wiklund, O.; Chapman, M.J.; Drexel, H.; Hoes, A.W.; Jennings, C.S.; Landmesser, U.; Pedersen, T.R.; et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur. Heart J.* **2016**, *37*, 2999–3058. [CrossRef] [PubMed]
80. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **2019**, *139*, e1082–e1143. [CrossRef] [PubMed]
81. Wilkinson, M.J.; Lepor, N.E.; Michos, E.D. Evolving Management of Low-Density Lipoprotein Cholesterol: A Personalized Approach to Preventing Atherosclerotic Cardiovascular Disease Across the Risk Continuum. *J. Am. Heart Assoc.* **2023**, *12*, e028892. [CrossRef] [PubMed]
82. Writing Committee; Lloyd-Jones, D.M.; Morris, P.B.; Ballantyne, C.M.; Birtcher, K.K.; Covington, A.M.; DePalma, S.M.; Minissian, M.B.; Orringer, C.E.; Smith, S.C.; et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. *J. Am. Coll. Cardiol.* **2022**, *80*, 1366–1418. [CrossRef] [PubMed]
83. Turpie, A.G.G. Burden of Disease: Medical and Economic Impact of Acute Coronary Syndromes. *Am. J. Manag. Care* **2006**, *12*, S430–S434. [PubMed]
84. Roffi, M.; Patrono, C.; Collet, J.-P.; Mueller, C.; Valgimigli, M.; Andreotti, F.; Bax, J.J.; Borger, M.A.; Brotons, C.; Chew, D.P.; et al. 2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* **2016**, *37*, 267–315. [CrossRef]

85. Koskinas, K.C.; Windecker, S.; Pedrazzini, G.; Mueller, C.; Cook, S.; Matter, C.M.; Muller, O.; Häner, J.; Gencer, B.; Crljenica, C.; et al. Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients With Acute Coronary Syndromes (EVOPACS). *J. Am. Coll. Cardiol.* **2019**, *74*, 2452–2462. [CrossRef]
86. Puri, R.; Mehta, V.; Duell, P.B.; Iyengar, S.S.; Yusuf, J.; Dalal, J.; Narasingan, S.N.; Kalra, D.; Kapoor, A.; Pradhan, A.; et al. Evidence for Intensive LDL-C Lowering for Acute Coronary Syndrome: Recommendations from the Lipid Association of India. *J. Clin. Lipidol.* **2022**, *16*, 261–271. [CrossRef]
87. Stone, N.J.; Robinson, J.G.; Lichtenstein, A.H.; Bairey Merz, C.N.; Blum, C.B.; Eckel, R.H.; Goldberg, A.C.; Gordon, D.; Levy, D.; Lloyd-Jones, D.M.; et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* **2014**, *63*, 2889–2934. [CrossRef]
88. Jellinger, P.S.; Handelsman, Y.; Rosenblit, P.D.; Bloomgarden, Z.T.; Fonseca, V.A.; Garber, A.J.; Grunberger, G.; Guerin, C.K.; Bell, D.S.H.; Mechanick, J.I.; et al. American association of clinical endocrinologists and american college of endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr. Pract. Off. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol.* **2017**, *23*, 1–87. [CrossRef] [PubMed]
89. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; et al. 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk. *Eur. Heart J.* **2020**, *41*, 111–188. [CrossRef] [PubMed]
90. Lipid Association of India Expert Consensus Statement on Management of Dyslipidemia in Indians 2020: Part III—PubMed. Available online: https://pubmed.ncbi.nlm.nih.gov/33350610/ (accessed on 6 October 2023).
91. Rong, S.; Li, B.; Chen, L.; Sun, Y.; Du, Y.; Liu, B.; Robinson, J.G.; Bao, W. Association of Low-Density Lipoprotein Cholesterol Levels with More than 20-Year Risk of Cardiovascular and All-Cause Mortality in the General Population. *J. Am. Heart Assoc. Cardiovasc. Cerebrovasc. Dis.* **2022**, *11*, e023690. [CrossRef] [PubMed]
92. Sung, K.-C.; Huh, J.H.; Ryu, S.; Lee, J.-Y.; Scorletti, E.; Byrne, C.D.; Kim, J.Y.; Hyun, D.S.; Ko, S.-B. Low Levels of Low-Density Lipoprotein Cholesterol and Mortality Outcomes in Non-Statin Users. *J. Clin. Med.* **2019**, *8*, 1571. [CrossRef] [PubMed]
93. Penson, P.E.; Long, D.L.; Howard, G.; Toth, P.P.; Muntner, P.; Howard, V.J.; Safford, M.M.; Jones, S.R.; Martin, S.S.; Mazidi, M.; et al. Associations between Very Low Concentrations of Low Density Lipoprotein Cholesterol, High Sensitivity C-Reactive Protein, and Health Outcomes in the Reasons for Geographical and Racial Differences in Stroke (REGARDS) Study. *Eur. Heart J.* **2018**, *39*, 3641–3653. [CrossRef] [PubMed]
94. Wang, X.; Dong, Y.; Qi, X.; Huang, C.; Hou, L. Cholesterol Levels and Risk of Hemorrhagic Stroke: A Systematic Review and Meta-Analysis. *Stroke* **2013**, *44*, 1833–1839. [CrossRef] [PubMed]
95. Ma, C.; Gurol, M.E.; Huang, Z.; Lichtenstein, A.H.; Wang, X.; Wang, Y.; Neumann, S.; Wu, S.; Gao, X. Low-Density Lipoprotein Cholesterol and Risk of Intracerebral Hemorrhage. *Neurology* **2019**, *93*, e445–e457. [CrossRef] [PubMed]
96. Rist, P.M.; Buring, J.E.; Ridker, P.M.; Kase, C.S.; Kurth, T.; Rexrode, K.M. Lipid Levels and the Risk of Hemorrhagic Stroke among Women. *Neurology* **2019**, *92*, e2286–e2294. [CrossRef]
97. Benn, M.; Nordestgaard, B.G.; Grande, P.; Schnohr, P.; Tybjaerg-Hansen, A. PCSK9 R46L, Low-Density Lipoprotein Cholesterol Levels, and Risk of Ischemic Heart Disease: 3 Independent Studies and Meta-Analyses. *J. Am. Coll. Cardiol.* **2010**, *55*, 2833–2842. [CrossRef]
98. Giugliano, R.P.; Mach, F.; Zavitz, K.; Kurtz, C.; Im, K.; Kanevsky, E.; Schneider, J.; Wang, H.; Keech, A.; Pedersen, T.R.; et al. Cognitive Function in a Randomized Trial of Evolocumab. *N. Engl. J. Med.* **2017**, *377*, 633–643. [CrossRef]
99. Giugliano, R.P.; Wiviott, S.D.; Blazing, M.A.; De Ferrari, G.M.; Park, J.-G.; Murphy, S.A.; White, J.A.; Tershakovec, A.M.; Cannon, C.P.; Braunwald, E. Long-Term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol. *JAMA Cardiol.* **2017**, *2*, 547–555. [CrossRef] [PubMed]
100. Goldstein, L.B.; Toth, P.P.; Dearborn-Tomazos, J.L.; Giugliano, R.P.; Hirsh, B.J.; Peña, J.M.; Selim, M.H.; Woo, D. Aggressive LDL-C Lowering and the Brain: Impact on Risk for Dementia and Hemorrhagic Stroke: A Scientific Statement From the American Heart Association. *Arterioscler. Thromb. Vasc. Biol.* **2023**, *43*, e404–e442. [CrossRef] [PubMed]
101. Wiviott, S.D.; Cannon, C.P.; Morrow, D.A.; Ray, K.K.; Pfeffer, M.A.; Braunwald, E. PROVE IT-TIMI 22 Investigators Can Low-Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low Low-Density Lipoprotein with Intensive Statin Therapy: A PROVE IT-TIMI 22 Substudy. *J. Am. Coll. Cardiol.* **2005**, *46*, 1411–1416. [CrossRef] [PubMed]
102. Ballantyne, C.M.; Raichlen, J.S.; Cain, V.A. Statin Therapy Alters the Relationship Between Apolipoprotein B and Low-Density Lipoprotein Cholesterol and Non–High-Density Lipoprotein Cholesterol Targets in High-Risk Patients: The MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin TherapY II) Trial. *J. Am. Coll. Cardiol.* **2008**, *52*, 626–632. [CrossRef] [PubMed]
103. Ballantyne, C.M.; Andrews, T.C.; Hsia, J.A.; Kramer, J.H.; Shear, C.; ACCESS Study Group. Atorvastatin Comparative Cholesterol Efficacy and Safety Study Correlation of Non-High-Density Lipoprotein Cholesterol with Apolipoprotein B: Effect of 5 Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors on Non-High-Density Lipoprotein Cholesterol Levels. *Am. J. Cardiol.* **2001**, *88*, 265–269. [CrossRef] [PubMed]
104. Johannesen, C.D.L.; Mortensen, M.B.; Langsted, A.; Nordestgaard, B.G. Apolipoprotein B and Non-HDL Cholesterol Better Reflect Residual Risk Than LDL Cholesterol in Statin-Treated Patients. *J. Am. Coll. Cardiol.* **2021**, *77*, 1439–1450. [CrossRef] [PubMed]

105. Sniderman, A.D.; Williams, K.; Contois, J.H.; Monroe, H.M.; McQueen, M.J.; de Graaf, J.; Furberg, C.D. A Meta-Analysis of Low-Density Lipoprotein Cholesterol, Non-High-Density Lipoprotein Cholesterol, and Apolipoprotein B as Markers of Cardiovascular Risk. *Circ. Cardiovasc. Qual. Outcomes* **2011**, *4*, 337–345. [CrossRef] [PubMed]
106. Jacobson, T.A.; Ito, M.K.; Maki, K.C.; Orringer, C.E.; Bays, H.E.; Jones, P.H.; McKenney, J.M.; Grundy, S.M.; Gill, E.A.; Wild, R.A.; et al. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1—Executive Summary. *J. Clin. Lipidol.* **2014**, *8*, 473–488. [CrossRef]

Journal of
Clinical Medicine

MDPI

Review

Comparison of Current International Guidelines for the Management of Dyslipidemia

Sevda Aygun * and Lale Tokgozoglu

Department of Cardiology, Hacettepe University Faculty of Medicine, 06100 Ankara, Turkey
* Correspondence: aygunsevda@gmail.com

Abstract: The dyslipidemia guidelines of the three major societies have been revised recently in light of new evidence. LDL-C is the primary target in the ESC, AHA/ACC/Multisociety and Canadian Cardiovascular Society (CCS) guidelines. These guidelines uniformly recommend intensifying lipid-lowering treatment with increased risk; however, the risk estimation systems are different across the guidelines. The ESC guidelines have LDL-C goals which have become more stringent over the years and advocate the use of statin and, if necessary, non-statin therapies to obtain these goals. AHA/ACC/Multisociety guidelines have LDL-C thresholds and advocate combination therapy less liberally and for selected patients. All three guidelines acknowledge the importance of shared decision making. Despite some divergent approaches and recommendations, the main principles and messages are the same across the guidelines. To combat the epidemic of cardiovascular disease, our focus should be not on the differences but on implementing the guidelines in our region.

Keywords: dyslipidemia; risk management; secondary prevention; primary prevention

Citation: Aygun, S.; Tokgozoglu, L. Comparison of Current International Guidelines for the Management of Dyslipidemia. *J. Clin. Med.* **2022**, *11*, 7249. https://doi.org/10.3390/jcm11237249

Academic Editor: Nathan Wong

Received: 23 October 2022
Accepted: 2 December 2022
Published: 6 December 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Despite modern therapies, atherosclerotic cardiovascular disease (ASCVD) is still the leading cause of mortality in most parts of the world [1]. The retention of apoprotein B-containing lipoproteins is the main driver of the initiation and progression of atherosclerotic plaques [2]. Lowering atherogenic lipids can change the trajectory of the disease favorably and prevent CV events. In light of new evidence on the causality of apoprotein B-containing lipoproteins and, mainly, LDL-C, guidelines for the management of dyslipidemia have been updated. The aim of this article is to systematically compare the 2018 AHA/ACC/Multisociety (MS) Blood cholesterol management guideline [3], the 2021 ESC Prevention of CV Disease Guidelines, endorsed by 12 European Societies [4], and the 2021 Canadian Cardiovascular Society's (CCS) [5] management of dyslipidemia for cardiovascular disease guidelines for basic approaches to dyslipidemias and the prevention of ASCVD.

2. Risk Estimation Tools and Definition of Risk Categories

All three guidelines base the intensity of their recommendations on the degree of risk. However, the best risk estimation system is the one that is derived from the population it is going to be used on. For this reason, guidelines differ in their risk calculation systems. The ESC guidelines define patients with ASCVD, diabetes mellitus (DM), chronic kidney disease (CKD) and individuals with specific risk factors as high and very high-risk groups automatically. Individuals who do not have these characteristics are considered as apparently healthy people, and management is determined according to risk estimation by the SCORE system. The most recent ESC guidelines have updated the risk stratification. SCORE2 is a new algorithm which is derived, calibrated and validated to predict 10-year risk of first-onset CVD in European populations, overcoming some of the limitations posed by the previous SCORE system. The previous SCORE only calculated the 10-year risk

of fatal events, whereas SCORE2 calculates the 10-year risk of total CV events. To improve the accuracy of risk prediction in adults over the age of 65, the new SCORE2-Older Persons (SCORE2-OP) model, which is competing-risk-adjusted, is recommended. Management is determined according to age, risk score and region. According to CVD mortality rates published by the WHO, regions are defined into four groups as low-risk countries, moderate-risk countries, high-risk countries, and very high-risk countries (Table 1).

Table 1. Classification of countries according to risk levels described by the WHO.

Risk Categories	Countries
Low-risk	Belgium, Denmark, France, Israel, Luxembourg, Norway, Spain, the Netherlands, the United Kingdom, Switzerland
Moderate-risk	Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Portugal, San Marino, Slovenia, and Sweden
High-risk	Albania, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Kazakhstan, Poland, Slovakia, and Turkey
Very high-risk	Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Republic of Moldova, Romania, Russian Federation, Serbia, Syria, The Former Yugoslav Republic (Macedonia), Tunisia, Ukraine, and Uzbekistan

In the AHA/ACC/MS guidelines, risk scores are calculated with Pooled Cohort Equations (PCEs). PCEs calculate the 10-year risk of developing ASCVD by including non-fatal myocardial infarction or coronary heart disease (CHD) death and fatal or non-fatal stroke, among people free from ASCVD.

The CCS uses the Framingham Risk Score (FRS) system as a risk assessment tool and divides individuals into three groups: low-risk (FRS < 10%), intermediate-risk (FRS 10–19.9%) and high-risk (FRS ≥ 20%), and bases recommendations according to the risk level. The risk stratification methods are summarized in Table 2.

Table 2. Comparison of risk categories according to guidelines.

	ESC GUIDELINES	AHA/ACC/MS GUIDELINES	CCS GUIDELINES
RISK CATEGORIES	10-year SCORE2/SCORE2-OP percentages (fatal and non-fatal CVD risk) **<50 years:** <2.5%, 2.5–7.5%, ≥7.5% **50–69 years:** <5%, 5–10%, ≥10% **≥70 years:** <7.5%, 7.5–15%, ≥15% (Low-to-moderate-risk, high-risk and very high-risk, respectively)	10-year risk ASCVD percentages (fatal and non-fatal ASCVD) **High:** ≥20% **Intermediate:** ≥7.5–<20% **Borderline:** 5–<7.5% **Low:** <5%	FRS 10-year CHD RİSK **Low-risk** FRS: <10% **Intermediate-risk** FRS: 10–19.9% or LDL-C ≥ 3.5 mmol/L or Non-HDL-C ≥ 4.2 mmol/L or ApoB ≥ 1.05 g/L or Men ≥ 50 and women ≥ 60 years with additional risk factors or with presence of other risk modifiers **High-risk** FRS: ≥ 20%

3. Risk Modifiers and Risk-Enhancing Factors

Risk-modifying/enhancing factors are important in making shared decisions regarding treatment initiation and the intensification of recommendations, especially in borderline and low-to-intermediate-risk adults. While there are divergent approaches in the ESC, AHA/ACC/MS and CCS guidelines, the basic approach is to clarify the patient's current risk level and refine recommendations according to risk modifiers (Table 3).

Table 3. Risk-modifying and enhancing factors.

ESC Risk Modifiers	AHA/ACC/MS Risk-Enhancing Factors	CCS Risk Modifiers
Family history of premature CVD (men: <55 years and women: <60 years)	Family history of premature ASCVD (males: <55 years; females: <65 years)	Family history of premature coronary artery disease
Obesity and central obesity	ABI < 0.9	Abdominal obesity
Physical inactivity Social deprivation and psychosocial stress, including vital exhaustion.	High-risk race/ethnicities (e.g., South Asian ancestry)	Physical inactivity Psychosocial factors
• Chronic immune-mediated inflammatory disorder. • Treatment for human immunodeficiency virus infection. • Major psychiatric disorders • Left ventricular hypertrophy. • Chronic kidney disease. • Atrial fibrillation • Obstructive sleep apnea syndrome • Non-alcoholic fatty liver disease • Migraine with aura	• Metabolic syndrome • Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L]) • Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL) optimally, three determinations • Chronic kidney disease • Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS	Excessive alcohol consumption Coronary Artery Calcium score [CAC] > 0 Agatston Units (AUs)
Sex-specific conditions: Pregnancy-related hypertension Preeclampsia/Eclampsia Erectile dysfunction	Biomarkers • Elevated high-sensitivity C-reactive protein (≥2.0 mg/L) • Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a) • Elevated ApoB ≥ 130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥ 130 mg/dL corresponds to an LDL-C ≥ 160 mg/dL and constitutes a risk-enhancing factor.	Biomarkers • High-sensitivity C-reactive protein ≥ 2.0 Mmol/L • High Lipoprotein(A) [Lp(a)] ≥ 50 mg/dL [≥100 Nmol/L]
	Sex-specific Conditions: Premature menopause (before age of 40) Pregnancy-associated conditions (preeclampsia, eclampsia)	Sex-pecific conditions: Pregnancy-related hypertension Preeclampsia/eclampsia

Recent studies have demonstrated the importance of the Coronary Artery Calcium (CAC) score to improve risk prediction. The ESC guideline states that CAC scoring may be considered to improve risk classification around treatment decision thresholds. Plaque detection by carotid ultrasound is an alternative when CAC scoring is unavailable or not feasible. AHA/ACC/MS guidelines give recommendations for the possible use of the CAC score if the decision about statin treatment is uncertain in intermediate and borderline-risk adults. If the CAC score is above 100, it is reasonable to initiate statin treatment. If the CAC score is 1 to 99, it is reasonable to use statins in individuals ≥ 55 years. If the CAC score is zero, there is no need to use statins (unless smoking, premature CVD history and DM are present), but reassessment is suggested in 5–10 years.

The CCS suggest that the CAC score might be considered for two major situations: risk classification of asymptomatic adults ≥ 40 years in the intermediate-risk group if the treatment plan is uncertain and for low-risk individuals who have a family history of premature ASCVD events to reevaluate the risk level. It is not recommended to use the CAC score for patients already under statin treatment and asymptomatic low-risk individuals.

Population studies have shown that some of ethnic groups have a higher risk of CVD events [6]. The ESC guidelines recommend using a country and ethnicity-specific risk calculator. Because of the variation of risk levels between ethnic groups, multiplying the calculated risk level by 1.3 for South Asians, 1.1 for other Asians and by 0.7 for Black African and Chinese populations is recommended. ACC/AHA/MS guidelines underline some racial/ethnic issues and differences between Asian Americans, Hispanic/Latino Americans and Black/African Americans and recommend considering the different ethnic features of individuals to make a decision in treatment and when adjusting the intensity of statin treatment. The CCS recommends earlier screening for some specific groups such as South Asians. It also emphasizes the extremely high level of Lp(a) in the South Asian and Latin American populations.

4. Lipid Measurement

All guidelines recommend LDL-C level measurements as the primary lipid analysis method and recommends using the non-fasting plasma lipid profile for screening in the general population. However, LDL-C levels may be miscalculated in non-fasting measurements in groups who have high triglyceride (TG) levels. For this reason, fasting or the direct measurement of LDL-C is recommended for individuals with high TG levels (especially patients with metabolic syndrome, diabetes mellitus or familial hypertriglyceridemia) [7,8]. AHA/ACC/MS guidelines emphasize fasting lipid profile measurement, especially if TG levels are 400≥mg/dL (or ≥4.5 mmol/L).

Patients with diabetes mellitus, obesity or metabolic syndrome have a residual lipid risk, which can be captured by non-HDL-C and ApoB measurements [8]. The ESC recommends non-HDL-C and ApoB measurements in all individuals with high TG levels, diabetes mellitus, obesity and metabolic syndrome. Conversely, AHA/ACC/MS guidelines do not routinely recommend ApoB measurement because of cost-effectiveness issues. It emphasizes the importance of ApoB measurement, especially in individuals with TG $\geq$ 200 mg/dL. The CCS guidelines recommend non-HDL-C or ApoB measurement if LDL-C $\geq$ 1.5 mmol/L.

The Lp(a) level is a genetically determined, causal and prevalent risk factor for ASCVD. It has been shown that individuals with an Lp(a) level > 180 mg/dL (>430 nmol/L) have a similar ASCVD event risk as individuals with heterozygous FH [9,10]. The ESC guidelines recommend Lp(a) measurements once in each individual's lifetime. Lp(a) measurement is especially recommended in individuals with a family history of premature ASCVD. Lp(a) levels may also be used to define and reclassify patients in moderate-to-high-risk patients. The AHA/ACC/MS guidelines recommend Lp(a) measurement in individuals with a family history or a history of premature ASCVD and consider a Lp(a) level $\geq$ 50 mg/dL (125 nmol/L) as a risk-enhancing factor. The CCS guidelines also recommend measuring Lp(a) at least once in a lifetime.

5. Primary Prevention

All three guidelines highlight the importance of lifestyle and a heart-healthy diet as the first step in prevention in all individuals. All guidelines also emphasize the importance of being physically active and avoiding a sedentary life. Individuals are encouraged to exercise at a moderate-to-high intensity several times a week. The ESC guidelines also recommend performing resistance exercises 2–3 days a week to reduce all-cause mortality.

The causality of LDL-C is well established; therefore, it is the primary target of therapy in all guidelines [11]. Since the publication of previous guidelines, large RCTs with combination therapy have shown that lowering LDL-C below 70 mg/dL leads to better CV outcomes in high-risk patients. For this reason, LDL-C goals have become more stringent in the recent ESC guidelines. In addition, Lp(a) measurement is recommended once in a lifetime for all individuals. For a primary prevention in individuals categorized as ''the apparently healthy people", the ESC guidelines personalize therapy according to the age and SCORE2 risk of the patient and risk modifiers. The ESC guidelines recommend targeting the

ultimate goals of ≥50% LDL-C reduction from baseline and an LDL-C goal of <1.4 mmol/L (55 mg/dL) in very high-risk groups, <1.8 mmol/L (<70 mg/dL) in high-risk groups, a goal of <2.6 mmol/L (<100 mg/dL) in moderate-risk groups and a goal of <3.0 mmol/L (<116 mg/dL) in low-risk groups. The guidelines recommend a stepwise approach, with consideration of CVD risk, treatment benefit, comorbidities, frailty and patient preferences. First-line treatment should be a high-intensity statin prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group. If goals are not achieved, despite maximally tolerated statin dosage, a combination of ezetimibe is recommended. For the very high-risk group, if LDL-C goals are not achieved under statin and ezetimibe treatment, PCSK9 inhibitors are recommended. The ESC guidelines recommend treatment intensification until goals are reached. The ESC guidelines recommend lower LDL-C levels than the recommended treatment thresholds in the AHA/ACC/MS and CCS guidelines. These goals have been determined from the recent trials with combination therapy showing further benefit when LDL-C is lowered beyond 70 mg/dL.

The AHA/ACC/MS and CCS guidelines recommend starting statin treatment and intensification according to LDL-C thresholds. In the AHA/ACC/MS guidelines, lifestyle changes and healthy behaviors are recommended in low and borderline-risk groups. In the 2018 ACC/AHA/MS guidelines, the statin-benefit groups remain the same as the previous guidelines, but for secondary prevention, the LDL-C threshold has been defined as ≥70 mg/dL, where the addition of a non-statin lipid-lowering drug to statin treatment is recommended. The new guidelines place emphasis on shared decision making and using the calcium score to aid decisions. In the intermediate-risk group, statin initiation is recommended and an LDL-C reduction of 30–49% is targeted. If the patient is in the gray zone for treatment decisions, a Coronary Artery Calcium (CAC) score assessment is reasonable to use for the determination of statin therapy. Moderate-intensity statin therapy is recommended in adults 40 to 75 years of age with diabetes mellitus or LDL-C ≥ 70 to <190 mg/dL. In high-risk groups and in those with an LDL-C level ≥ 190 mg/dL, high-intensity statin initiation is recommended and an LDL-C reduction of ≥50% is targeted. An assessment of response and adherence to treatment after 4–12 weeks and 3–12 months following statin initiation is recommended and, according to the evaluation, treatment intensification is recommended, if needed. Ezetimibe or PCSK9 inhibitors are suggested in a manner of cost effectiveness and shared decision making with patients. In patients at a very high-risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) and patients with severe primary hypercholesterolemia on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is deemed reasonable.

The 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering provides additional guidance on the newer non-statin therapies [12]. For adults with ASCVD at very high-risk, if the patient does not have a ≥50% reduction or LDL-C < 55 mg/dL or non-HDL-C<85 mg/dL, despite maximally tolerated statin therapy, ezetimibe and/or PCSK9 inhibitors are recommended as first-line non-statin agents. As the second line of treatment, bempedoic acid and/or inclisiran may be considered. Agents that may be used to treat HoFH under care of a lipid specialist are evinacumab, lomitapide or LDL apheresis.

In primary prevention, if LDL-C is still ≥190 mg/dL, despite maximally tolerated statins, to achieve a ≥50% LDL-C reduction and LDL-C < 100 mg /dL or non-HDL-C < 130 mg/dL, non-statin agents, ezetimibe and/or PCSK-9 inhibitors are the first line of treatment, bempedoic acid or inclisiran are the second line and evinacumab, lomitapide and/or LDL apheresis the third line, respectively.

In adults without ASCVD or diabetes with an LDL-C level of 70–189 mg/dL, and if the patient has a ≥20% risk, and in adults with diabetes without ASCVD and with an LDL-C < 190 mg/dL, if a ≥50%reduction in the LDL-C level or LDL-C < 70 mg/dL or non-HDL-C < 100 mg/dL are not achieved, despite statin therapy, ezetimibe addition may be considered. The conditions requiring treatment intensification with non-statin agents are shown in Table 4.

Table 4. LDL-C goals and thresholds for beginning combination therapy with non-statin agents.

	PRIMARY PREVENTION	SECONDARY PREVENTION
ESC Guidelines	Despite maximally tolerated statin dosage, ≥50% LDL-C reduction from baseline and LDL-C goal of <1.4 mmol/L (55 mg/dL) in very high-risk groups, <1.8 mmol/L (<70 mg/dL) in high-risk groups, <2.6 mmol/L (<100 mg/dL) in moderate-risk groups <3.0 mmol/L (<116 mg/dL) in low-risk groups is not achieved, treatment intensification with non-statin agents is recommended.	If LDL-C ≥ 55 mg/dL, despite maximally tolerated statin dosage, addition of ezetimibe or PCSK9 inhibitors after ezetimibe initiation is recommended.
AHA/ACC/MS Guideline *	In adults without ASCVD or diabetes with LDL-C level of 70–189 mg/dL, if patient has ≥20% risk, and In adults with diabetes without ASCVD and with LDL-C < 190 mg/dL, if ≥50% reduction in LDL-C level or LDL-C < 70 mg/dL or non-HDL-C < 100 mg/dL are not achieved, despite statin therapy, ezetimibe additon may be reasonable. In adults without ASCVD and LDL-C ≥ 190 mg/dL, if ≥50% reduction in LDL-C level or LDL-C < 100 mg/dL or non-HDL-C < 130 mg/dL are not achieved, despite statin therapy, non-statin agents are recommended.	Patients with ASCVD and at very high-risk adults with ASCVD at very high-risk, if ≥50% reduction of LDL-C level or LDL-C < 55 mg/dL are not achieved despite statin therapy, non-statin agents are recommended. For patients with ASCVD but without very high-risk, if ≥50% reduction of LDL-C level or LDL-C < 70 mg/dL are not achieved despite statin therapy non-statin agents are recommended.
CCS Guideline	Despite maximally tolerated statin dose, LDL-C ≥ 2.0 mmol/L or ApoB ≥ 0.8 g/L or Non-HDL-C ≥ 2.6 mmol/L, ezetimibe and/or PCSK-9 inhibitors are recommended; Despite maximally tolerated statin dose with or without ezetimibe, for patients with heterozygous FH without clinical ASCVD, if LDL-C ≥ 2.5 mmol/L or <50% reduction from baseline; or ApoB ≥ 0.85 g/L or non-HDL-C ≥ 3.2 mmol/L) PCSK-9 inhibitors are recommended.	Despite maximally tolerated statin dose, LDL-C ≥ 1.8–2.2 mmol/L or ApoB ≥ 0.7–0.8 g/dL or Non-HDL-C ≥ 2.4–2.9 mmol/L PCSK9 inhibitors with or without ezetimibe ar recommended. Despite maximally tolerated statin dose, LDL-C ≥ 2.2 mmol/L or ApoB ≥ 0.8 g/L or Non-HDL-C ≥ 2.9 mmol/L, PCSK9 inhibitors with or without ezetimibe are recommended.

* Based on the 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk.

Screening recommendations have continued in the CCS guidelines, recommending blood cholesterol screening in all individuals aged ≥40 years or with risk factors. Thresholds have been defined for treatment initiation and intensification. CAC score measurement is recommended for screening in asymptomatic and intermediate-risk patients ≥40-years-old. In the CCS guidelines, for primary prevention, patients are divided into three groups according to the FRS. In low-risk groups, lifestyle changes are first-line recommendations, and statin initiation is not recommended. Individuals without high-risk conditions who may benefit from statin therapy are the following: (a) LDL-C ≥ 5.0 mmol/L or Apo B ≥ 1.45 g/L or non-HDL-C ≥ 5.8 mmol/L, (b) FRS 5–9.9% with LDL-C ≥ 3.5 mmol/L or non-HDL-C ≥ 4.2 mmol/L or ApoB ≥ 1.05 g/L, with additional risk modifiers such as Lp(a) ≥ 50 mg/dL, CAC > 0 AU and familial or genetic dyslipidemias. Statin treatment is recommended along with lifestyle changes for intermediate-risk individuals (FRS 10–19%) with LDL-C ≥ 3.5 mmol/L and high-risk patients (FRS ≥ 20%). Despite maximally tolerated statin dose, if LDL-C ≥ 2.0 mmol/L, or ApoB ≥ 0.8 g/L or non-HDL-C > 2.6 mmol/L are present, treatment intensification is recommended with ezetimibe.

All guidelines agree that therapy needs to be intensified in patients as the risk increases. The major difference between these guidelines is that there are defined LDL-C goals in the European guidelines, which are more stringent for patients at high risk or above compared

to other guidelines. All guidelines agree that statins are recommended as the first-line treatment, and non-statin treatment (ezetimibe and PCSK-9 inhibitors) are the second-line treatment. The AHA/ACC/MS and CCS guidelines recommend cost-effective approaches for treatment intensification in primary prevention.

6. Secondary Prevention

All guidelines recommend immediate lipid-lowering treatment initiation in secondary prevention. The ESC guidelines define patients who have ASCVD to be automatically at very high-risk and recommends at least a 50% reduction from baseline, with a goal of below 55 mg/dL. If the patient experiences a recurrent ASCVD event within 2 years after the first event, an LDL-C goal below 40 mg/dL may be considered. After high-intensity statin initiation, patients are evaluated in 4–6 weeks for treatment response. If the LDL-C level is above 55 mg/dL, despite maximally tolerated statin dosage, the addition of ezetimibe or initiation of PCSK9 inhibitors after ezetimibe is recommended for add-on therapy. The ESC guidelines are more liberal in recommending non-statin therapies to obtain the goal. In addition to lipid lowering, the ESC guidelines have introduced the consideration of anti-inflammatory therapy in the form of low-dose colchicine (0.5 mg o.d.) in patients with ASCVD, poorly controlled risk factors or those who experience recurrent events on optimal medical therapy, according to new studies [13].

The AHA/ACC/MS guidelines recommend high-intensity statin treatment and a 50% reduction in LDL-C level or, if not tolerated, moderate-intensity statin treatment and a 30–49% reduction in the LDL-C level in high-risk patients with ASCVD. If the desired reduction is not achieved, the first option is the addition of ezetimibe. If LDL-C levels are 70 mg/dL (1.8 mmol/L) or higher or the non–HDL-C level is 100 mg/dL (2.6 mmol/L) or higher under the statin and ezetimibe combination, the addition of an PCSK9 inhibitor may be considered.

The CCS guidelines also recommend high-intensity statin treatment for secondary prevention. If LDL-C remains $\geq$1.8–2.2 mmol/L or non-HDL-C $\geq$ 2.4–2.9 mmol/L or ApoB $\geq$ 0.7–0.8 g/L, while receiving the maximally tolerated statin dose, PCSK9 inhibitors with or without ezetimibe are recommended. If LDL-C remains $\geq$ 2.2 mmol/L or non-HDL-C $\geq$ 2.9 mmol/L or ApoB $\geq$ 0.8 g/L, while receiving the maximally tolerated statin dose, PCSK9 inhibitors with or without ezetimibe are recommended.

7. Very High-Risk Patients

There is no universal consensus on the definition of very high-risk patients, but it is recommended to intensify preventive approaches for these patients in all guidelines. The very high-risk patient category definition is different between guidelines (Table 5).

Table 5. Definitions of very high-risk patients.

ESC GUIDELINES	AHA/ACC/MS GUIDELINES	CCS GUIDELINES
To have one of these conditions below	Two or more major ASCVD events OR One major event and >1 high-risk condition	To have one of these conditions below
• Documented clinical ASCVD • Unequivocal ASCVD on imaging predictive of ASCVD events • Type 2 diabetes mellitus with target organ damage (microalbuminuria, retinopathy, or neuropathy), or at least three major risk factors, or early onset T1DM of long duration (>20 y) • Severe CKD (eGFR < 30 mL/min per 1.73 m^2). • A calculated SCORE $\geq$ 10% or 10-year risk of fatal CVD • FH with ASCVD or with another major risk factor	Major ASCVD events • Recent ACS (within the past 12 months) • History of MI (other than the recent ACS event listed above) • History of ischemic stroke • Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation) High-risk conditions • Age $\geq$ 65 years • Diabetes mellitus • Hypertension • CKD (eGFR 15–59 mL/min per 1.73 m^2) • History of congestive heart failure • Current smoking • Heterozygous FH • History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s) • Persistently elevated LDL-C $\geq$ 100 mg/dL (2.6 mmol/L), despite maximally tolerated statin therapy and ezetimibe	Recent acute coronary event (ACS): • Hospitalized index ACS to 52 weeks post index ACS Clinically evident ASCVD and any of the following: • Diabetes mellitus or metabolic syndrome • Polyvascular disease (vascular disease in $\geq$2 arterial beds) • Symptomatic PAD • Recurrent MI • MI in the past 2 years • Previous CABG surgery • LDL-C $\geq$ 2.6 mmol/L or heterozygous FH • Lipoprotein(a) $\geq$ 60 mg/dL (120 nmol/L) High-risk conditions for primary prevention: • CKD • Diabetes mellitus in patients > 40 years or patients > 30 years and with 15 or more years' duration of diabetes or with microvascular complications • Abdominal aortic aneurysm > 3.0 cm or previous aortic aneurysm surgery.

8. Familial Hypercholesterolemia

LDL-C is not only causal but also has a cumulative effect. There is a logarithmic increase between the exposure time and the risk of developing ASCVD. Earlier intervention prevents LDL-C accumulation and changes the trajectory of the disease. Patients with familial hypercholesterolemia (FH) have genetically elevated LDL-C levels and are exposed to elevated LDL-C from early on in life [14]. It is particularly important to diagnose FH early and start treatment. The ESC guidelines automatically classify individuals with FH as being at high-risk and recommend a $\geq$50% reduction from baseline, with an LDL-C goal of <70 mg/dL. If individuals have FH and one or more additional risk factor such as diabetes mellitus, coronary artery disease or chronic kidney disease, they are classified as being at very high-risk, and the goal is a $\geq$50% reduction from baseline and an LDL-C goal of <1.4 mmol/L (55 mg/dL). To reach this goal, maximally tolerated statin treatment and, if not at goal, a combination with ezetimibe, is recommended. PCSK-9 inhibitors may be added into therapy if the goal is still not reached. The AHA/ACC/MS guidelines define patients with primary severe hypercholesterolemia (LDL-C levels $\geq$ 190 mg/dL [$\geq$4.9 mmol/L]) as a statin-benefit group with a high-risk of ASCVD, recommending high-intensity statins. If the LDL-C level is above 2.6 mmol/L (>100 mg/dL), despite statins, it is deemed reasonable to add ezetimibe. If LDL-C is still above 100 mg/dL, the addition of PCSK-9 inhibitors may be considered. The CCS guidelines categorize FH patients as being at high-risk and having a condition requiring statins. If the LDL-C level is above 2.5 mmol/L, despite statins, ezetimibe or PCSK9 inhibitors may be added. PCSK-9 inhibitors are recommended in the following patients: (a) In heterozygous FH patients without clinical ASCVD and LDL-C levels $\geq$2.5 mmol/L, if a $\geq$50% reduction

of LDL-C levels, or ApoB ≥ 0.85 g/L or non-HDL-C ≥ 3.2 mmol/L. (b) In heterozygous FH patients with ASCVD whose target LDL-C levels remain ≥1.8 mmol/L, or ApoB ≥ 0.7 g/L or non-HDL-C ≥ 2.4 mmol/L, despite a maximally tolerated statin and ezetimibe combination.

9. Other Specific Groups

9.1. Diabetes Mellitus

In all the guidelines, diabetes is given special consideration. The ESC guidelines divide diabetic patients into three categories according to concomitant risk factors, target organ damage and age. Patients with well-controlled short-duration diabetes (no evidence of target organ damage or ASCVD risk factors) are classified as moderate-risk; patients without ASCVD or target organ damage not fulfilling moderate-risk criteria are high-risk; while patients with at least three risk factors or type 1 diabetes of a >20 years duration are classified as very-high risk. Other patients between very high and moderate-risk groups are identified as high-risk groups. LDL-C goals depend on the risk. The AHA/ACC/MS guidelines divide diabetes patients into moderate or high-risk groups and recommend moderate-intensity statin treatment to all patients with diabetes. In diabetics at a higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is deemed reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%. The CCS considers patients ≥ 40 years of age and patients ≥ 30 years with a 15-year or more duration of diabetes or with microvascular complications to be at high-risk and recommends statin initiation initially, with add-on ezetimibe if necessary.

9.2. Chronic Kidney Disease

The ESC guidelines define CKD patients to be at high risk (eGFR 30–59 mL/min per 1.73 m^2) and very high-risk (eGFR < 30 mL/min per 1.73 m^2). Statins or statin–ezetimibe use is recommended in all CKD patients not on dialysis. The AHA/ACC/MS guidelines define CKD (estimated glomerular filtration rate 15–59 mL/min per 1.73 m^2) as a risk enhancing factor and underline that statin initiation is reasonable in patients not treated with dialysis or renal transplantation. The CCS recommends statin initiation to all patients with a GFR < 60 mL/min/1.73 m^2 and with a preserved GFR but who have an increased urinary albumin-to-creatinine ratio (≥3 mg/mmol) for at least 3 months. The CCS guidelines define patients with CKD (>50 years) as being in the in high-risk category and recommends statin and/or ezetimibe therapy for patients not treated with dialysis or who have a kidney transplantation (patients with eGFR < 60 mL/min/1.73 m^2 and preserved eGFR). In all guidelines, statin continuation is recommended in patients treated with hemodialysis who are already on statins, but statin initiation is not recommended.

9.3. Hypertriglyceridemia

In the ESC guidelines, there are no TG goals, but TG level <1.7 mmol/L (<150 mg/dL) indicates a lower cardiovascular risk. To address atherogenic triglyceride-rich lipoproteins such as remnants, the ESC guidelines have secondary goals of non-HDL-C < 2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high, high, and moderate-risk people, respectively. ApoB secondary goals are <65, 80, and 100 mg/dL for very high, high, and moderate-risk people, respectively.

The ESC guidelines recommend statin treatment as the first line of treatment in high-risk individuals with plasma fasting TG levels > 2.3 mmol/L (>200 mg/dL), despite lifestyle changes. In high-risk patient groups who have achieved LDL-C goals but have TG levels > 2.3 mmol/L (>200 mg/dL), fibrates may be considered in addition to statin treatment. Furthermore, the ESC guidelines recommend considering the combination of n-3 PUFAs (icosapent ethyl 2 g twice a day) with statins in high and very high-risk patient groups with TG levels between 1.5 and 5.6 mmol/L (135–499 mg/dL).

The AHA/ACC/MS guidelines recommend optimizing diet and lifestyle as the first step, ruling out secondary causes of hypertriglyceridemia, and considering statin therapy

in those with moderate hypertriglyceridemia and elevated 10-year ASCVD risk. The more recent ACC 2021 expert consensus on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia also recommends considering icosapent ethyl in high-risk patients [15].

The CCS also recommends the use of high-dose icosapent ethyl to decrease the risk of CV events in patients with ASCVD, or with diabetes and ≥1 CVD risk factors, who have an elevated fasting triglyceride level of 1.5–5.6 mmol/L, despite treatment with maximally tolerated statin therapy.

10. Conclusions

The ESC, AHA/ACC/MS and CCS guidelines are based on the principle that LDL-C lowering is a key strategy to prevent CV events. Although divergent interpretations of the evidence result in some differences in treatment recommendations, the main principles are similar [16]. All guidelines strongly advocate that LDL-C should be our primary target and the intensity of treatment should increase as the risk of the patient increases. The ESC guidelines take into account contemporary evidence from combination therapy and imaging trials, setting more stringent LDL-C goals for high-risk patients than any other guidelines. The validity and safety of this approach have been demonstrated by the recent FOURIER-OLE trial [17]. Furthermore, having LDL-C goals motivates the patient and the physician. The shared decision-making approach, as well as using imaging for risk discrimination, recommended in the AHA/ACC/MS and CCS guidelines, is an important step forward. Instead of focusing on differences, we should aim to implement guidelines as much as possible. A universal problem is the under implementation of the guidelines and nonadherence to lifestyle and medications. Real-life registries all over the world highlight the underuse of statins in high doses and combination therapy, as well as discontinuation of medications, resulting in the underachievement of goals. Euroaspire III, IV and V studies have provided important information about the under implementation of guidelines and the underachievement of goals across Europe [18,19]. Only a third of the patients achieved their LDL-C goals in Euroaspire V [20]. The more recent Da Vinci trial confirmed these findings and also pointed out the underutilization of combination therapy and high-intensity statins [21].

We are entering a new era of precision medicine, with the aim of delivering the right treatments, at the right time, to the right person [22]. Lifelong exposure to CVD risk factors is better captured by genetic susceptibility since genetic risk is accumulated continuously over a person's life span [23,24]. The future of risk prediction and management lies in shifting from population-based risk scores towards personalized risk prediction, where genetic, omics and imaging information is integrated to personalized lifetime risk prediction and management.

The significant reductions in cardiovascular events that we see in trials can be achieved in real-world patient care if we are able to significantly improve the implementation of the evidence-based treatments and achieve recommended lipid targets based on these and other international guidelines.

Author Contributions: S.A.: writing—original draft preparation and editing; L.T.: review, editing and supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: Aygun have no confict or competing interest relevant to this manuscript. Tokgozoglu reports participation in a Speaker/Advisory Board for Abbott, Amgen, Astra Zeneca, Bayer, Daiichi-Sankyo, Janssen, Mylan, Novartis, Novo Nordisk, Pfizer, Recordati, Sanofi, Servier and she reports being the Past President of the European Atherosclerosis Society and the Past President of the Turkish Society of Cardiology.

References

1. Parini, P.; Frikke-Schmidt, R.; Tselepis, A.D.; Moulin, P.; von Eckardstein, A.; Binder, C.J.; Catapano, A.L.; Ray, K.K.; Tokgözoğlu, L. Taking action: European Atherosclerosis Society targets the United Nations Sustainable Development Goals 2030 agenda to fight atherosclerotic cardiovascular disease in Europe. *Atherosclerosis* **2021**, *322*, 77–81. [CrossRef] [PubMed]
2. Libby, P.; Tokgözoğlu, L. Chasing LDL cholesterol to the bottom—PCSK9 in perspective. *Nat. Cardiovasc. Res.* **2022**, *1*, 554–561. [CrossRef]
3. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; De Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: A report of the American College of Cardiology/American Heart association task force on clinical practice guidelines. *Circulation* **2019**, *139*, e1082–e1143. [PubMed]
4. Visseren, F.L.; Mach, F.; Smulders, Y.M.; Carballo, D.; Koskinas, K.C.; Bäck, M.; Benetos, A.; Biffi, A.; Boavida, J.M.; Capodanno, D.; et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur. Heart J.* **2021**, *42*, 3227–3337.
5. Pearson, G.J.; Thanassoulis, G.; Anderson, T.J.; Barry, A.R.; Couture, P.; Dayan, N.; Francis, G.A.; Genest, J.; Grégoire, J.; Grover, S.A.; et al. Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. *Can. J. Cardiol.* **2021**, *37*, 1129–1150. [CrossRef]
6. Hippisley-Cox, J.; Coupland, C.; Brindle, P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: Prospective cohort study. *BMJ* **2017**, *357*, j2099. [CrossRef]
7. Miida, T.; Nishimura, K.; Okamura, T.; Hirayama, S.; Ohmura, H.; Yoshida, H.; Miyashita, Y.; Ai, M.; Tanaka, A.; Sumino, H.; et al. A multicenter study on the precision and accuracy of homogeneous assays for LDL-cholesterol: Comparison with a beta-quantification method using fresh serum obtained from non-diseased and diseased subjects. *Atherosclerosis* **2012**, *225*, 208–215. [CrossRef]
8. Sniderman, A.D.; Williams, K.; Contois, J.H.; Monroe, H.M.; McQueen, M.J.; de Graaf, J.; Furberg, C.D. A meta-analysis of lowdensity lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ. Cardiovasc. Qual. Outcomes* **2011**, *4*, 337–345. [CrossRef]
9. Kamstrup, P.R.; Tybjaerg-Hansen, A.; Nordestgaard, B.G. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. *J. Am. Coll. Cardiol.* **2013**, *61*, 1146–1156. [CrossRef]
10. Van der Valk, F.M.; Bekkering, S.; Kroon, J.; Yeang, C.; Van den Bossche, J.; van Buul, J.D.; Ravandi, A.; Nederveen, A.J.; Verberne, H.J.; Scipione, C.; et al. Oxidized phospholipids on lipoprotein(a) elicit arterial wall inflammation and an inflammatory monocyte response in humans. *Circulation* **2016**, *134*, 611–624. [CrossRef]
11. Borén, J.; Chapman, M.J.; Krauss, R.M.; Packard, C.J.; Bentzon, J.F.; Binder, C.J.; Daemen, M.J.; Demer, L.L.; Hegele, R.A.; Nicholls, S.J.; et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: Pathophysiological, genetic, and therapeutic insights: A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur. Heart J.* **2020**, *41*, 2313–2330.
12. Writing Committee; Lloyd-Jones, D.M.; Morris, P.B.; Ballantyne, C.M.; Birtcher, K.K.; Covington, A.M.; DePalma, S.M.; Minissian, M.B.; Orringer, C.E.; Smith, S.C.; et al. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: A report of the American College of Cardiology solution set oversight committee. *J. Am. Coll. Cardiol.* **2022**, *80*, 1366–1418. [PubMed]
13. Nidorf, S.M.; Fiolet, A.T.L.; Mosterd, A.; Eikelboom, J.W.; Schut, A.; Opstal, T.S.J.; The, S.H.K.; Xu, X.F.; Ireland, M.A.; Lenderink, T.; et al. Colchicine in patients with chronic coronary disease. *N. Engl. J. Med.* **2020**, *383*, 1838–1847. [CrossRef] [PubMed]
14. McGowan, M.P.; Hosseini Dehkordi, S.H.; Moriarty, P.M.; Duell, P.B. Diagnosis and treatment of heterozygous familial hypercholesterolemia. *J. Am. Heart Assoc.* **2019**, *8*, e013225. [CrossRef]
15. Virani, S.S.; Morris, P.B.; Agarwala, A.; Ballantyne, C.M.; Birtcher, K.K.; Kris-Etherton, P.M.; Ladden-Stirling, A.B.; Miller, M.; Orringer, C.E.; Stone, N.J. 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: A report of the American college of cardiology solution set oversight committee. *J. Am. Coll. Cardiol.* **2021**, *78*, 960–993. [CrossRef] [PubMed]
16. Orringer, C.E.; Tokgozoglu, L.; Maki, K.C.; Ray, K.K.; Saseen, J.J.; Catapano, A.L. Transatlantic lipid guideline divergence: Same data but different interpretations. *J. Am. Heart Assoc.* **2020**, *9*, e018189. [CrossRef]
17. O'Donoghue, M.L.; Giugliano, R.P.; Wiviott, S.D.; Atar, D.; Keech, A.; Kuder, J.F.; Im, K.; Murphy, S.A.; Flores-Arredondo, J.H.; López, J.A.; et al. Long-term evolocumab in patients with established atherosclerotic cardiovascular disease. *Circulation* **2022**, *146*, 1109–1119. [CrossRef]

18. Kotseva, K.; Wood, D.; Backer, G.D.; Bacquer, D.D.; Pyörälä, K.; Keil, U.; EUROASPIRE Study Group. EUROASPIRE III: A survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur. J. Cardiovasc. Prev. Rehabil.* **2009**, *16*, 121–137. [CrossRef]
19. Kotseva, K.; Wood, D.; De Bacquer, D.; De Backer, G.; Rydén, L.; Jennings, C.; Gyberg, V.; Amouyel, P.; Bruthans, J.; Castro Conde, A.; et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur. J. Prev. Cardiol.* **2016**, *23*, 636–648. [CrossRef]
20. De Backer, G.; Jankowski, P.; Kotseva, K.; Mirrakhimov, E.; Reiner, Ž.; Ryden, L.; Tokgözoğlu, L.; Wood, D.; De Bacquer, D.; De Backer, G.; et al. Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries. *Atherosclerosis* **2019**, *285*, 135–146. [CrossRef]
21. Ray, K.K.; Molemans, B.; Schoonen, W.M.; Giovas, P.; Bray, S.; Kiru, G.; Murphy, J.; Banach, M.; De Servi, S.; Gaita, D.; et al. EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: The DA VINCI study. *Eur. J. Prev. Cardiol.* **2021**, *28*, 1279–1289. [CrossRef] [PubMed]
22. Tokgozoglu, L.; Torp-Pedersen, C. Redefining cardiovascular risk prediction: Is the crystal ball clearer now? *Eur. Heart J.* **2021**, *42*, 2468–2471. [CrossRef]
23. Dainis, A.; Ashley, E. Cardiovascular precision medicine in the genomics era. *J. Am. Coll. Cardiol. Basic Trans. Sci.* **2018**, *3*, 313–326. [CrossRef] [PubMed]
24. Landstrom, A.P.; Kim, J.J.; Gelb, B.D.; Helm, B.M.; Kannankeril, P.J.; Semsarian, C.; Sturm, A.C.; Tristani-Firouzi, M.; Ware, S.M.; American Heart Association Council on Genomic and Precision Medicine; et al. Genetic testing for heritable cardiovascular diseases in pediatric patients: A scientific statement from the American Heart Association. *Circ. Genom. Precis. Med.* **2021**, *14*, e000086. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Review

Screening and Management of Dyslipidemia in Children and Adolescents

Juliette M. Schefelker and Amy L. Peterson *

Department of Pediatrics, Division of Pediatric Cardiology, School of Medicine and Public Health, University of Wisconsin, Madison, WI 53792, USA
* Correspondence: apeterson@pediatrics.wisc.edu; Tel.: +1-608-262-5024; Fax: +1-608-265-8065

Abstract: This review provides an overview of pediatric dyslipidemia emphasizing screening and treatment recommendations. The presence of risk factors for cardiovascular disease in childhood poses significant risk for the development of atherosclerotic cardiovascular disease and cardiovascular events in adulthood. While atherogenic dyslipidemia is the most common dyslipidemia seen in children and can be suspected based on the presence of risk factors (such as obesity), familial hypercholesterolemia can be found in children with no risk factors. As such, universal cholesterol screening is recommended to identify children with these disorders in order to initiate treatment and reduce the risk of future cardiovascular disease. Treatment of pediatric dyslipidemia begins with lifestyle modifications, but primary genetic dyslipidemias may require medications such as statins. As pediatric lipid disorders often have genetic or familial components, it is important that all physicians are aware that cardiovascular risk begins in childhood, and can both identify these disorders in pediatric patients and counsel their adult patients with dyslipidemia to have their children screened.

Keywords: dyslipidemia; pediatric; atherosclerotic cardiovascular disease; familial hypercholesterolemia; cholesterol screening; universal screening

Citation: Schefelker, J.M.; Peterson, A.L. Screening and Management of Dyslipidemia in Children and Adolescents. *J. Clin. Med.* **2022**, *11*, 6479. https://doi.org/10.3390/jcm11216479

Academic Editors: Nathan Wong and Cesare R. Sirtori

Received: 28 September 2022
Accepted: 29 October 2022
Published: 31 October 2022

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) and its long-term sequelae are the leading cause of death worldwide [1]. The pathologic process of atherosclerosis begins in youth and increases risk for cardiac events such as heart disease, myocardial infarction, and stroke later in life. Risk factors for ASCVD that are found in childhood include lifestyle factors, medical conditions which increase risk (such as obesity or diabetes), as well as genetic conditions which increase lipid levels, such as Familial Hypercholesterolemia (FH). The purpose of this article is to discuss screening and treatment recommendations for pediatric dyslipidemias. It is known that ASCVD risk factors present during childhood are very likely to track into adulthood and are associated with increased risk for cardiovascular events in adulthood [2,3]. Recently, this association between childhood risk factors and adult ASCVD events was demonstrated [4]. Children with an average age of 11.8 years underwent evaluation including body mass index (BMI), total cholesterol (TC), triglycerides (TG), systolic blood pressure (SBP), and smoking and were reevaluated 35 years later. At a mean age of 46 years, 3.8% of participants had an ASCVD event, and 0.8% had a fatal event. The association between events and risk factors was significant for each individual risk factor, and was even greater when combining risk factors. Importantly, this study demonstrated duration of cholesterol elevation is predictive of ASCVD events. This highlights the importance of early recognition and intervention in pediatric patients to prevent future ASCVD events.

As pediatric dyslipidemias can be identified via screening and have long-lasting impact, we present the following summary of the different disorders and evidence-based treatments to help facilitate care to patients and families. It is important to note that normal

lipid and lipoprotein concentrations are different between children and adults. Pediatric reference ranges are listed in Table 1 [5].

Table 1. Reference Ranges for Pediatric Lipid and Lipoprotein Concentrations.

	Acceptable	Borderline	High
Total Cholesterol	<170	170–199	≥200
LDL-C	<110	110–129	≥130
HDL-C	>45	40–45	<40
Non-HDL-C	<120	120–144	≥145
Triglycerides			
0–9 years old	<75	75–99	≥100
10–19 years old	<90	90–129	≥130
Apolipoprotein B	<90	90–109	≥110
Apolipoprotein A-I	>120	115–120	<115

All values are in mg/dL.

2. Heterozygous Familial Hypercholesterolemia (HeFH)

Familial Hypercholesterolemia is an autosomal dominant genetic condition that results in elevated LDL-C levels starting at birth. In its heterozygous form, it is the most common severe genetic dyslipidemia in pediatric patients. A global meta-analysis estimated the prevalence in the general population is 1 in 311 [6], while data in the US have shown rates to be as high as 1 in 250 adults [7].

2.1. Diagnosis

Several sets of criteria have been developed to diagnose HeFH; however, most were developed primarily for adults and so their use in children can be limited (Table 2). All sets of criteria rely on elevated LDL-C and many incorporate family history and physical exam findings indicative of elevated cholesterol (primarily tendinous xanthomas or arcus cornealis). However, physical exam findings associated with hypercholesterolemia are vanishingly rare in children with HeFH. In fact, if such physical findings are identified in a child, the clinician should consider rarer dyslipidemias, including homozygous familial hypercholesterolemia, sitosterolemia, or cerebrotendinous xanthomatosis as more likely than HeFH.

For ease of diagnosis, the American Heart Association recommended clinical criteria for diagnosis of HeFH in children, including LDL-C $\geq$ 160 mg/dL in a child with family history of elevated cholesterol or premature ASCVD in a parent or grandparent, or LDL-C $\geq$ 190 mg/dL (irrespective of family history), once secondary causes of hypercholesterolemia are excluded [8]. Genetic testing can be utilized to aid in diagnosis but is not required to make a clinical diagnosis of HeFH. However, a recent study found an association between receiving a genetic diagnosis of FH and willingness to be treated with a statin medication, suggesting a genetic diagnosis of HeFH may be perceived differently by patients and their families [9].

Table 2. Diagnostic criteria for heterozygous familial hypercholesterolemia in children [10]. Reprinted with permission from Peterson AL, McNeal CJ, and Wilson DP. Prevention of atherosclerotic cardiovascular disease in children with familial hypercholesterolemia. Curr Atheroscler Rep. 2021 Aug 27;23(10):64. 2021, Springer Nature.

Simon Broome criteria [11]				
Definite or Probable diagnosis of HeFH requires elevated cholesterol: • Total cholesterol > 260 mg/dL or LDL-C > 155 mg/dL if ≤ 15 years • Total cholesterol > 290 mg/dL or LDL-C > 190 mg/dL if ≥ 16 years PLUS One or more additional findings: Definite HeFH: additional findings 1. Tendon xanthoma in the child, first-degree relative, or second-degree relative 2. Genetic testing of a confirmed pathogenic variant (LDLR, ApoB, or PCSK9) POSSIBLE HeFH: additional findings 1. Family history of myocardial infarction ≤ 60 years in a first-degree relative or ≤50 years in a second-degree relative 2. Family history of a total cholesterol ≥ 290 mg/dL in a first or				
MEDPED criteria [12]				
A child is considered to have HeFH if total cholesterol meets or exceeds the threshold listed below. Thresholds vary based upon whether or not there is a first-, second-, or third-degree relative known to have HeFH.				
Child's age	Does the child have one or more relatives with HeFH?			
≤19 years	Yes			No
	First degree	Second degree	Third degree	N/A
Total cholesterol	≥220 mg/dL	≥230 mg/dL	≥240 mg/dL	≥270 mg/dL
Dutch lipid clinic network criteria [13]				
Diagnosis of HeFH is based on the total number of points obtained. Definite HeFH, >8 points. Probable HeFH, 6–8 points. Possible HeFH, 3–5 points. Unlikely HeFH, <3 points				
Criterion:				Points:
Family history:				
First-degree relative with known premature ASCVD (<55 years in men, <60 years in women), OR first-degree relative with LDL-C ≥ 95%ile				1
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR pediatric first degree relative with LDL-C ≥ 95%ile				2
Clinical history:				
Patient with premature ASCVD (<55 years in men, <60 years in women)				2
Patient with premature cerebral or peripheral vascular disease				1
Physical Examination:				
Tendinous xantomata				6
Arcus cornealis with onset prior to 45 years				4
Patient's cholesterol levels:				
LDL-C ≥ 330 mg/dL				8
LDL-C 250–329 mg/dL				5
LDL-C 190–249 mg/dL				3
LDL-C 155–189 mg/dL				1

Table 2. *Cont.*

Genetic testing	
Pathogenic variant in LDLR, APOB, or PCSK9	8
American Heart Association criteria [8]	
Children ($\leq$18 years) with LDL-C $\geq$ 160 mg/dL AND Family history of elevated cholesterol or premature ASCVD AND No evidence of secondary causes of hypercholesterolemia	

2.2. Treatment of Pediatric HeFH

The first step in treatment of any pediatric dyslipidemia is addressing lifestyle factors, which may be exacerbating dyslipidemia, and accelerating risk factor development (Table 3). Specifically, for pediatric HeFH and for patients with other forms of elevated LDL-C, it is important to emphasize a diet that limits saturated fats, trans fats, and dietary cholesterol [5, 14]. If these initial dietary modifications are unsuccessful, adherence to the CHILD-2 LDL-C diet [5] with further restriction of saturated fat and dietary cholesterol as well as emphasizing increased fiber intake may provide further LDL-C lowering benefit [14]. These measures should be implemented with the goal of optimizing diet and exercise for at least 3–6 months before considering medications in most circumstances.

Table 3. Lifestyle modifications for Pediatric Dyslipidemias [14–16]. Adapted from the following: 1. Williams, L.A.; Wilson, D.P. Nutritional Management of Pediatric Dyslipidemia. In Endotext; Feingold, K.R., Anawalt, B., Boyce, A., et al., Eds.; MDText.com, Inc.: 2000. Available online: http://www.ncbi.nlm.nih.gov/books/NBK395582/ (accessed on 30 June 2022). Piercy, K.L.; Troiano, R.P.; Ballard, R.M.; Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD. The Physical Activity Guidelines for Americans. JAMA 2018, 320, 2020–2028. 3. U.S. Department of Agriculture; U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020–2025, 9th ed.; 2020. Available online: DietaryGuidelines.gov (accessed on 30 June 2022).

Activity	
Increase physical activity	Recommend 60 min daily of moderate to vigorous physical activity which increases the heart rate, such as running, walking, dancing, biking, swimming, or sports like soccer or tennis.
Include muscle strengthening	Recommend 3 days per week, which can be integrated with the 60 min of daily activity above. This could include activities such as climbing on playground equipment, jumping rope, gymnastics, or skiing or snowboarding.
Diet	
Emphasize nutritionally dense foods	Encourage diets rich in a variety of fruits and vegetables, whole grains, proteins such as lean meat, seafood, and eggs, legumes, unsalted nuts and seeds, as well as dairy products including fat-free or low-fat options, yogurt, and cheese in appropriate portion sizes
Decrease saturated fat and trans fat intake	Saturated fats are included in red or fatty meats (such as sausage or bacon), high- fat dairy products, butter and other cooking fats. Trans fats are often found in processed foods and snacks including such as baked or fried goods.
Minimize sugar-sweetened beverages	Common sugar-sweetened beverages include soda, sports drinks, and coffee or tea drinks with added sugars. Consuming excess amounts of otherwise healthy beverages (such as fruit juice or chocolate milk) can be unwitting sources of sugar in the diet as well.

Table 3. *Cont.*

Increase beverages without added sugars	Encourage beverages such as water, fat-free or low-fat plain milk, or lactose free or fortified soy milk alternatives.
Eat the whole fruit	Try to eat fruits in whole forms when possible. While 100% fruit juice can be part of a healthy diet, it is lower in fiber than its whole fruit counterpart, and can be very calorie dense. Stick to the serving sizes to avoid excess sugar intake!
Behaviors	
Smoking	Counsel children and parents about smoking cessation and encourage against initiating smoking.

Although pharmacotherapy is rarely required to treat most pediatric dyslipidemia, HeFH is the most common indication for lipid lowering therapy use in pediatrics. Similar to adults, most pediatric patients with HeFH will require medications to meet LDL-C reduction goals. The first line agents for pediatric HeFH are statins, all of which are FDA-approved for use in pediatrics.

The vast majority of pediatric HeFH patients achieve LDL-C reduction goals with statin monotherapy. Before a statin is considered, most eligible pediatric patients have LDL-C $\geq$ 160 mg/dL after 3–6 months of lifestyle modifications. For most pediatric patients with HeFH, statin dose is titrated to LDL-C level with the goal of LDL-C < 130 mg/dL on treatment [17]. Table 4 shows pediatric-specific considerations when prescribing statins.

Statins have been found to be safe and effective in pediatric populations, with studies showing effective LDL-C reduction and minimal side effects in the short to intermediate term [13,17–22]. Luirink et al. (2019) performed a 20-year follow-up of pediatric HeFH patients treated with pravastatin and found that these patients had lower rates of ASCVD-related cardiac events than their affected parents who had not started statins until early adulthood. Of the 213 participants followed, only four discontinued the medication due to side effects, and no participants reported serious adverse effects such as rhabdomyolysis [22]. Anagnostis et al. (2020) found no adverse events related to statin use, with over 50% of patients meeting LDL-C reduction goals with a high-dose statin [20].

Table 4. Dosing and Expected Effect of Statins Currently Approved for Use in Children and Adolescents.

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Rosuvastatin	Pitavastatin
Ages approved by FDA	≥10 years	≥10 years	≥10 years	≥8 years	≥10 years	≥8 years	≥8 years
Approved Pediatric Doses	5 mg, 10 mg, 20 mg, 40 mg	20 mg, 40 mg, 80 mg	10 mg, 20 mg, 40 mg, 80 mg	10 mg, 20 mg, 40 mg	5 mg, 10 mg, 20 mg, 40 mg	5 mg, 10 mg, 20 mg	1 mg, 2 mg, 4 mg
Expected LDL reduction at maximum pediatric dose (%) [23]	≥50%	30–49%	30–49%	30–49%	30–49%	≥50%	38%
Supplied as	10 mg, 20 mg, 40 mg, 80 mg tablets	20 mg and 40 mg capsules; 80 mg XR tablet	10 mg, 20 mg, 40 mg tablets; 20 mg, 40 mg, 60 mg XR tablets	10 mg, 20 mg, 40 mg, 80 mg tablets	5 mg, 10 mg, 20 mg, 40 mg, 80 mg tablets; Suspension: 20 mg/5 mL, 40 mg/5 mL	5 mg, 10 mg, 20 mg, 40 mg tablets; 5 mg, 10 mg, 20 mg, 40 mg sprinkle capsule	1 mg, 2 mg, 4 mg tablets
Notes		If LDL-C reduction ≥ 50% is needed, select a higher intensity statin (atorvastatin or rosuvastatin)	If LDL-C reduction ≥ 50% is needed, select a higher intensity statin (atorvastatin or rosuvastatin)	If LDL-C reduction ≥ 50% is needed, select a higher intensity statin (atorvastatin or rosuvastatin)	Simvastatin 80 mg should not be used due to myopathy risk. If LDL-C reduction goal cannot be achieved with simvastatin 40 mg, switch to higher intensity statin (atorvastatin or rosuvastatin)		

If statin monotherapy does not sufficiently lower LDL-C levels, other medications can be considered as secondary agents. The most common non-statin agent used for pediatric HeFH is ezetimibe, which is FDA approved for youth 10 years of age and older for HeFH. Its most common application is for additional LDL reduction while on statin therapy; however, it can be used as monotherapy for pediatric FH. Evolocumab, a proprotein subtilisin/kexin type 9 (PCSK9) inhibitor, is approved for additional LDL-C reduction in pediatric patients with HeFH who are 10 years and older. The HAUSER-RCT study demonstrated 44.5% reduction in LDL-C compared to placebo in pediatric patients aged 10–17 years old on a background of stable lipid lowering therapy, with similar incidence of adverse events between evolocumab and placebo [24,25].

Other medications used to treat adults with HeFH are currently undergoing pediatric trials. The ODDYSSEY KIDS trial of alirocumab in pediatric patients with HeFH demonstrated LDL-C reductions of 45% in individuals taking higher doses with favorable adverse effect profiles [26]. The ORION-16 trial investigating inclisiran vs. placebo for treatment of pediatric HeFH is underway [27].

3. Atherogenic Dyslipidemia

Atherogenic dyslipidemia is the most common dyslipidemia in childhood and is highly associated with childhood obesity or metabolic syndrome, affecting 33% of overweight and 43% of obese children [28]. Similar to adults, it is also commonly found in children who have insulin resistance, type 2 diabetes mellitus, and/or non-alcoholic fatty liver disease (NAFLD) [5,23,29–31].

3.1. Diagnosis

A fasting lipid panel can readily diagnose atherogenic dyslipidemia. The results are characterized by elevations in TG levels and decreased levels of HDL-C, a pattern similar to adults. In children, LDL-C levels are generally normal, although the LDL that is present is in the form of the more atherogenic small dense LDL particles. Importantly, the normal ranges for TG are different for children compared to adults; for children 0–9 years old, TG < 75 mg/dL is normal, and for children and adolescents 10–19 years old, TG < 90 mg/dL is normal [5]. See Table 1 for pediatric lipid and lipoprotein values.

3.2. Treatment of Pediatric Atherogenic Dyslipidemia

Treatment is primary through lifestyle changes, with a major focus on diet and activity modifications. For children with excess body fat, a modest decrease in weight has been shown to significantly reduce TG levels as well as increase HDL-C levels [32,33].

Sedentary lifestyle is a significant concern for children. The Physical Activity Guidelines for Americans recommend 60 min daily of moderate to vigorous physical activity along with muscle strengthening exercise 3 days per week for children aged 6–17 years old. Children aged 3–5 are encouraged to be physically active throughout the day via active play [15].

Dietary changes are a key consideration for improving cardiometabolic health. All dietary changes should be discussed through shared decision making with parents or guardians, as well as the child to be sure that cultural norms as well as cost and access to food are considered. Throughout the lifespan, focus on a variety of nutrient-dense foods and minimizing foods and beverages with excess added sugars is essential. When treating dyslipidemia, initial focus on adhering to diet suggested by the Dietary Guidelines for Americans can be helpful [16]. If there is insufficient improvement, it may be appropriate to consider a more restrictive diet. For children with elevated TG, limiting saturated fats and refined carbohydrates has been found to be effective [34]. With this in mind, minimizing intake of sugar-sweetened beverages as much as possible is fundamental when treating children, as these often are inadvertent but significant sources of sugar and empty calories. Increasing fiber and omega-3-fatty acid intake are helpful [14]. Working with a

registered dietician can be extremely beneficial in ensuring that families are provided with comprehensive plans [35].

Very little evidence exists to guide the use of nutritional supplements in pediatric dyslipidemias, and the focus of treatment is generally a healthy diet. Further information regarding supplements can be found at the following resource [34].

4. Mixed Dyslipidemia

Pediatric patients with a mixed dyslipidemia have more modest elevations in LDL-C and TG, and generally normal HDL-C. They often have a clinical picture that is neither clearly attributable to lifestyle factors nor a known genetic diagnosis such as FH. Using the diagnosis of mixed dyslipidemia in these circumstances has the utility of helping to guide clinical decision making for these patients, as the dyslipidemia in these children often has an environmental component, but genetic etiologies should also be considered, particularly if patients do not respond to lifestyle therapy.

4.1. Diagnosis

On a lipid panel, these patients typically have elevations in LDL-C, but not to the level which would be expected in HeFH, as well as elevations in TG. HDL-C is generally normal.

4.2. Treatment

As the clinical picture may appear unclear, treatment is a combination of previously described strategies. Lifestyle factors must first be optimized to help determine next steps in management. Re-assessment of lipid levels after initial changes can determine if the initial modifications were adequate or if further treatment is necessary. If LDL-C levels continue to be sufficiently elevated despite 3–6 months of interventions, initiation of pharmacotherapy with statins may be appropriate. Greater insight into when statin treatment is recommended based on a patient's risk factors can be found at the following resource [23].

5. Rare Lipid Disorders

5.1. Homozygous Familial Hypercholesterolemia

Homozygous familial hypercholesterolemia (HoFH) can present in childhood and affects approximately 1 in 160,000 to 1 in 400,000 individuals. The disease often comes to clinical attention when children develop xanthomas, or it can be found through cholesterol screening. Children with HoFH will have LDL-C levels typically ranging from 500 mg/dL to 1,000 mg/dL and can develop overt coronary artery disease in the first decade of life.

Treatment of these individuals in childhood uses strategies similar to those used in adulthood and focuses on aggressive LDL-C reduction from the time of diagnosis. While HeFH can be managed in the primary care setting, pediatric lipid specialists should be consulted if HoFH is suspected. Treatment options often depend on whether or not affected individuals have functional LDL-receptor (LDL-R) activity. For those with functional LDL-R activity, statins and ezetimibe have been the primary therapy. Recently, evolocumab was approved by the FDA for patients 13 years of age or older with HoFH. Other therapies act independently from the LDL receptor. Lomitapide can be used to lower LDL-C but carries risk of hepatotoxicity. Evinacumab, an inhibitor of angiopoietin-like 3 protein (ANGTPL3) is approved for use in individuals 12 years and older for treatment of HoFH. LDL apheresis has traditionally been a mainstay of therapy but has additional challenges associated with pediatric use, including vascular access, circulating blood volume, and patient cooperation. Liver transplant has been used to treat this disease [36].

5.2. Severe Hypertriglyceridemia

As with adults, pediatric hypertriglyceridemia can be divided into primary and secondary causes. Most pediatric patients with hypertriglyceridemia have atherogenic dyslipidemia as described above. Important secondary causes of hypertriglyceridemia in pediatric

patients include hypothyroidism, kidney disease (nephrotic syndrome), diabetes, liver disease, hypercortisolism, and medications. Pregnancy and excessive alcohol intake are important differentials in pediatric patients as well as adults. A comprehensive list of medications associated with hypertriglyceridemia is found in the 2018 AHA/ACC Multisociety Guideline on the Management of Blood Cholesterol [23]. Medications causing hypertriglyceridemia that are most commonly encountered in pediatrics include isotretinoin, L-asparaginase, oral estrogens, glucocorticoids, atypical antipsychotics, and immunosuppressive agents like tacrolimus, sirolimus, and cyclosporine.

Primary hypertriglyceridemia in children is associated with severe elevations in fasting triglycerides, generally $\geq$500 mg/dL, although many have triglycerides $\geq$1000 mg/dL. Genetic testing should be considered to determine the underlying etiology of the disorder, as therapeutic lifestyle changes are the primary form of therapy but vary according to the underlying diagnosis. For familial chylomicronemia syndrome, caused by mutations in lipoprotein lipase, a specialized very low-fat diet is needed to prevent pancreatitis [37]. For individuals with other forms of hypertriglyceridemia, most commonly familial combined hyperlipidemia, dietary modifications are focused on reducing sugar and simple carbohydrate intake. In these cases, prescription omega-3 fatty acids (DHA and EPA in combination or EPA-only formulations) are used off-label to treat adolescents with hypertriglyceridemia, although they are not FDA-approved for this indication [38].

5.3. Hypobetalipoproteinemia and Abetalipoproteinemia

Very low LDL-C is occasionally diagnosed in pediatric patients. It is not generally associated with higher risk of ASCVD. Acquired causes of low LDL-C such as malignancy, malabsorption, medications, and severe illness or infection should be excluded. There is a group of very rare disorders that can cause very low levels of LDL-C, usually $\leq$25 mg/dL but many $\leq$10 mg/dL. They include homozygous hypobetalipoproteinemia (caused by mutations in apolipoprotein B) and abetalipoproteinemia (caused by mutations in microsomal triglyceride transfer protein). Typically, these children will present to medical attention with symptoms such as fat malabsorption, failure to thrive, hepatomegaly, and manifestations of fat-soluble vitamin deficiencies [39]. Management focuses on monitoring for and treating fat-soluble vitamin deficiencies and monitoring for hepatic steatosis [40].

Individuals who are heterozygous for hypobetalipoproteinemia have LDL-C levels below average and are usually asymptomatic. They are generally thought to be at reduced risk for ASCVD, but they could develop hepatic steatosis. No treatment is generally indicated but individuals should be monitored occasionally for steatohepatitis.

6. Lipoprotein(a)

Lipoprotein (a) [Lp(a)] is an LDL-C moiety with an ApoB protein covalently bound to apolipoprotein (a). Plasma levels of Lp(a) are incredibly variable and are 70- 90% determined by genotype. The prevalence of elevated Lp(a) in children is presumably the same as for adults, as there is thought to be little variability in Lp(a) levels throughout the lifespan. There are very few studies in children, but data indicate that high Lp(a) in a child is a risk factor for arterial ischemic stroke [41] and venous thromboembolism [42]. Pediatric values for Lp(a) are the same as those used for adults.

There is no FDA-approved therapy for treatment of elevated Lp(a) in children, and medications shown to lower Lp(a) in adults, namely PCSK9 inhibitors, are only used very rarely in children. Therefore, any efforts to screen children for elevated Lp(a) must balance concerns about privacy, autonomy, and provoking anxiety against the potential benefits of future therapies. The National Lipid Association identifies four pediatric groups in which Lp(a) testing is reasonable: (1) Clinically suspected or genetically confirmed familial hypercholesterolemia; (2) Family history of a first-degree relative with premature ASCVD (<55 years in men, <65 years in women); (3) Pediatric ischemic stroke with unknown cause; or (4) Parent or sibling with elevated Lp(a) [43].

7. Screening for Pediatric Dyslipidemias

Fundamentally, the purpose of lipid screening in childhood is to identify children with dyslipidemia in order to pursue early treatment through lifestyle modification and/or medical management and decrease risk of ASCVD events in adulthood. Several different screening strategies exist, including selective, universal, and cascade screening.

7.1. Selective Screening

Selective screening involves screening children with high-risk medical conditions or with family history that increases their likelihood of developing ASCVD. High-risk medical conditions commonly encountered in children include obesity, diabetes, and elevated blood pressure, as well as less common conditions like childhood cancer, solid organ transplantation, Kawasaki disease with persistent aneurysms, kidney disease, and some forms of congenital heart disease. Selective screening should also be considered for a child with a significant family history of early cardiovascular disease or diabetes. Selective lipid screening can be performed as young as 2 years of age, and can be done at any age thereafter when the high-risk medical condition is diagnosed. Details for screening and management of high-risk medical conditions in pediatrics can be found in the American Heart Association guideline [17].

7.2. Universal Screening

However, selective screening alone has been shown to be inadequate in capturing all cases of severe dyslipidemia, particularly HeFH. The CARDIAC study of 10-year-olds in West Virginia demonstrated that using selective screening as the sole strategy for detecting severe pediatric dyslipidemia would have missed 37% of children who met criteria for pharmacotherapy [44]. Relying on family history in pediatrics can be particularly challenging as they are time consuming to acquire, and can be inaccurate, incomplete, or unavailable. Additionally, due to widespread use of statins in adults, reliance on a family history of premature cardiac events becomes less appropriate as premature events in children's relatives are prevented. As such, universal screening of children is the most effective method to identify children with HeFH and other severe dyslipidemias [44,45].

Universal screening is recommended by the National Heart, Lung, and Blood Institute and endorsed by the American Academy of Pediatrics. The United States Preventive Services Task Force reviewed universal pediatric cholesterol screening in 2016 with an "I" recommendation, indicating the evidence was insufficient to recommend for or against screening [46]. Screening in children should be performed between 9–11 years old, before the onset of puberty. It may be useful to note that some racial backgrounds may have earlier onset puberty (such as African American females) and as such timing of screening should reflect this [47]. Screening can be performed with either a non-fasting or a fasting lipid panel, with the understanding that non-fasting lipid panels yielding extremely elevated results should be repeated as a fasting lab.

However, studies on current screening practices demonstrate that implementation of this recommendation has been slow, and most children are still not being screened for these disorders [48,49]. Furthermore, screening rates are potentially different among different types of pediatric clinicians, due to conflicting recommendations from guidelines [50].

7.3. Cascade Screening

Cascade screening is a method in which the family members of a patient diagnosed with a medical condition are subsequently screened for the disorder [51]. This is particularly ideal for autosomal dominant disorders such as HeFH, where relatives have a high probability of having the disorder [18]. This method has also been found to be cost-effective for HeFH detection when compared to the costs incurred from treating cardiovascular disease over time [52].

Cascade screening is traditionally done by screening children and other relatives of the index case. In pediatrics, this is often done through "reverse" cascade screening; diagnosing

parents and other older relatives after lipid abnormalities are diagnosed in children. A cascade screening mentality is essential when diagnosing any patient with HeFH, and it is crucial to recognize that affected parents should have their children screened. As such, all adult patients identified with these disorders should be informed of the risk to first-degree relatives so that their family members, including their children, can be screened.

8. Conclusions

Although there has been increasing awareness of the need for screening and treatment of pediatric dyslipidemias, education and action from healthcare teams is still lagging, resulting in potential gaps in care. Lack of awareness of screening and treatment guidelines for pediatric dyslipidemia has even been seen among pediatric cardiologists [53], and is particularly true when considering HeFH [54]. As such, it remains critical that adults with HeFH or elevated cholesterol levels have their children screened.

In this report are tools for all providers to utilize in their practice to help attain these goals. Universal pediatric lipid screening as well as screening family members of those diagnosed with severe dyslipidemia can help to further identify at-risk populations. Lifestyle modifications such as increasing intake of fruits and vegetables and elimination of sugar-sweetened beverages in children are good first steps in treatment. Finally, statins, the first-line pharmacotherapy for severe elevations in LDL-C, are rarely needed but are both safe and effective in lowering LDL-C in pediatric populations and thus lowering these children's risk of future cardiac events. Responsibility to ensure the health of children and to decrease future morbidity and mortality from ASCVD lies with all healthcare providers, not solely those with a focus on pediatrics.

Author Contributions: Conceptualization, A.L.P.; Writing—original draft preparation, J.M.S.; Writing—review and editing, J.M.S. and A.L.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: Juliette M. Schefelker declares no conflict of interest. Amy L. Peterson serves as a Steering Committee member for Novartis Pharmaceuticals, compensation paid to institution.

References

1. Murphy, S.L.; Kochanek, K.D.; Xu, J.; Arias, E. Mortality in the United States, 2020. *NCHS Data Brief* **2021**, *427*, 1–8.
2. Berenson, G.S.; Srinivasan, S.R.; Bao, W.; Newman, W.; Tracy, R.E.; Wattigney, W. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N. Engl. J. Med.* **1998**, *338*, 1605–1606. [CrossRef] [PubMed]
3. McGill, H.C.J.; McMahan, C.A. Determinants of atherosclerosis in the young. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Am. J. Cardiol.* **1998**, *82*, 30T–36T. [CrossRef]
4. Jacobs, D.R.; Woo, J.G.; Sinaiko, A.R.; Daniels, S.R.; Ikonen, J.; Juonala, M.; Kartiosuo, N.; Lehtimäki, T.; Magnussen, C.G.; Viikari, J.S.A.; et al. Childhood Cardiovascular Risk Factors and Adult Cardiovascular Events. *N. Engl. J. Med.* **2022**, *386*, 1877–1888. [CrossRef] [PubMed]
5. Daniels, S.R.; Benuck, I.; Christakis, D.A.; Dennison, B.A.; Gidding, S.S.; Gillman, M.W.; Gottesman, M.M.; Kwiterovich, P.O.; McBride, P.E.; McCrindle, B.W.; et al. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. *Pediatrics* **2011**, *128* (Suppl. 5), S213–S256. [CrossRef]
6. Beheshti, S.O.; Madsen, C.M.; Varbo, A.; Nordestgaard, B.G. Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects. *J. Am. Coll. Cardiol.* **2020**, *75*, 2553–2566. [CrossRef]
7. De Ferranti, S.D.; Rodday, A.M.; Mendelson, M.M.; Wong, J.B.; Leslie, L.K.; Sheldrick, R.C. Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation* **2016**, *133*, 1067–1072. [CrossRef]
8. Gidding, S.S.; Champagne, M.A.; de Ferranti, S.D.; Defesche, J.; Ito, M.K.; Knowles, J.W.; McCrindle, B.; Raal, F.; Rader, D.; Santos, R.D.; et al. The Agenda for Familial Hypercholesterolemia. *Circulation* **2015**, *132*, 2167–2192. [CrossRef]
9. Peretti, N.; Vimont, A.; Mas, E.; Ferrières, J.; Tounian, P.; Lemale, J.; Boccara, F.; di Filippo, M.; Charriere, S.; Moulin, P.; et al. Factors predicting statin initiation during childhood in familial hypercholesterolemia: Importance of genetic diagnosis. *J. Pediatr.* **2022**. [CrossRef]

10. Peterson, A.L.; McNeal, C.J.; Wilson, D.P. Prevention of Atherosclerotic Cardiovascular Disease in Children with Familial Hypercholesterolemia. *Curr. Atheroscler. Rep.* **2021**, *23*, 64. [CrossRef]
11. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* **1991**, *303*, 893–896. [CrossRef] [PubMed]
12. Williams, R.R.; Hunt, S.C.; Schumacher, M.C.; Hegele, R.A.; Leppert, M.F.; Ludwig, E.H.; Hopkins, P.N. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am. J. Cardiol.* **1993**, *72*, 171–176. [CrossRef]
13. Nordestgaard, B.G.; Chapman, M.J.; Humphries, S.E.; Ginsberg, H.N.; Masana, L.; Descamps, O.S.; Wiklund, O.; Hegele, R.A.; Raal, F.H.; Defesche, J.C.; et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: Guidance for clinicians to prevent coronary heart disease. *Eur. Heart J.* **2013**, *34*, 3478–3490. [CrossRef] [PubMed]
14. Williams, L.A.; Wilson, D.P. Nutritional Management of Pediatric Dyslipidemia. In *Endotext*; Feingold, K.R., Anawalt, B., Boyce, A., et al., Eds.; MDText.com, Inc.: South Dartmouth, MA, USA, 2000. Available online: http://www.ncbi.nlm.nih.gov/books/NBK395582/ (accessed on 30 June 2022).
15. Piercy, K.L.; Troiano, R.P.; Ballard, R.M.; Carlson, S.A.; Fulton, J.E.; Galuska, D.A.; George, S.M.; Olson, R.D. The Physical Activity Guidelines for Americans. *JAMA* **2018**, *320*, 2020–2028. [CrossRef]
16. U.S. Department of Agriculture; U.S. Department of Health and Human Services. *Dietary Guidelines for Americans, 2020–2025*, 9th ed.; US Dept of Agriculture: Washington, DC, USA, 2020. Available online: DietaryGuidelines.gov (accessed on 15 July 2022).
17. De Ferranti, S.D.; Steinberger, J.; Ameduri, R.; Baker, A.; Gooding, H.; Kelly, A.S.; Mietus-Snyder, M.; Mitsnefes, M.M.; Peterson, A.L.; St-Pierre, J.; et al. Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement from the American Heart Association. *Circulation* **2019**, *139*, e603–e634. [CrossRef]
18. Goldberg, A.C.; Hopkins, P.N.; Toth, P.P.; Ballantyne, C.M.; Rader, D.J.; Robinson, J.G.; Daniels, S.R.; Gidding, S.S.; de Ferranti, S.D.; Ito, M.K.; et al. Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients: Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J. Clin. Lipidol.* **2011**, *5* (Suppl. 3), S1–S8. [CrossRef]
19. Watts, G.F.; Gidding, S.; Wierzbicki, A.S.; Toth, P.P.; Alonso, R.; Virgil Brown, W.; Bruckert, E.; Defesche, J.; Kah Lin, K.; Livingston, M.; et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int. J. Cardiol.* **2014**, *171*, 309–325. [CrossRef]
20. Anagnostis, P.; Vaitsi, K.; Kleitsioti, P.; Mantsiou, C.; Pavlogiannis, K.; Athyros, V.G.; Mikhailidis, D.P.; Goulis, D.G. Efficacy and safety of statin use in children and adolescents with familial hypercholesterolaemia: A systematic review and meta-analysis of randomized-controlled trials. *Endocrine* **2020**, *69*, 249–261. [CrossRef]
21. Vuorio, A.; Kuoppala, J.; Kovanen, P.T.; Kovanen, P.T.; Humphries, S.E.; Tonstad, S.; Wiegman, A.; Drogari, E.; Ramaswami, U.; Cochrane Cystic Fibrosis and Genetic Disorders Group. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst. Rev.* **2019**, *7*. [CrossRef]
22. Luirink, I.K.; Wiegman, A.; Kusters, D.M.; Hof, M.H.; Groothoff, J.W.; de Groot, E.; Kastelein, J.J.P.; Hutten, B.A. 20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia. *N. Engl. J. Med.* **2019**, *381*, 1547–1556. [CrossRef]
23. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **2019**, *139*, e1082–e1143. [CrossRef] [PubMed]
24. Gaudet, D.; Langslet, G.; Gidding, S.S.; Luirink, I.K.; Ruzza, A.; Kurtz, C.; Lu, C.; Romaratne, R.; Raal, F.J.; Wiegman, A. Efficacy, safety, and tolerability of evolocumab in pediatric patients with heterozygous familial hypercholesterolemia: Rationale and design of the HAUSER-RCT study. *J. Clin. Lipidol.* **2018**, *12*, 1199–1207. [CrossRef] [PubMed]
25. Santos, R.D.; Ruzza, A.; Hovingh, G.K.; Wiegman, A.; Mach, F.; Kurtz, C.E.; Hamer, A.; Bridges, I.; Bartuli, A.; Begeron, J.; et al. Evolocumab in Pediatric Heterozygous Familial Hypercholesterolemia. *N. Engl. J. Med.* **2020**, *383*, 1317–1327. [CrossRef] [PubMed]
26. Daniels, S.; Caprio, S.; Chaudhari, U.; Manvelian, G.; Baccara-Dinet, M.T.; Brunet, A.; Scemama, M.; Loizeau, V.; Bruckert, E. PCSK9 inhibition with alirocumab in pediatric patients with heterozygous familial hypercholesterolemia: The ODYSSEY KIDS study. *J. Clin. Lipidol.* **2020**, *14*, 322–330.e5. [CrossRef] [PubMed]
27. Reijman, M.D.; Schweizer, A.; Peterson, A.L.; Bruckert, E.; Stratz, C.; Defesche, J.C.; Hegele, R.A.; Wiegman, A. Rationale and design of two trials assessing the efficacy, safety, and tolerability of inclisiran in adolescents with homozygous and heterozygous familial hypercholesterolaemia. *Eur. J. Prev. Cardiol.* **2022**, *29*, 1361–1368. [CrossRef]
28. CDC Obesity: Centers for Disease Control and Prevention (CDC). Prevalence of abnormal lipid levels among youths—United States, 1999–2006. *MMWR Morb. Mortal. Wkly. Rep.* **2010**, *59*, 29–33.
29. Yan, Y.; Bazzano, L.A.; Juonala, M.; Raitakari, O.T.; Viikari, J.S.A.; Prineas, R.; Dwyer, T.; Sinaiko, A.; Burns, T.L.; Daniels, S.R.; et al. Long-Term Burden of Increased Body Mass Index from Childhood on Adult Dyslipidemia: The i3C Consortium Study. *J. Clin. Med.* **2019**, *8*, 1725. [CrossRef]
30. Henriksson, P.; Sandborg, J.; Henström, M.; Nystrom, C.D.; Ek, E.; Ortega, F.B.; Lof, M. Body composition, physical fitness and cardiovascular risk factors in 9-year-old children. *Sci. Rep.* **2022**, *12*, 2665. [CrossRef]

31. Turer, C.B.; Brady, T.M.; de Ferranti, S.D. Obesity, Hypertension, and Dyslipidemia in Childhood Are Key Modifiable Antecedents of Adult Cardiovascular Disease. *Circulation* **2018**, *137*, 1256–1259. [CrossRef]
32. Nemet, D.; Barkan, S.; Epstein, Y.; Friedland, O.; Kowen, G.; Eliakim, A. Short- and Long-Term Beneficial Effects of a Combined Dietary–Behavioral–Physical Activity Intervention for the Treatment of Childhood Obesity. *Pediatrics* **2005**, *115*, e443–e449. [CrossRef]
33. Becque, M.D.; Katch, V.L.; Rocchini, A.P.; Marks, C.R.; Moorehead, C. Coronary risk incidence of obese adolescents: Reduction by exercise plus diet intervention. *Pediatrics* **1988**, *81*, 605–612. [CrossRef] [PubMed]
34. Williams, L.; Baker-Smith, C.M.; Bolick, J.; Carter, J.; Kirkpatrick, C.; Ley, S.L.; Peterson, A.L.; Shah, A.S.; Sikand, G.; Ware, A.L.; et al. Nutrition interventions for youth with dyslipidemia: A National Lipid Association clinical perspective. *J. Clin. Lipidol.* **2022**, *11*, 38. [CrossRef]
35. Pahkala, K.; Laitinen, T.T.; Niinikoski, H.; Kartiosuo, N.; Rovio, S.P.; Langstrom, H.; Loo, B.M.; Salo, P.; Jokinen, E.; Magnussen, C.G.; et al. Effects of 20-year infancy-onset dietary counselling on cardiometabolic risk factors in the Special Turku Coronary Risk Factor Intervention Project (STRIP): 6-year post-intervention follow-up. *Lancet Child Adolesc. Health* **2020**, *4*, 359–369. [CrossRef]
36. Cuchel, M.; Bruckert, E.; Ginsberg, H.N.; Raal, F.J.; Santos, R.D.; Hegele, R.A.; Kuivenhoven, J.A.; Nordestgaard, B.G.; Descamps, O.S.; Steinhagen-Thiessen, E.; et al. Homozygous familial hypercholesterolaemia: New insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur. Heart J.* **2014**, *35*, 2146–2157. [CrossRef] [PubMed]
37. Williams, L.; Rhodes, K.S.; Karmally, W.; Welstead, L.A.; Alexander, L.; Sutton, L. Familial chylomicronemia syndrome: Bringing to life dietary recommendations throughout the life span. *J. Clin. Lipidol.* **2018**, *12*, 908–919. [CrossRef] [PubMed]
38. Skulas-Ray, A.C.; Wilson, P.W.F.; Harris, W.S.; Brinton, E.A.; Kris-Etherton, P.M.; Richter, C.K.; Jacobson, T.A.; Engler, M.G.; Miller, M.; Robinson, J.G.; et al. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory from the American Heart Association. *Circulation* **2019**, *140*, e673–e691. [CrossRef]
39. Hartz, J.; Hegele, R.A.; Wilson, D.P. Low LDL cholesterol—Friend or foe? *J. Clin. Lipidol.* **2019**, *13*, 367–373. [CrossRef]
40. Lee, J.; Hegele, R.A. Abetalipoproteinemia and homozygous hypobetalipoproteinemia: A framework for diagnosis and management. *J. Inherit. Metab. Dis.* **2014**, *37*, 333–339. [CrossRef]
41. Sultan, S.M.; Schupf, N.; Dowling, M.M.; DeVeber, G.A.; Kirton, A.; Elkind, M.S.V. Review of Lipid and Lipoprotein(a) Abnormalities in Childhood Arterial Ischemic Stroke. *Int. J. Stroke* **2014**, *9*, 79–87. [CrossRef]
42. Boffa, M.B.; Koschinsky, M.L. Lipoprotein (a): Truly a direct prothrombotic factor in cardiovascular disease? *J. Lipid Res.* **2016**, *57*, 745–757. [CrossRef]
43. Wilson, D.P.; Jacobson, T.A.; Jones, P.H.; Koschinsky, M.L.; McNeal, C.J.; Nordestgaard, B.G.; Orringer, C.E. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. *J. Clin. Lipidol.* **2019**, *13*, 374–392. [CrossRef] [PubMed]
44. Ritchie, S.K.; Murphy, E.C.S.; Ice, C.; Cottrell, L.A.; Minor, V.; Elliott, E.; Neal, W. Universal Versus Targeted Blood Cholesterol Screening Among Youth: The CARDIAC Project. *Pediatrics* **2010**, *126*, 260–265. [CrossRef] [PubMed]
45. Psaty, B.M.; Rivara, F.P. Universal Screening and Drug Treatment of Dyslipidemia in Children and Adolescents. *JAMA* **2012**, *307*, 257–258. [CrossRef] [PubMed]
46. US Preventive Services Task Force. Screening for Lipid Disorders in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. *JAMA* **2016**, *316*, 625–633. [CrossRef] [PubMed]
47. Biro, F.M.; Greenspan, L.C.; Galvez, M.P.; Pinney, S.M.; Teitelbaum, S.; Windham, G.C.; Deardorff, J.; Herrick, R.L.; Succop, P.A.; Hiatt, R.A.; et al. Onset of Breast Development in a Longitudinal Cohort. *Pediatrics* **2013**, *132*, 1019–1027. [CrossRef]
48. De Ferranti, S.D.; Rodday, A.M.; Parsons, S.K.; Cull, W.L.; O'Connor, K.G.; Daniels, S.R.; Leslie, L.K. Cholesterol Screening and Treatment Practices and Preferences: A Survey of United States Pediatricians. *J. Pediatr.* **2017**, *185*, 99–105.e2. [CrossRef]
49. Allen-Tice, C.; Steinberger, J.; Murdy, K.; Zierhut, H. Pediatric cholesterol screening practices in 9- to 11-year-olds in a large midwestern primary care setting. *J. Clin. Lipidol.* **2020**, *14*, 224–230. [CrossRef]
50. Zhang, X.; DeSantes, K.; Dodge, A.; Larson, M.; Eichoff, J.; Moreno, M.; Peterson, A.L. Practices and Attitudes Regarding Pediatric Cholesterol Screening Recommendations Differ Between Pediatricians and Family Medicine Clinicians. *Pediatr. Cardiol.* **2022**, *43*, 631–635. [CrossRef]
51. Morris, J.K.; Wald, D.S.; Wald, N.J. The evaluation of cascade testing for familial hypercholesterolemia. *Am. J. Med. Genet. A* **2012**, *158*, 78–84. [CrossRef]
52. Jackson, C.L.; Huschka, T.; Borah, B.; Agre, K.; Sordok, M.; Farwati, M.; Moriarty, J.; Kullo, I.J. Cost-effectiveness of cascade genetic testing for familial hypercholesterolemia in the United States: A simulation analysis. *Am. J. Prev. Cardiiol.* **2021**, *8*, 100245. [CrossRef]
53. Hokanson, J.S.; Arce, A.B.; Ahmed, S.A.; Zhang, X.; Dodge, A.M.; Peterson, A.L. Preventive Medicine in Pediatric Cardiology Practice. *J. Pediatr.* **2022**. [CrossRef] [PubMed]
54. Block, R.C.; Bang, M.; Peterson, A.; Wong, N.D.; Karalis, D.G. Awareness, diagnosis and treatment of heterozygous familial hypercholesterolemia (HeFH)—Results of a US national survey. *J. Clin. Lipidol.* **2021**, *15*, 682–689. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Review

New Trends and Therapies for Familial Hypercholesterolemia

Fahad Alnouri [1] and Raul D. Santos [2,3,*]

[1] Cardiovascular Prevention Unit, Department of Adult Cardiology, Prince Sultan Cardiac Centre, Riyadh 12233, Saudi Arabia
[2] Lipid Clinic Heart Institute (InCor), Medical School Hospital, University of Sao Paulo, Sao Paulo 05403-000, Brazil
[3] Academic Research Organization, Hospital Israelita Albert Einstein, Sao Paulo 05652-900, Brazil
* Correspondence: raul.santos@incor.usp.br; Tel.: +55-1126615320

Abstract: Familial hypercholesterolemia (FH) is associated with an elevated risk of atherosclerosis. The finding of monogenic defects indicates higher atherosclerotic risk in comparison with hypercholesterolemia of other etiologies. However, in heterozygous FH, cardiovascular risk is heterogeneous and depends not only on high cholesterol levels but also on the presence of other biomarkers and genes. The development of atherosclerosis risk scores specific for heterozygous FH and the use of subclinical coronary atherosclerosis imaging help with identifying higher-risk individuals who may benefit from further cholesterol lowering with PCSK9 inhibitors. There is no question about the extreme high risk in homozygous FH, and intensive LDL-cholesterol-lowering therapy must be started as soon as possible. These patients have gained life free of events in comparison with the past, but a high atherosclerosis residual risk persists. Furthermore, there is also the issue of aortic and supra-aortic valve disease development. Newer therapies such as inhibitors of microsomal transfer protein and angiopoietin-like protein 3 have opened the possibility of LDL-cholesterol normalization in homozygous FH and may provide an alternative to lipoprotein apheresis for these patients. Gene-based therapies may provide more definite solutions for lowering high LDL cholesterol and consequent atherosclerosis risk for people with FH.

Keywords: familial hypercholesterolemia; atherosclerosis; PCSK9; ANGPTL3

Citation: Alnouri, F.; Santos, R.D. New Trends and Therapies for Familial Hypercholesterolemia. *J. Clin. Med.* **2022**, *11*, 6638. https://doi.org/10.3390/jcm11226638

Academic Editor: Karol Kaminski

Received: 19 September 2022
Accepted: 5 November 2022
Published: 9 November 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. New Trends in Genetics, Epidemiology, and Atherosclerotic Cardiovascular Disease Risk in Familial Hypercholesterolemia

The new trends in FH are summarized in Table 1.

Table 1. Current facts and new trends in familial hypercholesterolemia.

Genetics	1-Monogenic defects implicated in higher atherosclerotic risk in comparison with hypercholesterolemia of other etiologies [1]. 2-LDL-C concentrations depend not only on defects on canonical genes but also on polygenic effects [2].
Atherosclerosis risk	1-Risk in heterozygous FH is heterogenous and depends not only on LDL-C but also other biomarkers, genes and subclinical atherosclerosis [3–6]. 2-Specific FH risk scores [7,8] and coronary atherosclerosis imaging ae useful in risk stratification [4,6]. 3-Risk of homozygous FH is very high, but therapies (drugs and apheresis) have changed the natural history of disease, and with reduction in CHD but persistence of aortic valve disease [9–11].
Therapies	1-Statin therapy reduces ASCVD risk in FH [12,13] 2-PCSK9 inhibitors have changed the way we treat heterozygous FH but should be used in those at highest risk when not available for all [14]. 3-Combination of statins, ezetimibe, PCSK9 inhibitors, MTP inhibitors and anti ANGPTL3 antibodies may normalize LDL-C in homozygous FH [15,16]. 4-Genetic therapies are being developed for FH and may bring more definitive LDL-C lowering.

1.1. Genetics of FH

Familial hypercholesterolemia (FH) is an autosomal disorder caused by genetic variants affecting the removal from plasma of low-density lipoprotein (LDL) [17] and is a cause of early atherosclerotic cardiovascular disease (ASCVD). Most frequently (95% of cases), FH is caused by loss-of-function variants in the low-density lipoprotein receptor (LDLR) gene (*LDLR*) located on chromosome 19. Occasionally the phenotype may be caused by pathogenic variants in apolipoprotein B (*APOB*), gain-of-function variants in proprotein convertase subtilisin/kexin type 9 (*PCSK9*), LDL receptor adaptor protein (*LDLRAP1*) and apolipoprotein E genes (*APOE*) [17,18]. Recently, the *STAP-1* (signal-transducing adaptor family member 1) gene was discarded as a cause of the FH phenotype [19]. Finally, phenocopies of FH may occur due to defects in *ABCG5/ABCG8* (sitosterolemia) [20] and *LIPA* (lysosomal acid lipase) [17].

LDLR is responsible for codifying the expression of LDL receptors on the extracellular surfaces of many types of cells, most important in hepatocytes, where they function to bind and internalize circulating LDL into cells for onward catabolism [17,18]. Loss-of-function variants in *LDLR* result in the reduced capacity of the cell–surface mechanism to bind and internalize circulating LDL particles and thereby lead to hypercholesterolemia.

In heterozygous FH, a single mutant allele of *LDLR*, *APOB* or *PCSK9* is inherited from either of the parents carrying the genetic variant, while in homozygous FH, two variants are inherited, one from each parent [17,18], thereby following a co-dominant pattern. Consequently, individuals with homozygous FH typically present a more severe phenotype than heterozygous FH [3]. In most situations, the homozygous FH phenotype results from the inheritance of the same defective allele of the same gene from each parent (i.e., true homozygotes, in most situations the LDLR gene). However, it may also occur from the inheritance of two different alleles of the same gene, one from each parent (compound heterozygotes) or from alleles of different genes (double heterozygotes). The homozygous FH phenotype may also occur as the inheritance of one recessive allele of *LDLRAP1* from each parent (autosomal recessive hypercholesterolemia) [17].

The phenotype severity and thus ASCVD risk in FH [2] may also be consequent to additional inheritance of small-effect genes that when aggregated further raise LDL-cholesterol (LDL-C) additionally to variants on the FH canonical genes [2]. These genes can be evaluated based on polygenic scores, and their effects may explain phenotypic variability in individuals from the same family bearing similar variants in the canonical genes. This occurs due to the variable transmission of these small-effect genes [21].

1.2. Epidemiology

A recent meta-analysis indicates a global prevalence of 1:313 individuals for heterozygous FH [22]. Homozygous FH is rare disease with a global prevalence estimated in (1:160,000–300,000) in the general population [23]. However, the prevalence of FH varies according to world region as shown in a recent registry from the Arabian Gulf region that showed an estimated heterozygous FH prevalence of 1:112, about 3-fold the estimated prevalence worldwide [22,24]. The latter may have important implications for the occurrence of cases of homozygous FH in Arabia considering its elevated rates of consanguineous marriages.

1.3. Heterogeneity in Atherosclerotic Cardiovascular Disease Risk

The pathophysiologic hallmark of FH is the increased build-up of atherosclerosis due to cumulative lifetime exposure to high-circulating LDL-C concentrations [25]. The lifetime cardiovascular events risk for untreated heterozygous FH individuals was estimated as 3.9-fold (88% absolute risk during lifetime) greater than that of non-FH subjects presenting a similar risk profile except for plasma cholesterol concentrations [26]. Khera et al. encountered a 3.7-fold higher risk of coronary artery disease presence in molecularly proven FH individuals in comparison with people with severe hypercholesterolemia

(LDL-C $\geq$ 190 mg/dL), where FH-causing variants in the canonical genes were not encountered [1].

A recent multinational registry with 61,612 individuals with the diagnosis of heterozygous FH from 56 countries (42,167 adults, mean age 46.2 years, 53.6% women) indicates an ASCVD frequency of 17.4% (2.1% for stroke and 5.2% for peripheral artery disease) [27]. For homozygous FH, a similar registry comprising 751 patients with the phenotype (75% with proven molecular diagnosis) from 38 countries (median age of diagnosis 12.0 years, 52% females) indicates a prevalence of clinical ASCVD or aortic stenosis of 9% at diagnosis [28]. Another study, this one from 8 Iberoamerican countries, comprised 134 individuals with the homozygous FH phenotype, 71 adults (mean age 39.3 years, 62% females) and 63 children (mean age 8.8 years, 51.2% females), 96% of them with confirmed molecular diagnosis [29]. The prevalence of clinical or subclinical ASCVD and aortic or supra-aortic valve diseases was 48% and 67%, respectively, in children and adults. Indeed, the advent of statin and lipoprotein apheresis therapies changed the natural history of homozygous FH with reductions in both coronary heart and supra-aortic valve diseases but with a persistence of calcified aortic valve stenosis [9,10]. Whether early diagnosis and aggressive LDL-C lowering will modify the course of aortic valve disease remains to be determined.

Despite a higher ASCVD risk in comparison with the one encountered in the general population, the latter varies significantly among individuals with heterozygous FH. This risk depends not only on type of molecular defect on the FH canonical genes and consequent LDL-C concentrations but also on the presence of risk biomarkers such as older age, male sex, smoking, low HDL-C, obesity, late onset of lipid-lowering therapy, higher lipoprotein(a) [Lp(a)] concentrations and presence of subclinical coronary atherosclerosis [3,4,30].

Even considering the robust effects of the autosomal dominant molecular defects on LDL-C and the ensuing ASCVD risk other genes may influence on the onset of the latter in people affected by FH [2,5]. In addition to genes that modify LDL-C concentrations [2], other variants that predispose to atherosclerosis development may influence coronary heart disease variability. Fahed et al. [5] elegantly showed that the risk of the latter varied from 18% to 76% at the age of 75 years depending on the percentile of a polygenic atherosclerosis risk score in individuals with monogenic FH-causing defects.

Currently, there is consensus that adults with FH should receive the highest-tolerated dose of statins with the aim of reducing LDL-C by at least 50% [3,31,32]. Ezetimibe therapy can also add 15–20% further LDL-C reduction with safety and low cost. PCSK9 inhibitors, e.g., the monoclonal antibodies alirocumab and evolocumab and the recently approved small-interference RNA inclisiran may add up to 40–60% average reduction in LDL-C in adults with heterozygous FH [33–35]. In pediatric heterozygous FH patients, evolocumab was approved after the age of 10 years and provides an additional 35–44% LDL-C reduction on top of that from usual care [36,37].

Consensus documents are unanimous in recommending PCSK9 inhibitors for heterozygous FH patients for secondary prevention [3,31,32] since most will persist with elevated LDL-C concentrations despite statin and ezetimibe therapy [38]. However, the reduced access to PCSK9 inhibitors when reimbursement is concerned precludes a more widespread use of these safe and efficacious therapies. There is evidence from prospective studies that risk stratification with clinical risk scores such as the SAFEHEART risk equation [7] and the Familial Hypercholesterolemia Risk Score [8] may help with gauging ASCVD risk in heterozygous FH. Furthermore, coronary artery calcification detected on cardiac computed tomography [6], a marker of atherosclerotic plaque burden, alone or when added to the latter [4,39], may help discriminate primary prevention heterozygous FH patients according to level of risk. In the 45% of heterozygous FH patients where CAC is absent (calcium score of zero) [40], there is an indication [4,6] that statins and ezetimibe reduced ASCVD risk [14] and no further therapies may be necessary in median 2.7- to 3.7-year follow-ups [41]; however this needs further confirmation from longer-term studies.

For homozygous FH, there is no discussion of the need to use all available therapies to reduce LDL-C such as statins, ezetimibe, and PCSK9 inhibitors if patients are respon-

sive [33,42]. Indeed, lipoprotein apheresis has been instrumental in LDL-C reduction in people with both severe heterozygous and homozygous FH [43]. There is evidence from observational studies that lipoprotein apheresis not only reduces atherosclerosis progression but also increases ASCVD event-free survival [44]. Indeed, the procedure can be used very early in the therapy algorithm of homozygous FH (Figure 1). Unfortunately, lipoprotein apheresis is not widely available, it has high monetary cost and it is not reimbursed in most countries. Therefore, robust pharmacological LDL-C-lowering therapies that act independently of LDLR such as the MTP (microsomal triglyceride transfer protein) inhibitor lomitapide [15,45] or the recently approved anti-ANGPTL3 (angiopoietin like 3 protein) monoclonal antibody evinacumab [16] are necessary [3]. These therapies may indeed reduce LDL-C concentrations to values seen in the general population [16]. However, there are severe cost issues with either apheresis or the new pharmacological therapies, and therefore access to them is low in most countries, as shown in the two recent published homozygous FH registries [28,29].

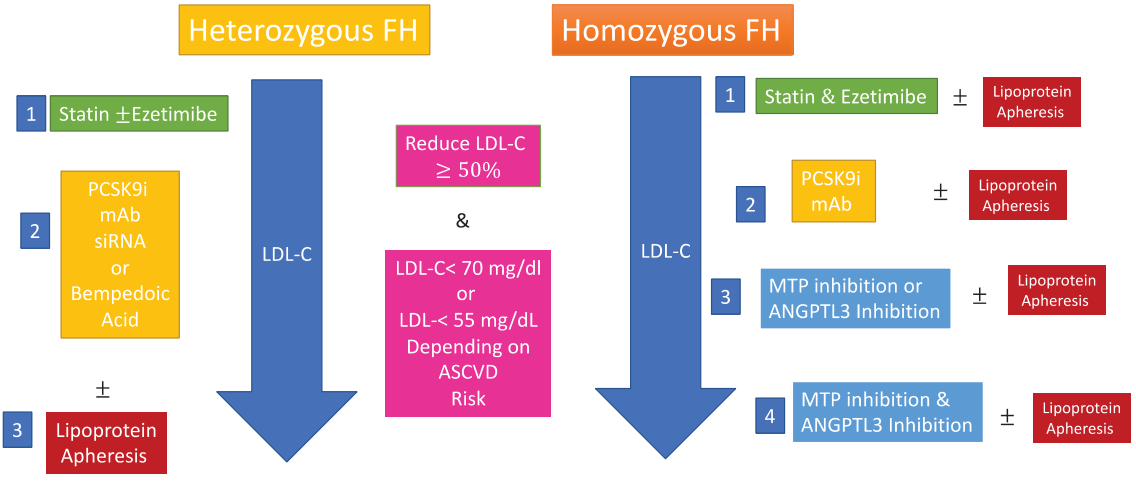

Figure 1. Treatment algorithms for heterozygous and homozygous familial hypercholesterolemia. Here are shown treatment algorithms for both heterozygous and homozygous forms of familial hypercholesterolemia. LDL-C reductions are recommended according to guidelines and consensus papers [3,32]. All adult patients should have at least a ≥50% reduction in LDL-C. Further goals of <70 mg/dL or 55 mg/dL are based on ASCVD risk (high or very high). Recommendations are based on approved drugs, especially for homozygous FH. For homozygous FH, lipid apheresis can be started at all algorithm levels. Drug choices should be based on regulatory issues, country approval and availability. In homozygous FH, PCSK9 inhibitors should be suspended if they do not provide adequate LDL-C and one should move from step 2 to 3. mAB-monoclonal antibody; siRNA-small interfering RNA.

Given that the risk and severity of ASCVD in FH patients vary depending on the type of genetic defects [17,18] as well as other risk biomarkers [18], and considering the development of novel therapies, the treatment of FH patients is changing from generalized to individualized (tailored) approaches. The following part of the present review aims to evaluate the trends in the of therapies for FH.

1.4. Impact of Statin Therapy and Ezetimibe on LDL-C and ASCVD Risk in FH

Statin therapy is a lifelong preventive treatment of choice for individuals with FH [46]. Statins reduce LDL-C by diminishing hepatic cholesterol synthesis acting on the 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA)-reductase. That leads to the upregulation of hepatic LDLR expression and the increased uptake of circulating LDL particles with

consequent higher biliary cholesterol excretion in the feces [47]. Reductions in cholesterol synthesis also result in less production of VLDL (very-low-density lipoprotein), a precursor of LDL. Overall, statins reduce the hepatic output of cholesterol to peripheral arteries, hence decreasing cholesterol plaque buildup assessed by a surrogate progression of carotid intima–media thickening and the risk of ASCVD events and mortality [12,46,48].

Several observational studies have indicated that statin therapy protects against ASCVD in people with FH [10–13]. In a cohort study, Versmissen et al. [12] enrolled 2146 patients with a confirmed genetic diagnosis of FH without previous coronary heart disease (CHD) manifestation from 27 outpatient lipid clinics in the Netherlands. The cohort was started on statin therapy (with lower doses of simvastatin, 33 mg/day or atorvastatin, 49 mg/day) and monitored for risk of CHD during a mean follow-up period of 8.5 years. At the end of the follow-up, statin therapy had reduced LDL-C by an average 44% in comparison with the baseline and the risk of myocardial infarction by 76% (hazard ratio, 0.24 [95% confidence interval, 0.18 to 0.30]) to a level comparable with that of the age-matched general population (hazard ratio, 1.44 95% confidence interval 0.80 to 2.60) [12]. However, findings from the study by Versmissen et al. [12] should be interpreted with caution considering its observational nature, lack of a randomized control group and wide confidence intervals when the risk was compared with the one from the non-FH population.

Acknowledging the differential ASCVD risk between heterozygous and homozygous FH subpopulations, three studies have evaluated the impact of statin therapy in these groups individually [11,13,49]. An observational multicenter study by Besseling et al. [13] evaluated the risk of CHD in individuals with heterozygous FH that had been diagnosed and followed in the Netherlands cascade screening program. A total of 1559 patients free of coronary artery disease (CAD) at baseline were started on 40 mg/day of either simvastatin (23.1%) and atorvastatin (22.8%) (n = 1041) or no treatment (n = 518). There were, respectively, 89 and 17 CAD and mortality events during 11,674 person-years of follow-up in the statin group. These values were significantly lower than the 22 and 9 events, respectively, during the 4892 person-years of follow-up in the non-statin group. Overall, the rates of CAD events were 5.3 vs. 8.8 per 1000 person-years in those receiving statins or not; $p < 0.001$. After adjustment for confounders, the rates of CAD and all-cause mortality were reduced by 44% with a hazard ratio of 0.56 (95% confidence interval: 0.33 to 0.96).

A 20-year prospective observational study [49] comprising 214 Dutch pediatric FH patients (98% with confirmed molecular diagnosis) emphasized the need for early cholesterol-lowering therapy in heterozygous FH. A 32% reduction in LDL-C with statins (mostly pravastatin) was associated with the normalization of carotid intima–media thickness progression when compared with nonaffected siblings. Most important, there were reductions in ASCVD and cardiovascular mortality when compared with parents who had not been treated in the past. At the age of 39 years, cardiovascular events and mortality were, respectively, 1% and 26% and 0% and 7%, respectively, in children who became adults and in their untreated parents. Therapy was safe and well tolerated. The results of course should be interpreted considering the limitations inherent in an observational study.

Raal et al. [11] evaluated the effect of statin therapy on CVD morbidity and mortality in a cohort of 149 homozygous FH patients (81 females) from two specialized lipid clinics in South Africa. The hazard ratios of the benefit from lipid-lowering therapy, mostly with statins, were 0.49 (95% confidence interval: 0.22–1.07; p = 0.07) and 0.34 (95% CI: 0.14–0.86; p = 0.02) for major adverse cardiovascular disease events and death, respectively. Surprisingly, results were seen despite a mean relative reduction in LDL-C of only 26.4% (from 620 $\pm$ 152 to 456 $\pm$ 132 mg/dL).

Ezetimibe is prescribed as a second-line therapy for LDL-C lowering in FH patients who persist with inadequate LDL-C concentrations [50]. It is a cholesterol-absorption inhibitor that acts at the "brush border" of the inner wall of the small intestines. Ezetimibe binds the sterol transporter protein, called Niemann-Pick C1 like 1 (NPC1L1) protein, hence reducing intestinal cholesterol absorption and increasing its fecal excretion [51]. Ezetimibe usually adds 10–15% additional LDL-C reduction to isolated statin therapy, and in both

heterozygous and homozygous FH patients, a significant further absolute reduction in LDL-C levels is achieved by combination therapy [52,53]. Indeed, even considering the lower impact on LDL-C reduction when compared with PCSK9 inhibitors, there is a strong recommendation to start with the highest-tolerated statin dose and ezetimibe combination rather than statin therapy alone in people with FH [54]. However, particularly in those with FH and previous ASCVD or in those with high subclinical atherosclerosis burden, there is the unmet need of still-elevated LDL-C [14,38], and these patients will often require a third-line pharmacological intervention such as PCSK9 inhibitors to achieve the target LDL-C goals [55,56]. PCSK9 inhibitors are among the current targeted molecular therapies for FH, which are discussed in detail in the subsequent sections.

2. New Trends in Therapies for FH

Several new targeted therapies were developed, and some are being tested to achieve the LDL-C goals for high-/very-high-risk FH patients as recommended by the ESC/EAS 2016–2019 guidelines [50]. The mechanism of action and impact on LDL-C plasma concentrations for both heterozygous and homozygous FH are shown in Table 2. The advantage of targeted therapies is that they provide clinicians with the power to practice personalized or precision medicine with the aim of achieving better risk/benefit and cost/effectiveness of therapies. This is important considering the elevated costs of monoclonal antibodies and RNA-targeted therapies.

Table 2. Mechanism of action and efficacy of approved therapies to treat familial hypercholesterolemia.

	Compound	Target	Mechanism of Action	Efficacy in Heterozygous FH (LDL-C Reduction)	Efficacy in Homozygous FH (LDL-C Reduction)
Statins	Small molecule	HMG-CoA-reductase	Reduces cholesterol synthesis and VLDL production. Increases hepatic LDLR expression [47].	30–50% [57].	10–25% [53].
Ezetimibe	Small molecule	NPC1L1	Reduces intestinal cholesterol absorption and increases hepatic LDLR expression [47].	10–15% [57].	10–15% [53].
Bempedoic acid	Small molecule	ACL	Reduces cholesterol synthesis and VLDL production. Increases LDLR expression [58].	16.5% in a pooled group of FH and other hypercholesterolemia patients [58].	N.A.
Lomitapide *	Small molecule	MTP	Reduces VLDL synthesis [47].	N.A.	33–50% depending on the dose [15,45,59].
Alirocumab &Evolocumab	Monoclonal antibody	Circulating PCSK9	Reduces LDLR degradation [47].	50–60% [3,33] adults and 35–38% pediatric patients for evolocumab [36,37].	20–34% (depends on *LDLR* variant 0–50%) [33,42].
Inclisiran	Small-interfering RNAs	Hepatic PCSK9 synthesis	Reduces LDLR degradation [60].	44.3% reduction [35].	Study ongoing.
Evinacumab *	Monoclonal antibody	Circulating ANGPTL3	Possibly increases the removal of VLDL and IDL particles by LDLR independent pathways [61].	38.5–56% reduction depending on dose regimen and patient [62].	49% [16].
Lipoprotein apheresis	Device	Circulating LDL, Lp(a) and VLDL particles	Reduces pro-atherogenic apoB-100-containing lipoproteins LDL, Lp(a), and VLDL as well as pro-inflammatory biomarkers [43].	60–80% [3].	60–80% [3].

Note: HMG-CoA hydroxy methyl glutaryl Coenzime A; NPC1L1- Niemann-Pick C1 Like 1; ACL-Adenosine triphosphate citrate lyase enzyme (ACL); MTP-Microsomal triglyceride transfer protein; PCSK9-proprotein convertase subtilisin/kexin type 9; ANPTL3-Angiopoietin Like 3 Protein); LDLR-LDL receptor; *LDLR*-LDL receptor gene; Lp(a)-lipoprotein(a); * approved only for homozygous FH.

2.1. PCSK9 Inhibitors

PCSK9 inhibitors are a new class of cholesterol-lowering drugs currently used as a third-line treatment for FH or for statin-intolerant or very-high-ASCVD-risk patients. PCSK9 is an enzyme produced mainly in the liver that is secreted into the plasma and plays a critical role in LDL catabolism. LDL normally clears from peripheral blood as a complex with the LDLR that enters the hepatocyte [63]. PCSK9 binds the LDLR at the hepatocyte

surface, reducing its recycling from cytoplasm to cell membrane and consequently diminishing LDL clearance [64]. A previous animal study demonstrated that mice overexpressing PCSK9 protein have decreased LDLR function and elevated plasma LDL-C, while PCSK9 knockout mice have increased LDLR activity and lower plasma LDL-C levels [65]. Studies in humans showed that gain- and loss-of-function variants in PCSK9 were associated with an FH phenotype [66] and lower LDL-C concentrations and ASCVD risk [67], respectively.

These findings formed the basis for the development of PCSK9 inhibitors, whose mechanisms, as the name suggests inhibits the activity of PCSK9 proteins via different mechanisms. Three different subclasses of PCSK9 inhibitors are discussed.

Human monoclonal antibodies against PCSK9 (PCSK9-mAb) primarily include alirocumab and evolocumab [33,42,68]. The primary mechanism of action of PCSK9-mAb is via their binding activity on PCSK9 in the plasma, thereby blocking PCSK9 from binding the LDLR. The latter means that more receptors are available for the binding of ApoB100-LDL complex for the onward clearance of circulating LDL particles [47,69].

Alirocumab and evolocumab are indicated for homozygous and heterozygous FH patients who persist with elevated LDL-C despite the use of statins and ezetimibe therapies. They are administered subcutaneously in bimonthly doses of 75–150 mg for alirocumab or 140 mg for evolocumab or 300 mg and 420 mg, respectively, for alirocumab and evolocumab once monthly. A recent open-label, single-arm multicenter study by Santos et al. (TAUSSIG) [38] evaluated the safety and efficacy of evolocumab in 300 patients aged $\geq$12 years with HoFH (n = 106) and severe HeFH (n = 194) who at the time of enrolment were on stable lipid-lowering therapy. Patients were started on evolocumab (420 mg monthly and later to 420 mg bimonthly as needed) or 420 mg bimonthly if on lipoprotein apheresis. At 12 weeks of evolocumab treatment, LDL-C decreased by 59.8 mg/dL (21.2%) and 104.4 mg/dL (54.9%) in patients with HoFH and HeFH, respectively; effects were sustained during a median follow-up of 4.1 years. A total of 26% of patients on active apheresis (severe heterozygous FH only) had their blood-filtering therapy discontinued to LDL-C control, and the overall rate of CVD events was only 2.7%, suggesting cardiovascular benefit of the drug in comparison with historical controls. Adverse reactions occurred in 89.3% of patients, which included nasopharyngitis, influenza, upper respiratory tract infection and headache [38]. The latter, however, did not lead to drug discontinuation. In the same study, Raal et al. [7] demonstrated that in homozygous FH, the presence of *LDLR* null variants was associated with a lower or absent reduction in LDL-C with evolocumab in comparison with those with defective variants.

Blom et al. evaluated the effects of alirocumab in homozygous FH [8]. In a randomized, double-blind, placebo-controlled, parallel-group study, 69 patients on high-intensity lipid-lowering therapy including statins, ezetimibe, lomitapide and apheresis were enrolled. Patients were randomized to receive 150 mg alirocumab treatment every 2 weeks (n = 46; baseline LDL-C = 295 mg/dL) or placebo (n = 23; baseline LDL-C = 259 mg/dL) for a duration of 12 weeks. Alirocumab significantly decreased LDL-C by 26.9% compared with 8.6% for placebo ($p < 0.0001$). Similar to evolocumab [38], alirocumab was generally well tolerated, with a safety profile comparable with that of placebo [8]. Both studies show that PCSK9-mAb may be useful for LDL-C reduction in either severe heterozygous or homozygous FH, although the efficacy in the latter is much less pronounced.

Evolocumab was approved for pediatric patients (older than 10 years) with HeFH based on results from the HAUSER trial [36]. In HAUSER, evolocumab (420 mg once a month) was administered in a randomized 2:1 double-blind fashion to 157 pediatric patients (mean age 13.7 years) who persisted with LDL-C > 135 mg/dL despite usual statin and/or ezetimibe therapy (mean baseline LDL-C 185 $\pm$ 45 mg/dL). After 24 weeks, there was a mean 38.3% reduction ($-$44.5% vs. $-$6.2%) in LDL-C versus placebo. Adverse events were similar in comparison with placebo, with nasopharyngitis and headache being the most frequent. Recently Santos et al. [37] have published the long-term open label follow-up of HAUSER. In that study, 150 patients received evolocumab and completed the open-label extension with a median follow-up of 80.3 weeks. The main study objective was safety and

tolerability; treatment-associated adverse events occurred in 70% of study participants and were similar to the ones occurring in the randomized double-blind phase. No event led to treatment discontinuation, and no patient developed anti-drug antibodies. There were no adverse events related to growth, sexual maturation, neurocognitive function, glucose homeostasis, steroid hormones or liposoluble-vitamin blood concentrations. At week 80, the mean percentage change from baseline in LDL cholesterol was −35.3% (standard deviation 28.0). The study clearly shows that evolocumab can add LDL-C reduction to usual therapy in heterozygous FH, is safe and is well tolerated.

Small-interfering RNA (siRNA) technology is a novel approach to PCSK9 inhibition [60]. The siRNA technology deploys a small double-stranded RNA molecule of 19–23 nucleotides in size to induce the silencing of the target gene. The siRNA inclisiran is a novel PCSK9 inhibitor for the treatment of heterozygous FH and common hypercholesterolemia [60]. Inclisiran blocks the translation of PCSK9 messenger RNA, leading to its degradation by the RNA-induced silencing complex (RISC) andthereby decreasing the concentrations of intrahepatic and plasma PCSK9 [35,60]. Compared with PCSK9-mAbs, inclisiran has a more convenient dose regimen of 300 mg twice-yearly injections and could be useful for enhancing patient compliance. In a recent phase 3, double-blind trial by Raal et al. [35], 482 adult heterozygous FH patients were randomized to receive 300 mg of inclisiran (n = 241) or matching placebo (n = 241) and followed up for 540 days. The mean reduction in the LDL-C level from day 90 to day 540 was 38.1% in the inclisiran group, while there was an increase of 6.2% in placebo ($p < 0.001$), a −44.3% difference. The most frequent adverse events not differing from placebo were nasopharyngitis, influenza, upper respiratory tract infection and back pain. In a pilot study, Hovingh et al. [70] tested the feasibility of PCSK9 suppression with inclisiran in four homozygous FH patients. LDL-C changes varied from +3% to −37% in 180 days, and PCSK9 plasma levels were reduced by −48.7% to −83.6% at day 90 and by −40.2% to −80.5% at day 180. This study paved the way for ORION 5 (NCT03851705) with a greater number of homozygous FH patients. However, results are not yet published.

At any rate, the infrequent dosing regimen and acceptable safety profile of inclisiran make it a suitable alternative to PCSK9-mAbs [35].

Oral PCSK9 inhibitors are being developed as an alternative to the subcutaneous PCSK9-mAbs and inclisiran. This presentation may be especially suitable for FH patients who cannot comply with subcutaneous injections of PCSK9-mAbs and inclisiran. MK-0616 is an orally bioavailable PCSK9 inhibitor and preliminary results from an ongoing phase I clinical trial by Johns et al. [71] were presented at the 2021 Scientific Sessions of the American Heart Association. The study involved 60 healthy male volunteers and has demonstrated that MK-0616 (10–300 mg) was well-tolerated with no adverse effects. In the second phase of the study, involving 40 hypercholesterolemic patients (male and female), MK-0616 lowered baseline LDL-C levels by 65% after 14 days of treatment. Further data are, however, necessary.

Gennemark et al. [72] developed a chemically modified PCSK9 antisense oligonucleotide (ASO) for oral delivery. Preliminary results showed that the subcutaneous injection of 90 mg ASO reduced PCSK9 by >90% in patients with elevated LDL-C levels with a predicted 80% steady state with a 25 mg monthly maintenance dose [72]. When ASO was co-formulated with sodium caprate (a permeation enhancer) in an oral tablet form and administered to dogs, it resulted in 7% hepatic bioavailability, which was 5 times greater than that of plasma. Using prediction models, 15 mg/day of oral ASO should suppress PCSK9 in peripheral blood by 80% steady state and therefore be viable for oral formulation [72].

PCSK9 inhibitors are frequently prescribed as third-line treatment in patients who could not respond well or tolerate conventional lipid-lowering therapies. They are ideal for those with heterozygous FH [73]. However, despite the use of high-dose statins and ezetimibe in combination with PCSK9 inhibitors, many patients with homozygous FH fail

to achieve optimal reductions of LDL-C levels [74]. Thus, more treatment strategies are still needed.

2.2. Bempedoic Acid

Bempedoic acid (BA) is an oral inhibitor of cholesterol biosynthesis approved for cholesterol reduction [58]. Its mechanism of action involves the inhibition of the adenosine triphosphate citrate lyase (ACL), which acts upstream of HMG-CoA-reductase in the cholesterol biosynthesis pathway. A recent randomized controlled trial enrolled 2230 patients with ASCVD, heterozygous FH or both, all on the maximum tolerated dose of statin monotherapy (mean baseline LDL-C = 103.2 $\pm$ 29.4 mg/dL) to receive either BA treatment (n = 1488) or placebo (n = 742). During the 52 weeks of treatment, the incidence of adverse effects was comparable between the two groups. At week 12, the BA group exhibited significant LDL-C reduction from baseline (16.5%). At 52 weeks, BA did not result in higher incident of adverse effects and LDL-C lowering effects were maintained [75]. Similar results, a 21% reduction in LDL-C level compared with placebo, were reported after 12 weeks in another randomized study that evaluated BA in patients with hypercholesterolemia and statin intolerance [76]. These findings, in general, indicate that BA is efficacious and safe for lowering LDL-C in patients with hyperlipidemia including heterozygous FH patients.

2.3. Angiopoietin-like 3 Protein (ANGPTL3) Inhibitors

Angiopoietin-like 3 protein (ANGPTL3) is an endogenous inhibitor of lipoprotein and endothelial lipases. Loss-of-function variants of the ANGPTL3 gene are associated with lower serum cholesterol and triglyceride levels and a lower ASCVD risk [77]. Evinacumab, a human monoclonal antibody for ANGPTL3 inhibition (ANGPTL3-mAbs), was approved for the treatment of adults and pediatric patients older than 12 years with homozygous FH [16,62]. Raal et al. [16] showed in a randomized double blind study that 15 mg/kg infusions of evinacumab every 4 weeks reduced LDL-c by 49% at week 24 in comparison with placebo in homozygous FH patients (n = 65, baseline LDL-C of 255 mg/dL) undergoing maximal lipid-lowering therapies (statins, ezetimibe, PCSK9 inhibitors, lomitapide and/or lipoprotein apheresis). Of importance, and different, from PCSK9 inhibitors, evinacumab provided robust LDL-C reduction ($-$43.4%) even in patients with *LDLR* null variants. Adverse events did not differ from placebo. Animal models suggest that evinacumab increases the removal of VLDL and IDL particles, precursors of LDL, by a non-LDLR related pathway [61].

In another double-blind, placebo-controlled, phase 2 trial, Rosenson et al. [46] enrolled 272 patients with and without heterozygous FH and with evidence of refractory hypercholesterolemia with atherosclerosis (LDL-C levels $\geq$ 70 mg/dL) or without atherosclerosis (LDL-c levels $\geq$ 100 mg/dL). Patients were randomly assigned to receive evinacumab at various dosing regimens (either subcutaneous or intravenous) or a placebo. After 16 weeks, evinacumab lowered LDL-C by 38.5–56% according to dose regimen compared with placebo, with low incidence of adverse effects (3–16%) across trial groups. Evinacumab is not yet approved for refractory heterozygous FH. Despite favorable results with monoclonal antibodies against ANGPTL3, recently, the development of an ASO against that protein, vupanorsen, was interrupted due to adverse liver events [78]. This clearly demonstrates that despite similar targets, different technologies vary when safety is concerned, and more clinical studies are warranted.

2.4. MTP Inhibitors

MTP is an enzyme essential for the assembly of VLDL in hepatocytes and chylomicrons in enterocytes. The inhibition of MTP blocks VLDL assembly and reduces LDL-C levels [47]. Lomitapide is an MTP inhibitor used as a lipid-lowering agent approved for the treatment of homozygous FH patients [15,59]. A previous single-arm, open-label, phase 3 multicenter study by Cuchel et al. [59] enrolled 29 homozygous FH patients to receive lomitapide in doses ranging from 5 to 60 mg/day depending on safety and tolerability.

Lomitapide achieved a 50% reduction in baseline LDL-C levels at 26 weeks and maintained steady states of 44% and 38% at weeks 56 and 78, respectively. However, the drug produced gastrointestinal adverse effects and liver steatosis, though this did not result in discontinuation.

Two studies [15,45] have provided long-term efficacy and safety data on lomitapide in patients with homozygous FH treated up to 5.9 years. Blom et al. [15], in an extension of the original study by Cuchel et al. [59], showed in 17 patients followed up for 5.1 years that lomitapide in a 40 mg dose reduced LDL-C by 45% with hepatic safety. The most important reported adverse events were diarrhea, nausea, dyspepsia and vomiting. Underberg et al. [45] showed in the LOWER-registry that the median lomitapide dose of 10 mg provided a sustained 33% reduction in LDL-C after 5.9 years. In those who remained on lomitapide therapy until the end of follow-up, LDL-C reduction was 45%, with 65.4% and 41.1% achieving an LDL-C < 100 mg/dL or <70 mg/dL, respectively. Treatment-related adverse events occurred in 54.6%, and 23.2% of patients, who discontinued the therapy due to that. Gastrointestinal and hepatic events occurred, respectively, in 13.5% and 15.1%. Overall, the studies reported consistent results demonstrating that lomitapide, when used in combination with other lipid-lowering therapies is effective in lowering LDL-C levels with an acceptable tolerability and safety profile [15,45].

Ben-Omran et al. [79] evaluated the effects of lomitapide (mean dose 24.5 $\pm$ 4.3 mg/day; during 20.0 $\pm$ 2.9 months) in a case series of 11 pediatric homozygous FH patients, mean age 11.6 $\pm$ 1.1 years and 64% males, undergoing statin and or ezetimibe therapy. LDL-C was reduced by 58.4 $\pm$ 6.8% from a baseline of 419 $\pm$ 74.6 mg/dL. The most frequent adverse events were nausea, vomiting and diarrhea but were well tolerated. A phase III study (NCT04681170) is testing the efficacy and safety of lomitapide in pediatric homozygous FH patients aged 5–17 years old with a duration of up to 80 weeks.

2.5. Gene Therapies

People affected by FH are ideal candidates for gene therapy, which is potentially the most definitive treatment for life. Possible gene therapies include CRISPR/Cas9 for heterozygous FH and viral vectors for homozygotes.

The Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)-Associated System 9 (Cas9) or simply CRISPR/Cas9 is the most promising genome editing tool for model systems including animal zygotes and human cells. CRISPR/Cas9 has useful applications in genetic research and is a promising tool for clinical applications in treating genetic disorders [80].

A recent in vivo animal study used a recombinant adeno-associated virus (AAV) vector carrying CRISPR/Cas9 gene editor (AAV-CRISPR/Cas9) and targeting an LDLR mutant mice model [81]. The mutant mice with loss of LDLR function exhibited severe atherosclerotic phenotypes when fed a high-fat diet. The AAV-CRISPR/Cas9-mediated gene editing partially corrected the point mutation in the LDLR gene expressed in hepatocytes and restored partial LDLR protein expression. The treatment significantly decreased total cholesterol, triglycerides, and LDL-c in the serum and, consequently, decreased the build-up of atherosclerotic plaques in the aorta. This finding shows that CRISPR/Cas9 is promising for the treatment of heterozygous FH.

A recombinant adeno-associated virus (AAV) vector carrying an *LDLR* transgene has been recently unveiled and is currently at phase 1/2a testing phase [82]. In animal studies, an LDLR-deficient mouse model (Ldlr$^{-/-}$, Apobec1$^{-/-}$ or double knockout—DKO) treated with AAV carrying an LDLR transgene at vectors doses as low as 3×10^{11} exhibited enhanced transgene expression and decreased serum LDL-C levels [83]. Findings from DKO mice indicate the potential of an AAV vector carrying an LDLR transgene to be used for the treatment of high-risk homozygous FH patients.

3. Conclusions

FH is a disease associated with an elevated risk of ASCVD that needs to be early diagnosed and adequately treated. The diagnosis of FH has implications not only for the index case but also for the relatives who need to be identified by cascade screening [17]. The molecular diagnosis is important since the presence of monogenic defects implies a higher ASCVD risk in comparison with hypercholesterolemia of other etiologies [1]. Despite the elevated atherosclerosis [3,30] risk in heterozygous FH, the latter is heterogeneous and depends not only on cholesterol levels but also on the presence or not of other genes and biomarkers. The development of ASCVD risk scores specific for FH and the use of coronary subclinical atherosclerosis imaging may help the institution of targeted further LDL-C-lowering therapies on top of statins and ezetimibe in heterozygous FH [14]. This is important considering the low worldwide access to novel robust LDL-C-lowering therapies such as the PCSK9 inhibitors.

There is no question about the extreme high risk to people with homozygous FH, and intensive LDL-C-lowering therapy must be started as soon as possible. These patients have gained life free of events in comparison with the past [10,11], but residual risk is still extremely elevated, and there is also the issue of aortic valve disease development [9]. The onset of MTP inhibitors [45] and monoclonal antibodies against ANGPTL3 [16] associated or not with lipoprotein apheresis and PCSK9 inhibitors has opened the possibility of the normalization of LDL-C in homozygous FH; these may even provide one alternative to the latter. Figure 1 shows a suggested therapy algorithm for both heterozygous and homozygous FH forms with available approved therapies. The aim is to reduce LDL-C at least 50% and attain the recommended LDL-C goals according to ASCVD risk [3,32], a barrier that with the newer therapies finally became possible to be trespassed. Certainly, there is still the important unmet need of access to these therapies that remains a barrier in most low- to middle-income countries [27–29]. Gene-based therapies [80] may deliver more definite solutions to LDL-C and consequent ASCVD risk reduction for people with FH.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: RDS is recipient of a scholarship from Conselho Nacional de Pesquisa e Desenvolvimento Tecnológico, Brazil, (CNPq) #303734/2018-3.

Conflicts of Interest: F.A. received honoraria related to consulting and speaker activities for Amgen. R.D.S. has received honoraria related to consulting, research and/or speaker activities from: Abbott, Ache, Amgen, Amryt, Astra Zeneca, Biolab, Esperion, Hypera Farma, Eli-Lilly, Getz Pharma, Kowa, Libbs, Novo-Nordisk, Novartis, Merck, Pfizer, PTC and Sanofi.

References

1. Khera, A.V.; Won, H.-H.; Peloso, G.M.; Lawson, K.S.; Bartz, T.M.; Deng, X.; van Leeuwen, E.M.; Natarajan, P.; Emdin, C.A.; Bick, A.G.; et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients with Severe Hypercholesterolemia. *J. Am. Coll. Cardiol.* **2016**, *67*, 2578–2589. [CrossRef] [PubMed]
2. Trinder, M.; Paquette, M.; Cermakova, L.; Ban, M.R.; Hegele, R.A.; Baass, A.; Brunham, L.R. Polygenic Contribution to Low-Density Lipoprotein Cholesterol Levels and Cardiovascular Risk in Monogenic Familial Hypercholesterolemia. *Circ. Genom. Precis. Med.* **2020**, *13*, 515–523. [CrossRef] [PubMed]
3. Santos, R.D.; Gidding, S.S.; Hegele, R.A.; Cuchel, M.A.; Barter, P.J.; Watts, G.F.; Baum, S.J.; Catapano, A.L.; Chapman, M.J.; Defesche, J.C.; et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: A consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol.* **2016**, *4*, 850–861. [CrossRef]
4. Gallo, A.; de Isla, L.P.; Charrière, S.; Vimont, A.; Alonso, R.; Muñiz-Grijalvo, O.; Díaz-Díaz, J.L.; Zambón, D.; Moulin, P.; Bruckert, E.; et al. The Added Value of Coronary Calcium Score in Predicting Cardiovascular Events in Familial Hypercholesterolemia. *JACC Cardiovasc. Imaging* **2021**, *14*, 2414–2424. [CrossRef] [PubMed]

5. Fahed, A.C.; Wang, M.; Homburger, J.R.; Patel, A.P.; Bick, A.G.; Neben, C.L.; Lai, C.; Brockman, D.; Philippakis, A.; Ellinor, P.T.; et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. *Nat. Commun.* **2020**, *11*, 3635. [CrossRef] [PubMed]
6. Miname, M.H.; Bittencourt, M.S.; Moraes, S.R.; Alves, R.I.; Silva, P.R.; Jannes, C.E.; Pereira, A.C.; Krieger, J.E.; Nasir, K.; Santos, R.D. Coronary Artery Calcium and Cardiovascular Events in Patients with Familial Hypercholesterolemia Receiving Standard Lipid-Lowering Therapy. *JACC Cardiovasc. Imaging* **2019**, *12*, 1797–1804. [CrossRef] [PubMed]
7. Perez de Isla, L.; Alonso, R.; Mata, N.; Fernández-Pérez, C.; Muñiz, O.; Díaz-Díaz, J.L.; Saltijeral, A.; Fuentes-Jiménez, F.; De Andrés, R.; Zambón, D.; et al. Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation* **2017**, *135*, 2133–2144. [CrossRef] [PubMed]
8. Paquette, M.; Bernard, S.; Cariou, B.; Hegele, R.A.; Genest, J.; Trinder, M.; Brunham, L.R.; Béliard, S.; Baass, A. Familial Hypercholesterolemia-Risk-Score: A New Score Predicting Cardiovascular Events and Cardiovascular Mortality in Familial Hypercholesterolemia. *Arter. Thromb. Vasc. Biol.* **2021**, *41*, 2632–2640. [CrossRef]
9. Bélanger, A.M.; Akioyamen, L.E.; Ruel, I.; Hales, L.; Genest, J. Aortic stenosis in homozygous familial hypercholesterolaemia: A paradigm shift over a century. *Eur. Heart J.* **2022**, *43*, 3227–3239. [CrossRef]
10. Thompson, G.R.; Blom, D.J.; Marais, A.D.; Seed, M.; Pilcher, G.J.; Raal, F.J. Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol. *Eur. Heart J.* **2018**, *39*, 1162–1168. [CrossRef]
11. Raal, F.J.; Pilcher, G.J.; Panz, V.R.; van Deventer, H.E.; Brice, B.C.; Blom, D.J.; Marais, A.D. Reduction in Mortality in Subjects with Homozygous Familial Hypercholesterolemia Associated with Advances in Lipid-Lowering Therapy. *Circulation* **2011**, *124*, 2202–2207. [CrossRef] [PubMed]
12. Versmissen, J.; Oosterveer, D.; Yazdanpanah, M.; Defesche, J.C.; Basart, D.C.G.; Liem, A.H.; Heeringa, J.; Witteman, J.C.; Lansberg, P.J.; Kastelein, J.J.P.; et al. Efficacy of statins in familial hypercholesterolaemia: A long term cohort study. *BMJ Clin. Res. Ed.* **2008**, *337*, a2423. [CrossRef] [PubMed]
13. Besseling, J.; Hovingh, G.K.; Huijgen, R.; Kastelein, J.J.P.; Hutten, B.A. Statins in Familial Hypercholesterolemia: Consequences for Coronary Artery Disease and All-Cause Mortality. *J. Am. Coll. Cardiol.* **2016**, *68*, 252–260. [CrossRef] [PubMed]
14. Mszar, R.; Nasir, K.; Santos, R.D. Coronary Artery Calcification in Familial Hypercholesterolemia: An Opportunity for Risk Assessment and Shared Decision Making with the Power of Zero? *Circulation* **2020**, *142*, 1405–1407. [CrossRef]
15. Blom, D.J.; Averna, M.; Meagher, E.A.; Theron, H.D.T.; Sirtori, C.R.; Hegele, R.A.; Shah, P.K.; Gaudet, D.; Stefanutti, C.; Vigna, G.; et al. Long-Term Efficacy and Safety of the Microsomal Triglyceride Transfer Protein Inhibitor Lomitapide in Patients with Homozygous Familial Hypercholesterolemia. *Circulation* **2017**, *136*, 332–335. [CrossRef]
16. Raal, F.J.; Rosenson, R.S.; Reeskamp, L.F.; Hovingh, G.K.; Kastelein, J.J.; Rubba, P.; Ali, S.; Banerjee, P.; Chan, K.-C.; Gipe, D.A.; et al. Evinacumab for Homozygous Familial Hypercholesterolemia. *N. Engl. J. Med.* **2020**, *383*, 711–720. [CrossRef]
17. Defesche, J.C.; Gidding, S.S.; Harada-Shiba, M.; Hegele, R.A.; Santos, R.D.; Wierzbicki, A.S. Familial hypercholesterolaemia. *Nat. Rev. Dis. Primers* **2017**, *3*, 17093. [CrossRef]
18. Rocha, V.Z.; Santos, R.D. Past, Present, and Future of Familial Hypercholesterolemia Management. *Methodist DeBakey Cardiovasc. J.* **2021**, *17*, 28–35. [CrossRef]
19. Loaiza, N.; Hartgers, M.L.; Reeskamp, L.F.; Balder, J.W.; Rimbert, A.; Bazioti, V.; Wolters, J.C.; Winkelmeijer, M.; Jansen, H.P.; Dallinga-Thie, G.M.; et al. Taking One Step Back in Familial Hypercholesterolemia: STAP1 Does Not Alter Plasma LDL (Low-Density Lipoprotein) Cholesterol in Mice and Humans. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40*, 973–985. [CrossRef]
20. Tada, M.T.; Rocha, V.Z.; Lima, I.R.; Oliveira, T.G.M.; Chacra, A.P.; Miname, M.H.; Nunes, V.S.; Nakandakare, E.R.; Castelo, M.H.C.G.; Jannes, C.E.; et al. Screening of *ABCG5* and *ABCG8* Genes for Sitosterolemia in a Familial Hypercholesterolemia Cascade Screening Program. *Circ. Genom. Precis. Med.* **2022**, *15*, e003390. [CrossRef]
21. Talmud, P.J.; Shah, S.; Whittall, R.; Futema, M.; Howard, P.; Cooper, J.A.; Harrison, S.C.; Li, K.; Drenos, F.; Karpe, F.; et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: A case-control study. *Lancet* **2013**, *381*, 1293–1301. [CrossRef]
22. Beheshti, S.; Madsen, C.; Varbo, A.; Nordestgaard, B. Worldwide prevalence of familial hypercholesterolemia: Meta-analyses of 11 million subjects. *J. Am. Coll. Cardiol.* **2020**, *75*, 2553–2566. [CrossRef] [PubMed]
23. Vallejo-Vaz, A.J.; Ray, K.K. Epidemiology of familial hypercholesterolaemia: Community and clinical. *Atherosclerosis* **2018**, *277*, 289–297. [CrossRef] [PubMed]
24. Alhabib, K.F.; Al-Rasadi, K.; Almigbal, T.H.; Batais, M.A.; Al-Zakwani, I.; Al-Allaf, F.A.; Al-Waili, K.; Zadjali, F.; Alghamdi, M.; Alnouri, F.; et al. Familial Hypercholesterolemia in the Arabian Gulf Region: Clinical results of the Gulf FH Registry. *PLoS ONE* **2021**, *16*, e0251560. [CrossRef] [PubMed]
25. Bilen, O.; Pokharel, Y.; Ballantyne, C.M. Genetic Testing in Hyperlipidemia. *Cardiol. Clin.* **2015**, *33*, 267–275. [CrossRef]
26. Villa, G.; Wong, B.; Kutikova, L.; Ray, K.K.; Mata, P.; Bruckert, E. Prediction of cardiovascular risk in patients with familial hypercholesterolaemia. *Eur. Heart J. Qual. Care Clin. Outcomes* **2017**, *3*, 274–280. [CrossRef]
27. Collaboration EASFHS. Global perspective of familial hypercholesterolaemia: A cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet* **2021**, *398*, 1713–1725. [CrossRef]
28. Tromp, T.R.; Hartgers, M.L.; Hovingh, G.K.; Vallejo-Vaz, A.J.; Ray, K.K.; Soran, H.; Freiberger, T.; Bertolini, S.; Harada-Shiba, M.; Blom, D.J.; et al. Worldwide experience of homozygous familial hypercholesterolaemia: Retrospective cohort study. *Lancet* **2022**, *399*, 719–728. [CrossRef]

29. Alves, A.C.; Alonso, R.; Diaz-Diaz, J.L.; Medeiros, A.M.; Jannes, C.E.; Merchan, A.; Vasques-Cardenas, N.A.; Cuevas, A.; Chacra, A.P.; Krieger, J.E.; et al. Phenotypical, Clinical, and Molecular Aspects of Adults and Children with Homozygous Familial Hypercholesterolemia in Iberoamerica. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40*, 2508–2515.
30. Miname, M.H.; Santos, R.D. Reducing cardiovascular risk in patients with familial hypercholesterolemia: Risk prediction and lipid management. *Prog. Cardiovasc. Dis.* **2019**, *62*, 414–422. [CrossRef]
31. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; De Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2019**, *73*, e285–e350. [CrossRef] [PubMed]
32. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur. Heart J.* **2020**, *41*, 111–188. [CrossRef] [PubMed]
33. Santos, R.D.; Stein, E.A.; Hovingh, G.K.; Blom, D.J.; Soran, H.; Watts, G.F.; López, J.A.G.; Bray, S.; Kurtz, C.E.; Hamer, A.W.; et al. Long-Term Evolocumab in Patients with Familial Hypercholesterolemia. *J. Am. Coll. Cardiol.* **2020**, *75*, 565–574. [CrossRef] [PubMed]
34. Kastelein, J.J.; Ginsberg, H.N.; Langslet, G.; Hovingh, G.K.; Ceska, R.; Dufour, R.; Blom, D.; Civeira, F.; Krempf, M.; Lorenzato, C.; et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur. Heart J.* **2015**, *36*, 2996–3003. [CrossRef] [PubMed]
35. Raal, F.J.; Kallend, D.; Ray, K.K.; Turner, T.; Koenig, W.; Wright, R.S.; Wijngaard, P.L.; Curcio, D.; Jaros, M.J.; Leiter, L.A.; et al. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. *N. Engl. J. Med.* **2020**, *382*, 1520–1530. [CrossRef]
36. Santos, R.D.; Ruzza, A.; Hovingh, G.K.; Wiegman, A.; Mach, F.; Kurtz, C.E.; Hamer, A.; Bridges, I.; Bartuli, A.; Bergeron, J.; et al. Cognitive function with evolocumab in pediatric heterozygous familial hypercholesterolemia. *N. Engl. J. Med.* **2020**, *383*, 1317–1327. [CrossRef]
37. Santos, R.D.; Ruzza, A.; Hovingh, G.K.; Stefanutti, C.; Mach, F.; Descamps, O.S.; Bergeron, J.; Wang, B.; Bartuli, A.; Buonuomo, P.S.; et al. Paediatric patients with heterozygous familial hypercholesterolaemia treated with evolocumab for 80 weeks (HAUSER-OLE): A single-arm, multicentre, open-label extension of HAUSER-RCT. *Lancet Diabetes Endocrinol.* **2022**, *10*, 732–740. [CrossRef]
38. Perez de Isla, L.; Alonso, R.; Watts, G.F.; Mata, N.; Saltijeral Cerezo, A.; Muñiz, O.; Fuentes, F.; Diaz-Diaz, J.L.; de Andrés, R.; Zambón, D.; et al. Attainment of LDL Cholesterol Treatment Goals in Patients with Familial Hypercholesterolemia at 5-year Follow-up: SAFEHEART Registry. *J. Am. Coll. Cardiol.* **2016**, *67*, 1278–1285. [CrossRef]
39. Miname, M.H.; Bittencourt, M.S.; Pereira, A.C.; Jannes, C.E.; Krieger, J.E.; Nasir, K.; Santos, R.D. Vascular age derived from coronary artery calcium score on the risk stratification of individuals with heterozygous familial hypercholesterolaemia. *Eur. Heart J. Cardiovasc. Imaging* **2019**, *21*, 251–257. [CrossRef]
40. Mszar, R.; Grandhi, G.R.; Valero-Elizondo, J.; Virani, S.S.; Blankstein, R.; Blaha, M.; Mata, P.; Miname, M.H.; Al Rasadi, K.; Krumholz, H.M.; et al. Absence of Coronary Artery Calcification in Middle-Aged Familial Hypercholesterolemia Patients without Atherosclerotic Cardiovascular Disease. *JACC Cardiovasc. Imaging* **2020**, *13*, 1090–1092. [CrossRef]
41. Santos, R.D.; Shapiro, M.D. Coronary Artery Calcification and Risk Stratification in Familial Hypercholesterolemia: Moving Forward but Not There Yet. *JACC Cardiovasc. Imaging* **2021**, *14*, 2425–2428. [CrossRef] [PubMed]
42. Blom, D.J.; Harada-Shiba, M.; Rubba, P.; Gaudet, D.; Kastelein, J.J.; Charng, M.J.; Pordy, R.; Donahue, S.; Ali, S.; Dong, Y.; et al. Efficacy and Safety of Alirocumab in Adults with Homozygous Familial Hypercholesterolemia: The ODYSSEY HoFH Trial. *J. Am. Coll. Cardiol.* **2020**, *76*, 131–142. [CrossRef] [PubMed]
43. Stefanutti, C.; Julius, U.; Watts, G.F.; Harada-Shiba, M.; Cossu, M.; Schettler, V.J.; De Silvestro, G.; Soran, H.; Van Lennep, J.R.; Pisciotta, L.; et al. Toward an international consensus—Integrating lipoprotein apheresis and new lipid-lowering drugs. *J. Clin. Lipidol.* **2017**, *11*, 858–871.e3. [CrossRef] [PubMed]
44. Stefanutti, C.; Thompson, G.R. Lipoprotein Apheresis in the Management of Familial Hypercholesterolaemia: Historical Perspective and Recent Advances. *Curr. Atheroscler. Rep.* **2015**, *17*, 465. [CrossRef] [PubMed]
45. Underberg, J.A.; Cannon, C.P.; Larrey, D.; Makris, L.; Blom, D.; Phillips, H. Long-term safety and efficacy of lomitapide in patients with homozygous familial hypercholesterolemia: Five-year data from the Lomitapide Observational Worldwide Evaluation Registry (LOWER). *J. Clin. Lipidol.* **2020**, *14*, 807–817. [CrossRef] [PubMed]
46. Lim, G.B. Benefit of early initiation of statins for FH. *Nat. Rev. Cardiol.* **2020**, *17*, 8. [CrossRef]
47. Santos, R.D. Expression of LDLRs (Low-Density Lipoprotein Receptors), Dyslipidemia Severity, and Response to PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) Inhibition in Homozygous Familial Hypercholesterolemia: Connecting the Dots. *Arterioscler. Thromb. Vasc. Biol.* **2018**, *38*, 481–483. [CrossRef] [PubMed]
48. Ginsberg, H.N. REVIEW: Efficacy and Mechanisms of Action of Statins in the Treatment of Diabetic Dyslipidemia. *J. Clin. Endocrinol. Metab.* **2006**, *91*, 383–392. [CrossRef]
49. Luirink, I.K.; Wiegman, A.; Kusters, D.M.; Hof, M.H.; Groothoff, J.W.; de Groot, E.; Kastelein, J.J.; Hutten, B.A. 20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia. *N. Engl. J. Med.* **2019**, *381*, 1547–1556. [CrossRef]

50. Garber, A.J.; Abrahamson, M.J.; Barzilay, J.I.; Blonde, L.; Bloomgarden, Z.T.; Bush, M.A.; Dagogo-Jack, S.; DeFronzo, R.A.; Einhorn, D.; Fonseca, V.A.; et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm—2019 Executive Summary. *Endocr. Pract.* **2019**, *25*, 69–101. [CrossRef]
51. Sugizaki, T.; Watanabe, M.; Horai, Y.; Kaneko-Iwasaki, N.; Arita, E.; Miyazaki, T.; Morimoto, K.; Honda, A.; Irie, J.; Itoh, H. The Niemann-Pick C1 Like 1 (NPC1L1) Inhibitor Ezetimibe Improves Metabolic Disease Via Decreased Liver X Receptor (LXR) Activity in Liver of Obese Male Mice. *Endocrinology* **2014**, *155*, 2810–2819. [CrossRef] [PubMed]
52. Stein, E.; Stender, S.; Mata, P.; Sager, P.; Ponsonnet, D.; Melani, L.; Lipka, L.; Suresh, R.; MacCubbin, D.; Veltri, E. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. *Am. Heart J.* **2004**, *148*, 447–455. [CrossRef] [PubMed]
53. Cuchel, M.; Bruckert, E.; Ginsberg, H.N.; Raal, F.J.; Santos, R.D.; Hegele, R.A.; Kuivenhoven, J.A.; Nordestgaard, B.G.; Descamps, O.S.; Steinhagen-Thiessen, E.; et al. Homozygous familial hypercholesterolaemia: New insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur. Heart J.* **2014**, *35*, 2146–2157. [CrossRef] [PubMed]
54. Ray, K.K.; Reeskamp, L.F.; Laufs, U.; Banach, M.; Mach, F.; Tokgözoğlu, L.S.; Connolly, D.L.; Gerrits, A.J.; Stroes, E.S.G.; Masana, L.; et al. Combination lipid-lowering therapy as first-line strategy in very high-risk patients. *Eur. Heart J.* **2022**, *43*, 830–833. [CrossRef]
55. Pasta, A.; Cremonini, A.L.; Formisano, E.; Fresa, R.; Bertolini, S.; Pisciotta, L. Long term follow-up of genetically confirmed patients with familial hypercholesterolemia treated with first and second-generation statins and then with PCSK9 monoclonal antibodies. *Atherosclerosis* **2020**, *308*, 6–14. [CrossRef] [PubMed]
56. Vavlukis, M.; Vavlukis, A. Statins Alone or in Combination with Ezetimibe or PCSK9 Inhibitors in Atherosclerotic Cardiovascular Disease Protection. In *Lipid Peroxidation Research*; IntechOpen: London, UK, 2019.
57. Nordestgaard, B.G.; Chapman, M.J.; Humphries, S.E.; Ginsberg, H.N.; Masana, L.; Descamps, O.S.; Wiklund, O.; Hegele, R.A.; Raal, F.J.; Defesche, J.C.; et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: Guidance for clinicians to prevent coronary heart disease: Consensus Statement of the European Atherosclerosis Society. *Eur. Heart J.* **2013**, *34*, 3478–3490. [CrossRef]
58. Agarwala, A.; Quispe, R.; Goldberg, A.C.; Michos, E.D. Bempedoic Acid for Heterozygous Familial Hypercholesterolemia: From Bench to Bedside. *Drug Des. Dev. Ther.* **2021**, *15*, 1955–1963. [CrossRef]
59. Cuchel, M.; Meagher, E.A.; Theron, H.D.T.; Blom, D.J.; Marais, A.D.; Hegele, R.A.; Averna, M.R.; Sirtori, C.R.; Shah, P.K.; Gaudet, D.; et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: A single-arm, open-label, phase 3 study. *Lancet* **2013**, *381*, 40–46. [CrossRef]
60. German, C.A.; Shapiro, M.D. Small Interfering RNA Therapeutic Inclisiran: A New Approach to Targeting PCSK9. *BioDrugs* **2020**, *34*, 1–9. [CrossRef]
61. Wang, Y.; Gusarova, V.; Banfi, S.; Gromada, J.; Cohen, J.C.; Hobbs, H.H. Inactivation of ANGPTL3 reduces hepatic VLDL-triglyceride secretion. *J. Lipid Res.* **2015**, *56*, 1296–1307. [CrossRef]
62. Rosenson, R.S.; Burgess, L.J.; Ebenbichler, C.F.; Baum, S.J.; Stroes, E.S.; Ali, S.; Khilla, N.; Hamlin, R.; Pordy, R.; Dong, Y.; et al. Evinacumab in Patients with Refractory Hypercholesterolemia. *N. Engl. J. Med.* **2020**, *383*, 2307–2319. [CrossRef] [PubMed]
63. Ouguerram, K.; Chetiveaux, M.; Zair, Y.; Costet, P.; Abifadel, M.; Varret, M.; Boileau, C.; Magot, T.; Krempf, M. Apolipoprotein B100 Metabolism in Autosomal-Dominant Hypercholesterolemia Related to Mutations in *PCSK9*. *Arter. Thromb. Vasc. Biol.* **2004**, *24*, 1448–1453. [CrossRef] [PubMed]
64. Seidah, N.G.; Awan, Z.; Chrétien, M.; Mbikay, M. PCSK9. *Circ. Res.* **2014**, *114*, 1022–1036. [CrossRef] [PubMed]
65. Maxwell, K.N.; Breslow, J.L. Adenoviral-mediated expression of Pcsk9 in mice results in a low-density lipoprotein receptor knockout phenotype. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 7100–7105. [CrossRef]
66. Abifadel, M.; Varret, M.; Rabès, J.-P.; Allard, D.; Ouguerram, K.; Devillers, M.; Cruaud, C.; Benjannet, S.; Wickham, L.; Erlich, D.; et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat. Genet.* **2003**, *34*, 154–156. [CrossRef]
67. Cohen, J.C.; Boerwinkle, E.; Mosley, T.H.; Hobbs, H.H. Sequence Variations inPCSK9, Low LDL, and Protection against Coronary Heart Disease. *N. Engl. J. Med.* **2006**, *354*, 1264–1272. [CrossRef]
68. Raal, F.J.; Hovingh, G.K.; Blom, D.; Santos, R.D.; Harada-Shiba, M.; Bruckert, E.; Couture, P.; Soran, H.; Watts, G.F.; Kurtz, C.; et al. Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: An interim subset analysis of the open-label TAUSSIG study. *Lancet Diabetes Endocrinol.* **2017**, *5*, 280–290. [CrossRef]
69. Ito, M.K.; Santos, R.D. PCSK9 Inhibition with Monoclonal Antibodies: Modern Management of Hypercholesterolemia. *J. Clin. Pharmacol.* **2017**, *57*, 7–32. [CrossRef]
70. Hovingh, G.K.; Lepor, N.E.; Kallend, D.; Stoekenbroek, R.M.; Wijngaard, P.L.J.; Raal, F.J. Inclisiran Durably Lowers Low-Density Lipoprotein Cholesterol and Proprotein Convertase Subtilisin/Kexin Type 9 Expression in Homozygous Familial Hypercholesterolemia: The ORION-2 Pilot Study. *Circulation* **2020**, *141*, 1829–1831. [CrossRef]
71. Abbasi, J. Highlights from the American Heart Association's Scientific Sessions-ApoB as a Risk Marker, an Oral PCSK9 Inhibitor, and Aspirin and Dementia. *JAMA* **2022**, *327*, 310–312. [CrossRef]

72. Gennemark, P.; Walter, K.; Clemmensen, N.; Rekić, D.; Nilsson, C.A.; Knöchel, J.; Hölttä, M.; Wernevik, L.; Rosengren, B.; Kakol-Palm, D.; et al. An oral antisense oligonucleotide for PCSK9 inhibition. *Sci. Transl. Med.* **2021**, *13*, eabe9117. [CrossRef] [PubMed]
73. Santos, R.D.; Watts, G.F. Familial hypercholesterolaemia: PCSK9 inhibitors are coming. *Lancet* **2015**, *385*, 307–310. [CrossRef]
74. Jiang, L.; Wang, L.-Y.; Cheng, X.-S. Novel Approaches for the Treatment of Familial Hypercholesterolemia: Current Status and Future Challenges. *J. Atheroscler. Thromb.* **2018**, *25*, 665–673. [CrossRef] [PubMed]
75. Ray, K.K.; Bays, H.E.; Catapano, A.L.; Lalwani, N.D.; Bloedon, L.T.; Sterling, L.R.; Robinson, P.L.; Ballantyne, C.M. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. *N. Engl. J. Med.* **2019**, *380*, 1022–1032. [CrossRef]
76. Laufs, U.; Banach, M.; Mancini, G.B.J.; Gaudet, D.; Bloedon, L.T.; Sterling, L.R.; Kelly, S.; Stroes, E.S.G. Efficacy and Safety of Bempedoic Acid in Patients with Hypercholesterolemia and Statin Intolerance. *J. Am. Heart Assoc.* **2019**, *8*, e011662. [CrossRef]
77. Lim, G.B. ANGPTL3: A therapeutic target for atherosclerosis. *Nat. Rev. Cardiol.* **2017**, *14*, 381. [CrossRef]
78. Bergmark, B.A.; Marston, N.A.; Bramson, C.R.; Curto, M.; Ramos, V.; Jevne, A.; Kuder, J.F.; Park, J.-G.; Murphy, S.A.; Verma, S.; et al. Effect of Vupanorsen on Non–High-Density Lipoprotein Cholesterol Levels in Statin-Treated Patients with Elevated Cholesterol: TRANSLATE-TIMI 70. *Circulation* **2022**, *145*, 1377–1386. [CrossRef]
79. Ben-Omran, T.; Masana, L.; Kolovou, G.; Ariceta, G.; Nóvoa, F.J.; Lund, A.M.; Bogsrud, M.P.; Araujo, M.; Hussein, O.; Ibarretxe, D.; et al. Real-World Outcomes with Lomitapide Use in Paediatric Patients with Homozygous Familial Hypercholesterolaemia. *Adv. Ther.* **2019**, *36*, 1786–1811. [CrossRef]
80. Liang, P.; Xu, Y.; Zhang, X.; Ding, C.; Huang, R.; Zhang, Z.; Lv, J.; Xie, X.; Chen, Y.; Li, Y.; et al. CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein Cell* **2015**, *6*, 363–372. [CrossRef]
81. Zhao, H.; Li, Y.; He, L.; Pu, W.; Yu, W.; Li, Y.; Wu, Y.-T.; Xu, C.; Wei, Y.; Ding, Q.; et al. In Vivo AAV-CRISPR/Cas9–Mediated Gene Editing Ameliorates Atherosclerosis in Familial Hypercholesterolemia. *Circulation* **2020**, *141*, 67–79. [CrossRef]
82. Ajufo, E.; Cuchel, M. Recent Developments in Gene Therapy for Homozygous Familial Hypercholesterolemia. *Curr. Atheroscler. Rep.* **2016**, *18*, 22. [CrossRef] [PubMed]
83. Wang, L.; Muthuramu, I.; Somanathan, S.; Zhang, H.; Bell, P.; He, Z.; Yu, H.; Zhu, Y.; Tretiakova, A.P.; Wilson, J.M. Developing a second-generation clinical candidate AAV vector for gene therapy of familial hypercholesterolemia. *Mol. Ther. Methods Clin. Dev.* **2021**, *22*, 1–10. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Review

Lipoprotein(a): Evidence for Role as a Causal Risk Factor in Cardiovascular Disease and Emerging Therapies

Harpreet S. Bhatia and Michael J. Wilkinson *

Division of Cardiovascular Medicine, Department of Medicine, University of California San Diego, La Jolla, CA 92093, USA
* Correspondence: mjwilkinson@health.ucsd.edu

Abstract: Lipoprotein(a) (Lp(a)) is an established risk factor for multiple cardiovascular diseases. Several lines of evidence including mechanistic, epidemiologic, and genetic studies support the role of Lp(a) as a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and aortic stenosis/calcific aortic valve disease (AS/CAVD). Limited therapies currently exist for the management of risk associated with elevated Lp(a), but several targeted therapies are currently in various stages of clinical development. In this review, we detail evidence supporting Lp(a) as a causal risk factor for ASCVD and AS/CAVD, and discuss approaches to managing Lp(a)-associated risk.

Keywords: lipoprotein(a); cardiovascular disease; risk factors; prevention

Citation: Bhatia, H.S.; Wilkinson, M.J. Lipoprotein(a): Evidence for Role as a Causal Risk Factor in Cardiovascular Disease and Emerging Therapies. *J. Clin. Med.* **2022**, *11*, 6040. https://doi.org/10.3390/jcm11206040

Academic Editors: Jose Luis Sanchez-Quesada and Nathan D. Wong

Received: 26 August 2022
Accepted: 7 October 2022
Published: 13 October 2022

1. Introduction

Lipoprotein(a) (Lp(a)) is a lipid-carrying particle composed of a low-density lipoprotein (LDL)-like particle containing apolipoproteinB-100 (apoB) linked by a disulfide bond to apolipoprotein(a) (apo(a)). Apo(a) contains varying numbers of three-dimensional structures called kringles [1]. Lp(a) is primarily genetically determined through the *LPA* gene, and variants in the *LPA* gene are associated with cardiovascular disease [2,3]. Elevated Lp(a) is highly prevalent, occurring at levels >30 mg/dL in an estimated 35% of individuals and at levels >50 mg/dL in 24% of individuals [4]. Smaller isoforms of apo(a) are associated with higher Lp(a) levels. Importantly, the apo(a) isoform size and Lp(a) levels vary by ethnicity [5].

The normal physiological function of Lp(a) is unknown [1]. However, Lp(a) is associated with increased risk for several cardiovascular diseases (CVD), including coronary artery disease (CAD)/atherosclerotic cardiovascular disease (ASCVD) [2], aortic stenosis/calcific aortic valve disease (AS/CAVD) [6], ischemic stroke [7,8], heart failure [9], atrial fibrillation [10], and peripheral arterial disease [11]. Lp(a) is associated with risk for CAD through multiple mechanisms (Figure 1) including atherogenesis mediated by apoB [12], vascular inflammation mediated by its carriage of oxidized phospholipids (OxPL) [13–16], and anti-fibrinolytic effects that may be related to the homology of apo(a) with plasminogen [17]. Lp(a) is associated with risk for AS/CAVD through the pro-inflammatory and pro-calcification effects of OxPL that are likely able to enter the aortic valve through binding by apo(a). Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and autotaxin, enzymes present on Lp(a), are also likely involved in the pathogenesis of AS/CAVD [18]. This review will summarize the evidence for Lp(a) as a causal risk factor for ASCVD, as well as current and emerging therapies for elevated Lp(a).

International society guidelines differ in their recommendations for Lp(a) testing; however, multiple international societies recommend testing in all individuals. The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Primary Prevention Guideline [19] and the 2018 Multi-Society Cholesterol Guideline [20] both recommend using Lp(a) as a risk enhancer to guide therapy among borderline and intermediate risk individuals, particularly among individuals with a family history of premature

CVD. The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) dyslipidemia guideline recommends measurement of Lp(a) once in every adult's lifetime [21]. Similarly, the Canadian Cardiovascular Society (CCS) dyslipidemia guideline recommends testing once for all individuals and use of Lp(a) as a risk modifier [22]. There is a need for standardization of Lp(a) measurement as there are multiple different assays and methods available [23]. Lp(a) measurement using an isoform-insensitive assay that is reported in nanomoles per liter (nmol/L) is recommended [24]. A recent study described a novel method for directly measuring Lp(a) cholesterol (Lp(a)-C) which also enables correction of LDL-cholesterol (LDL-C) as standard methods for measuring LDL-C also include Lp(a)-C [25].

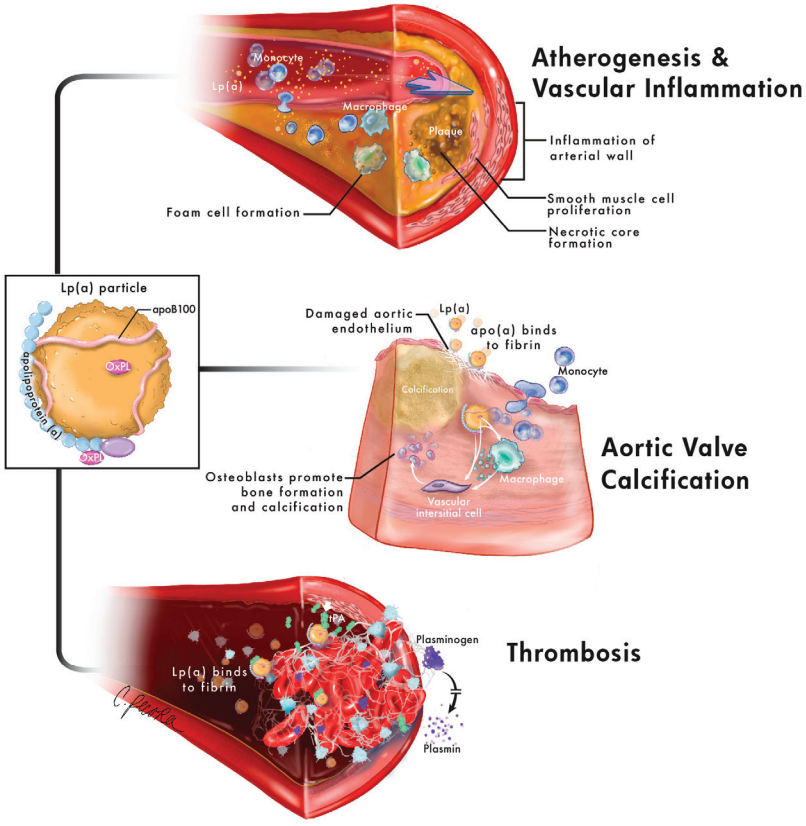

Figure 1. Mechanisms of cardiovascular risk related to Lp(a). Lipoprotein(a) and its individual components are associated with cardiovascular disease through multiple overlapping mechanisms. Lp(a) is composed of apolipoproteinB100 (apoB100) and apolipoprotein(a) (apo(a)), both of which contain oxidized phospholipids (OxPL). The apoB100 contributes to atherogenesis through similar mechanisms as low-density lipoprotein (LDL), including vessel wall binding, smooth muscle cell proliferation, foam cell formation and necrotic core formation. OxPL contribute to vascular inflammation through increased transmigration and cytokine production by monocytes as well as upregulation of inflammatory genes. Lp(a) contributes to aortic valve calcification as apo(a) binds to fibrin on injured aortic endothelium, and OxPL promote calcification and bone formation via vascular interstitial cells and upregulation of reactive oxygen species and proinflammatory cytokines in macrophages. Finally, apo(a) contributes to thrombosis by inhibiting fibrinolysis through competitive inhibition of tissue plasminogen activator (tPA) activation of plasminogen to plasmin and plasminogen binding to fibrin as well as promoting increased platelet activity.

2. Lipoprotein(a) and Risk for Atherosclerotic Cardiovascular Disease

Lp(a) is well established as a likely causal risk factor for ASCVD based on epidemiologic and genetic studies (Table 1).

Table 1. Key studies of Lp(a) as a risk factor for ASCVD.

Meta-Analyses		
Author	**Year**	**Key Findings**
The Emerging Risk Factors Collaboration [26]	2009	Lp(a) associated with CHD (RR per SD 1.13, 95% CI 1.09–1.18) Ischemic stroke (RR per SD 1.10, 95% CI 1.02–1.18)
O'donoghue, et al. [27]	2014	Lp(a) associated with MACE in population with CAD: Highest quintile: OR 1.40, 95% CI 1.15–1.71
Willeit, et al. [28]	2018	Lp(a) associated linearly with CVD at baseline and on-statin therapy in statin outcomes trials On statins: Lp(a) 15–30 mg/dL: HR 0.95 (95% CI 0.82–1.11) Lp(a) 30–50 mg/dL: HR 1.08 (95% CI 0.95–1.23) Lp(a) $\geq$50 mg/dL: HR 1.42 (95% CI 1.16–1.74)
Epidemiologic Studies		
Author	**Year**	**Key Findings**
Bennet, et al. [29]	2008	Top tertile of Lp(a) associated with CHD with OR 1.60 (95% CI 1.38–1.85)
Kamstrup, et al. [30]	2008	Lp(a) associated with risk for MI in men and women: Women > 95th percentile: HR 3.6 (95% CI 1.7–7.7) Men > 95th percentile: HR 3.7 (1.7–8.0)
Virani, et al. [31]	2012	Highest quintile of Lp(a) associated with incident CVD risk in: Black individuals (HR 1.35, 95% CI 1.06–1.74) White individuals (HR 1.27, 95% CI 1.10–1.47)
Paré, et al. [32]	2019	Lp(a) > 50 mg/dL associated with increased risk of MI (OR 1.48, 95% CI 1.32–1.67) overall and in all ethnic groups studied except African and Arab individuals
Jin, et al. [33]	2019	Lp(a) $\geq$ 50 mg/dL associated with increased risk of CVD in: Pre-diabetes (HR 2.67, 95% CI 1.38–5.42) Diabetes (HR 3.47, 95% CI 1.80–6.69)
Patel, et al. [34]	2021	Lp(a) associated with increased ASCVD risk with HR 1.11 (95% CI 1.10–1.12) per 50 nmol/L increment Consistent results seen in White, South Asian, and Black individuals
Genetic Studies		
Author	**Year**	**Key Findings**
Clarke, et al. [2]	2009	*LPA* locus had strongest association with coronary disease in large study of candidate SNPs *LPA* SNP rs10455872 OR 1.70 (95% CI 1.49–1.95) for coronary disease *LPA* SNP rs3798220 OR 1.92 (95% CI 1.48–2.49) for coronary disease
Kamstrup, et al. [35]	2009	Higher levels of Lp(a) and lower number of kringle IV repeats associated with greater MI risk: >95th percentile of Lp(a): HR 2.6 (95% CI 1.6–4.1) 1st quartile of KIV-2 repeats: HR 1.5 (95% CI 1.2–1.9)
CARDIoGRAMplusC4D Consortium [3]	2013	*LPA* SNP rs3798220 associated with CAD: OR 1.28 ($p < 0.001$)
Kamstrup, et al. [36]	2013	Addition of Lp(a) levels, KIV-2 repeats and carrier status for *LPA* SNP rs10455872 to traditional risk factors all improved risk prediction for MI and CHD
Kyriakou, et al. [37]	2014	A null allele (*LPA* SNP rs41272114) was associated with decreased Lp(a) levels and decreased CAD risk
Lim, et al. [38]	2014	Splice variants of Lp(a) associated with reduced Lp(a) levels and protection against CVD (OR 0.84, $p < 0.001$)
Lee, et al. [5]	2016	Lp(a) levels and SNPs vary by ethnicity. The addition of SNPs to Lp(a) levels did not appear to be clinically meaningful.
Salaheen, et al. [39]	2017	OR per 1-SD increment of Lp(a) for MI 1.10 (95% CI 1.05–1.14)

CAD = coronary artery disease, CHD = coronary heart disease, CVD = cardiovascular disease, KIV = kringle 4, MACE = major adverse cardiovascular events, MI = myocardial infarction, SNP = single nucleotide polymorphism.

2.1. Epidemiologic Studies of Lp(a) and Risk for ASCVD

Multiple prospective and epidemiologic studies including different populations have demonstrated an association between Lp(a) and various ASCVD outcomes. In a study of individuals with myocardial infarction (MI)/coronary heart disease (CHD) and controls from the Reykjavik Study, the top tertile of Lp(a) was independently associated with CHD risk (OR 1.60, 95% CI 1.38–1.85) [29]. In a large meta-analysis published in 2009, the Emerging Risk Factors Collaboration evaluated over 30 prospective studies including over 120,000 participants and demonstrated an association between higher Lp(a) levels and CHD and ischemic stroke [26]. A meta-analysis of 11 studies of individuals with CVD demonstrated an association between Lp(a) and CVD risk (highest quintile of Lp(a) OR 1.40, 95% CI 1.15–1.71) [27].

The association between Lp(a) and ASCVD risk has been shown across several different populations. In the Copenhagen City Heart Study (CCHS), Lp(a) was associated with MI in both men and women in a stepwise manner. In women, the 95th percentile of Lp(a) was associated with an HR of 3.6 (95% CI 1.7–7.7); in men, it was associated with an HR of 3.7 (95% CI 1.7–8.0) [30]. In Black and White participants from the Atherosclerosis Risk in Communities (ARIC) Study, Lp(a) levels were positively associated with CVD (coronary heart disease and ischemic stroke) events in a graded manner [31]. In a more recent study of seven ethnic groups, Lp(a) >50 mg/dL was associated with risk for myocardial infarction (overall OR 1.48, 95% CI 1.32–1.67). Again, a graded association between Lp(a) levels and outcomes was seen. Elevated Lp(a) was associated with increased risk in Chinese, European, Latin American, South Asian, and Southeast Asian individuals, but not in African or Arab individuals. The greatest population-attributable risk was noted in those of South Asian and Latin American descent [32]. In a very large recent study, however, the association between Lp(a) and CVD events was similar in White, South Asian and Black individuals, despite marked differences in median levels within these ethnic groups [34]. Lp(a) $\geq$ 50 mg/dL is also associated with increased risk for MI, stroke, and cardiovascular mortality in those with diabetes mellitus as well as pre-diabetes, with a graded association noted from Lp(a) 30–50 mg/dL and Lp(a) $\geq$50 mg/dL [33]. In a meta-analysis of statin outcome trials using individual patient level data from over 29,000 participants, Lp(a) was associated linearly with risk for CVD at baseline and on statin therapy [28]. Key features of these epidemiologic studies are the graded association between Lp(a) and events, suggestive of a true biological phenomenon, and the relative consistency across groups, including diverse racial/ethnic groups.

2.2. Genetic Studies of Lp(a) and Risk for ASCVD

Genetic studies have been critical in establishing Lp(a) as a likely causal risk factor for ASCVD with a robust evidence base. In a large genetic study of over 48,000 single-nucleotide polymorphisms (SNPs) from 2100 genes in over 3000 participants with coronary disease and over 3000 controls, the region of the *LPA* gene had the strongest association with coronary disease. In particular, the rs10455872 and rs3798220 SNPs were identified and both were associated with increased Lp(a) levels and with positive odds ratios for CAD of 1.70 (95% CI 1.49–1.95) and 1.92 (95% CI 1.48–2.49), respectively [2]. In another study, both plasma Lp(a) levels and Lp(a) kringle IV type 2 (KIV-2) size polymorphism genotype were associated with risk for MI [35]. In a genome wide association study (GWAS) of CAD in >60,000 CAD cases and >130,000 controls, the *LPA* SNP rs3798220 was again associated with CAD with an OR of 1.28 ($p < 0.001$) [3]. A prospective study of >8000 Danish individuals demonstrated that the addition of Lp(a) levels $\geq 80^{th}$ percentile, number of KIV-2 repeats, and carrier status for the *LPA* SNP rs10455872 improved MI and coronary heart disease (CHD) risk prediction in addition to traditional risk factors [36]. In a case-control study of individuals with CAD, an *LPA* null allele (rs41272114) was evaluated. The null allele was associated with decreased Lp(a) levels, as well as decreased CAD risk, compared to noncarriers [37]. Another study demonstrated that splice variants in *LPA*, associated with reduced Lp(a) levels, were protective against cardiovascular disease [38]. *LPA* SNPs

have also been shown to vary by ethnicity [5]. A recent Mendelian randomization study observed an OR per 1-SD increment in Lp(a) of 1.10 (95% CI 1.05–1.14) for MI [39].

The risk associated with Lp(a) has also been evaluated recently in the context of other risk factors. Lp(a) is independently associated with CVD even when accounting for family history of CHD [40]. The use of apolipoproteinB100 (apoB) as a risk marker has been a source of considerable interest recently. In one study, the risk associated with Lp(a) persisted when adjusting for apoB, while the risk associated with LDL-C was attenuated. These results suggest that apoB does not sufficiently encompass Lp(a)-associated risk [41]. Finally, one study evaluated CVD risk associated with Lp(a) stratified by high-sensitivity C-reactive protein (hsCRP), given the inflammatory risk associated with Lp(a). In this study, the independent risk associated with Lp(a) was only present with elevated hsCRP levels; however, this requires further study [42].

Lp(a) has been identified as a risk factor for ASCVD in many epidemiologic studies, often in a dose-dependent fashion, suggesting a pathophysiologic mechanism. Genetic studies have strengthened the evidence for Lp(a) as a causal risk factor, particularly Mendelian randomization studies that reduce confounding.

3. Lipoprotein(a) and Risk for Aortic Stenosis/Calcific Aortic Valve Disease

The other disease with which Lp(a) is most often associated is aortic stenosis (AS), or calcific aortic valve disease (CAVD). A number of epidemiologic and genetic studies support the association between Lp(a) and aortic valve calcification, AS, and progression of AS (Table 2).

Table 2. Key studies of Lp(a) as a risk factor for calcific aortic valve disease.

Author	Year	Key Findings
Lp(a) and AV Sclerosis		
Gotoh, et al. [43]	1995	Greater prevalence of aortic valve sclerosis in individuals with Lp(a) $\geq$ 30 mg/dL (36.1%) compared with <30 mg/dL (12.7%, $p < 0.001$)
Stewart, et al. [44]	1997	Lp(a) associated with increased risk for aortic valve stenosis or sclerosis (OR 1.23, 95% CI 1.14, 1.32)
Torzewski, et al. [45]	2017	Lp(a) and associated molecules including OxPL detected in AV leaflets of individuals with calcific AS
Lp(a) and AV Calcification		
Bozbas, et al. [46]	2007	Lp(a) independently associated with AVC (OR 1.01, 95% CI 1.00–1.03)
Vongpromek, et al. [47]	2015	OR per 10 mg/dL increase in Lp(a) 1.11 (95% CI 1.01–1.20) for AVC by CT
Bouchareb, et al. [48]	2015	Lp(a) transports autotaxin to the AV which contributes to inflammation and calcification of the valve
Despres, et al. [49]	2019	In individuals without clinical AS, elevated Lp(a) associated with AV microcalcification by PET/CT
Zheng, et al. [50]	2019	Higher Lp(a) and OxPL levels associated with greater aortic valve calcification activity by PET/CT Lp(a) induces osteogenic differentiation of vascular cells, mediated by OxPL
Lp(a) and AS		
Glader, et al. [51]	2003	Lp(a) $\geq$ 48 mg/dL associated with increased risk for AS (OR 3.4, 95% CI 1.1–11.2)
Kamstrup, et al. [52]	2014	Lp(a) associated with AS in a graded fashion: >95th percentile of Lp(a) (>90 mg/dL): OR 2.9 (95% CI 1.8–4.9)
Arsenault, et al. [53]	2014	Top tertile of Lp(a) associated with increased risk for AS: HR 1.57, 95% CI 1.02–2.42
Langsted, et al. [54]	2015	Each 1-SD increase in Lp(a) associated with HR 1.23 (95% CI 1.06–1.41) for AS

Table 2. *Cont.*

Author	Year	Key Findings
OxPL-apoB and AS		
Kamstrup, et al. [55]	2017	Dose-dependent association between OxPL-apoB and CAVD For >95th percentile of levels, OR 3.4 (95% CI 2.1–5.5)
Que, et al. [56]	2018	Inactivation of OxPL reduces development of AV calcification and AV gradient in mice
Lp(a), OxPL-apoB and AS Progression		
Capoulade, et al. [57]	2015	Top tertile of Lp(a) (OR 2.6, 95% CI 1.4–5.0) and top tertile of OxPL-apoB (OR 2.4, 95% CI 1.2–4.6) associated with rapid AS progression
Capoulade, et al. [58]	2018	Lp(a) (OR 1.10, 95% CI 1.03–1.19 per 10 mg/dL increase) and OxPL-apoB (OR 1.06, 95% CI 1.01–1.12 per 1 nM increase) levels linearly associated with faster AS progression, especially in younger participants.
Zheng, et al. [50]	2019	Higher Lp(a) and OxPL levels associated with faster progression of AV calcium score by CT and hemodynamic progression by echocardiography
Genetic Associations		
Thanassoulis, et al. [6]	2013	rs10455872 associated with AVC in GWAS (OR per allele 2.05, $p < 0.001$) *LPA* genotype associated with incident AS (HR per allele 1.68, 95% CI 1.32–2.15) and AV replacement (HR 1.54, 95% CI 1.05–2.27)
Kamstrup, et al. [52]	2014	Genotypes corresponding with Lp(a) levels associated with increased risk of AS (HR 1.6, 95% CI 1.2–2.1 per 10-fold Lp(a) increase)
Arsenault, et al. [53]	2014	Carriers of rs10455872 SNP have increased risk of AS: Heterozygous: HR 1.78, 95% CI 1.11–2.87 Homozygous: HR 4.83, 95% CI 1.77–13.20
Langsted, et al. [54]	2015	Causal risk ratio for AS based on *LPA* SNPs (rs3798220, rs10455872): 1.38 (95% CI 1.23–1.55) Causal risk ratio for AS based on *LPA* KIV-2 genotype: 1.21 (95% CI 1.06–1.40)

AS = aortic stenosis, AV = aortic valve, AVC = aortic valve calcification, CT = computed tomography, GWAS = genome-wide association study, KIV = kringle 4, OxPL = oxidized phospholipids, OxPL-apoB = oxidized phospholipids on apolipoprotein B, SNP = single nucleotide polymorphism.

3.1. Epidemiologic, Imaging, and Mechanistic Studies of Lp(a) and Calcific Aortic Valve Disease

Lp(a) has been associated with aortic valve sclerosis for many years, raising suspicion for Lp(a) as a cause of AS. In 1995, the prevalence of aortic valve sclerosis was observed to increase in association with Lp(a) levels [43]. In the Cardiovascular Health Study (CHS), Lp(a) was also associated with increased risk for aortic valve sclerosis or stenosis [44]. Importantly, Lp(a) and Lp(a)-associated molecules (e.g., OxPL) have been detected in the AV leaflets of individuals with calcific AS [45].

Lp(a) has also consistently been associated with aortic valve calcification (AVC) through imaging and basic studies, which may link Lp(a) and AS pathophysiologically. In an echocardiographic study, Lp(a) levels were independently associated with AVC [46]. In asymptomatic individuals with familial hypercholesterolemia, Lp(a) was significantly associated with AVC by computed tomography (CT) [47]. In another study utilizing 18F-sodium fluoride positron emission tomography (PET)/CT, elevated Lp(a) was associated with AV microcalcification even before the development of clinical AS [49]. Another PET/CT study similarly demonstrated that higher Lp(a) and OxPL levels were associated with increased AV calcification activity [50]. Autotaxin, transported by Lp(a) to the aortic valve, also promotes inflammation and calcification of the aortic valve [48].

In 2003, a study of individuals with severe AS and age-matched controls observed an association between elevated Lp(a) ($\geq$48 mg/dL) and risk for AS [51]. In a very large study of two prospective cohort studies, Lp(a) was significantly associated with AS in a dose-dependent fashion [52]. In the European Prospective Investigation into Cancer (EPIC)-Norfolk Study, the top tertile of Lp(a) levels was associated with increased risk for

AS [53]. In another large study, each standard deviation increase in Lp(a) was associated with an HR of 1.23 (95% CI 1.06–1.41) for AS [54].

Oxidized phospholipids, which are carried by Lp(a), are also implicated in AS, likely due to their role in inflammation and calcification [57]. In addition to Lp(a), OxPL are detected in the AV leaflets of individuals with calcific AS [45]. In a mouse model, inactivation of OxPL resulted in decreased AV calcification and reduced the development of AV gradients [56]. In humans, Lp(a) induces osteogenic differentiation of vascular cells, which is mediated by OxPL and inhibited by inactivating OxPL, again providing a possible mechanism for the link between Lp(a) and AS [50]. OxPL-apoB levels are also associated with risk for calcific aortic valve disease in a dose-dependent manner [55].

Lp(a) is also associated with faster progression of AS, which may be particularly meaningful clinically. In a study of individuals with mild-to-moderate AS in the ASTRONOMER trial, individuals in the top tertile of Lp(a) levels and OxPL-apoB levels had greater risk for rapid progression [57], and Lp(a) and OxPL-apoB levels were linearly associated with faster progression [58]. Higher Lp(a) and OxPL levels are also associated with increased progression of aortic valvular calcium score by CT and faster hemodynamic progression by echocardiography, as well as greater risk for aortic valve replacement and death [50].

3.2. Genetic Studies of Lp(a) and Calcific Aortic Valve Disease

Genetic studies have again been critical for establishing Lp(a) as a likely causal risk factor for AS and the only monogenic risk factor for AS. In a GWAS for AV calcification by CT, the *LPA* SNP rs10455872 was identified as the only SNP to meet genomewide significance. The *LPA* genotype was also associated with incident AS and the need for AV replacement [6]. In a Mendelian randomization study, the rs10455872 variant was also strongly associated with increased risk for AS with greater risk among homozygous carriers than heterozygous [53]. In a study incorporating multiple SNPs, genotypes corresponding with Lp(a) levels were associated with an increased risk for AS [52]. In another Mendelian randomization study, the *LPA* SNPs rs3798220 and rs10455872 and the *LPA* KIV-2 genotype were associated with AS [54].

In conclusion, a large body of evidence has established Lp(a) as a likely causal risk factor for calcific aortic valve disease and AS. Lp(a) and OxPL are associated with aortic valve calcification, even before the development of clinical AS, and are found in calcified aortic valve leaflets. *LPA* gene variants are similarly associated with calcification. Clinically, Lp(a), OxPL, and *LPA* variants are associated with the incidence of AS, in a dose-dependent manner, as well as the risk for progression of AS.

4. Current Therapies and Lipoprotein(a)

While there are no medications specifically approved in the United States for risk associated with elevated Lp(a), a number of currently available therapies have been evaluated (Table 3). Statins are a cornerstone of therapy for prevention of cardiovascular disease. However, statin therapy does not lower Lp(a) and may even increase it [59]. Of particular importance is that CVD risk associated with elevated Lp(a) persists in statin-treated patients with an HR of 1.43 (95% CI 1.15–1.76) for Lp(a) $\geq$ 50 mg/dL in statin-treated patients compared with an HR of 1.31 (1.08–1.58) prior to statin initiation in statin clinical trials [28]. Additionally, statins have not shown a benefit for reducing the progression of AS [60], and this may be partially explained by their lack of effect on Lp(a). Thus, while statins are an important therapy for primary and secondary prevention of CVD, they do not address Lp(a) levels and Lp(a)-mediated risk. Ezetimibe has also been evaluated, resulting in a 3% decrease in Lp(a) at 12 weeks [61] in one study and a 29% reduction at 12 weeks in another [62]. However, these data are limited, particularly in regard to their impact on outcomes.

Table 3. Current and emerging therapies for Lp(a).

Current Therapies				
Drug	**Target**	**Mechanism**	**Effect on Lp(a)**	**CVD Outcomes**
Lipid Lowering Therapy				
Statins	HMG-CoA reductase	Inhibit cholesterol production	Do not lower Lp(a) levels, may increase Lp(a) [59]	Reduced ASCVD risk, but Lp(a) associated risk persists in statin treated individuals [28]
Ezetimibe	Nieman Pick C1-like1 protein	Reduces absorption of cholesterol in the small intestine	Limited data (possible 3–29% decrease in Lp(a)) [61,62]	No known effect on Lp(a)-associated risk
Niacin	Multifactorial	Downregulates *LPA* gene promotor and reduces apoB and triglycerides, increases HDL [63]	AIM-HIGH: 21% reduction in Lp(a), low absolute reduction [64] HPS2-THRIVE: low absolute reduction [65]	AIM-HIGH trial: no effect on CVD events [64]. HPS2-THRIVE: no overall effect of niacin on major vascular events [65]
Mipomersen	apoB	Anti-sense inhibitor of apoB synthesis	Reduces Lp(a) by median 26% [66]	Unclear effect on CV outcomes. Risk of liver toxicity
Lomitapide	Microsomal triglyceride transfer protein (MTP)	Inhibition of MTP inhibits transfer of lipids onto apoB	Reduces Lp(a) by 17% [61]	Unclear effect on CV outcomes. Risk of liver toxicity
PCSK9i (alirocumab, evolocumab, inclisiran)	PCSK9	Inhibit degradation of LDL-receptor	Reduce Lp(a) by 19–27% [67–69]	Limited data, however, reduction in Lp(a) associated with a reduction in CVD events (15% per 25 nmol/L in FOURIER, 0.6% per 1 mg/dL in ODYSSEY OUTCOMES) [67,68], but may not address inflammatory risk associated with OxPL [70]
Lipoprotein apheresis	apoB-containing lipoproteins	Removal of apoB-containing lipoproteins from plasma	Immediate reduction in Lp(a) levels up to 75%, with 30–35% time-averaged reduction when performed every 1–2 weeks [71]	Reduction in Lp(a) and LDL-C translates into significant reduction in MACE events in observational studies [72,73] MultiSELECt is an ongoing multicenter prospective study [74]
Anti-platelet therapy				
Aspirin	COX (cyclooxygenase) [75]	Reduces platelet aggregation through irreversible inhibition of thromboxane A_2	–	In White women carriers of *LPA* rs3798220 SNP, aspirin associated with significant reduction in CVD risk (HR 0.44, 95% CI 0.20–0.94) in the Women's Health Study [75]. Similar results in the ASPREE trial with the same SNP or high genetic risk score [76].
Dual anti-platelet therapy (DAPT)	Multifactorial	Multifactorial	–	In CAD patients with Lp(a) >30 mg/dL who underwent PCI, DAPT >1 year resulted in a significant reduction in CVD events (HR 0.54, 95% CI 0.31–0.92) compared with DAPT $\leq$1 year [77]

Table 3. *Cont.*

Current Therapies				
Other				
Hormone replacement therapy (estrogen)	–	Possibly through increased Lp(a) uptake by LDL receptor or decreased Lp(a) production [78]	Reduction in Lp(a) of 7.9 nmol/L [79]	No impact on CHD events
L-carnitine	–	Possibly related to fatty acid oxidation	Reduction in Lp(a) of 8.8 mg/dL [80]	Unclear effect on CV outcomes L-carnitine associated with increased CVD risk [81]
Emerging Therapies				
Drug	**Target**	**Mechanism**	**Effect on Lp(a)**	**Current stage in development**
Pelacarsen	apo(a) mRNA	Antisense oligonucleotide (ASO), binds apo(a) mRNA, targets for degradation	Phase I: Dose-dependent, up to −77.8% [82,83]. Ligand-conjugated form: dose-dependent, up to −92% [83] Phase II: Ligand-conjugated form: dose-dependent, up to −80% [84]	Phase III/cardiovascular outcomes trial underway (80 mg monthly subcutaneous injection vs. placebo) (NCT04023552).
Olpasiran	apo(a) mRNA	Small interfering RNA (siRNA), binds apo(a) mRNA, targets for degradation	Phase I: Maximum mean percent change in Lp(a) from baseline: −71% to −97% [85]	Phase II underway (NCT04270760)
SLN360	apo(a) mRNA	siRNA, binds apo(a) mRNA and targets for degradation	Phase I: Maximal median percent reduction in Lp(a), dose-dependent, up to −98% [86]	Phase II planned for 2022 [87]

apoB = apolipoprotein B, ASCVD = atherosclerotic cardiovascular disease, CAD = coronary artery disease, CHD = coronary heart disease, CVD = cardiovascular disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein, mRNA = messenger ribonucleic acid, PCSK9 = proprotein convertase subtilisin/kexin type 9.

Niacin has been shown to lower Lp(a) levels but without a clear impact on cardiovascular outcomes. In the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes) trial, participants with low baseline HDL-C and CVD were randomized to simvastatin plus placebo or simvastatin plus niacin with ezetimibe if needed. Niacin reduced Lp(a) by 21% at 1 year, but Lp(a)-associated risk remained with an on-study HR of 1.18 ($p = 0.03$) compared with a baseline HR of 1.25 ($p = 0.001$) [64]. In the HPS2-THRIVE study (Heart Protection Study 2-Treatment of HDL to Reduce Incidence of Vascular Events), individuals with vascular disease were randomized for extended release niacin and laropiprant (to reduce the side effects of niacin) or placebo. There was no overall effect on vascular disease, but there was a modest absolute reduction in Lp(a) [65]. It should be noted that in both studies, the absolute reduction in Lp(a) was low, and the trials were not designed to assess the impact of niacin on CVD risk in elevated Lp(a). Additionally, these trials highlight the potential risks for significant side effects from niacin.

Lipoprotein apheresis, through multiple available techniques, is very effective at lowering Lp(a) levels, with an acute reduction up to 75% and a reduction in mean concen-

trations between sessions of up to 40% [71]. A retrospective study in the U.S. of 14 patients with CVD and elevated Lp(a) (mean 138 mg/dL) with normal LDL-C (mean 80 mg/dL) observed a reduction of 63% in Lp(a) and 64% in LDL-C with lipoprotein apheresis, translating into a 95% reduction in MACE over 48 months [72]. In Germany, a prospective study of 170 patients with CVD and mean LDL-C 99 mg/dL and Lp(a) of 108 mg/dL observed a reduction in Lp(a) of 68% with a single treatment, and a reduction in the MACE annual event rate from 0.58 to 0.11 with regular lipoprotein apheresis [73]. These studies demonstrate that lipoprotein apheresis is very effective in reducing Lp(a) levels, which may translate into a reduction in CVD events, but data are limited. Lipoprotein apheresis is currently the only FDA-approved therapy for elevated Lp(a), but further study is needed. MultiSELECt (A European Multicenter Study on the Effect of Lipoprotein(a) Elimination by Lipoprotein Apheresis on Cardiovascular outcomes) is an ongoing prospective cohort study to evaluate the effect of lipoprotein apheresis on events in individuals with elevated Lp(a) [74].

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are one of the most promising therapies currently available for addressing Lp(a)-associated risk. In an analysis from the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, evolocumab reduced Lp(a) levels by a median of 27%. In those with Lp(a) above the median, there was a more potent reduction in events with an absolute risk reduction of 2.5% compared to 1.0%. There was an estimated 15% lower risk per 25 nmol/L reduction in Lp(a) with adjustment for the change in LDL-C [67]. In an analysis of the ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab) trial, alirocumab reduced Lp(a) by 23%, and a 1 mg/dL reduction in Lp(a) was associated with an HR of 0.994 ($p = 0.008$) [68]. Additionally, baseline Lp(a) levels predicted the risk reduction with alirocumab with a greater reduction in risk with increasing quartile of Lp(a) [88]. PCSK9i also significantly lower Lp(a) levels in addition to background niacin therapy [89]. Taken together, these studies suggest that PCSK9i reduce Lp(a) levels modestly, and the reduction in Lp(a) potentially translates into risk reduction independent of LDL-C reduction. A newer PCSK9i siRNA, inclisiran, was also shown to reduce Lp(a) by 19–22% in the ORION-10 and ORION-11 trials, but these trials were not designed to evaluate the effects of inclisiran on MACE [69]. Despite modest Lp(a) lowering, however, individuals treated with PCSK9i have evidence of residual vascular inflammation [90]. A recent study demonstrated that PCSK9i did not lower OxPL, despite Lp(a)-lowering, which may partially explain this residual inflammatory risk [70]. Recent society guidelines have incorporated the use of PCSK9i into recommendations for management of individuals with elevated Lp(a). The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) dyslipidemia guidelines recommend consideration of PCSK9i in individuals with familial hypercholesterolemia and high Lp(a) (class IIa) [21], while the Canadian Cardiovascular Society (CCS) guidelines recommend consideration of PCSK9i for secondary prevention in individuals with Lp(a) $\geq$60 mg/dL [22].

Multiple other therapies have been evaluated with regard to Lp(a), again with unclear impact on outcomes. Mipomersen, an anti-sense oligonucleotide (ASO) apoB synthesis inhibitor, resulted in a reduction in Lp(a) by a median of 26% in four phase 3 trials of individuals with various hypercholesterolemic conditions [66]. However, in transgenic mice, free apo(a) levels were unaffected with mipomersen [91], and the impact of these findings on outcomes is unclear. Lomitapide, an inhibitor of microsomal triglyceride transfer protein (MTP) that transfers lipids to apoB, resulted in a 16% reduction in Lp(a) in one trial, but the impact on clinical outcomes was not evaluated [61]. Mipomersen and lomitapide are approved for individuals with homozygous familial hypercholesterolemia [92], but their use is limited by potential liver toxicity.

Finally, non-lipid therapies have also been studied for addressing Lp(a)-associated risk. Anti-platelet therapies have been evaluated for both primary and secondary prevention given Lp(a)'s association with coagulation and platelet aggregation pathways. For primary

prevention, aspirin was studied in a secondary analysis of the Women's Health Study, which randomized healthy women to aspirin 100 mg every other day vs. a placebo. In over 25,000 White women who were genotyped, aspirin was associated with a dramatic reduction in CVD events among carriers of the *LPA* rs3798220 SNP (which was associated with 2-fold increased CVD risk in the placebo group) with an HR of 0.44 (95% CI 0.20–0.94). Aspirin use was not associated with a reduction in risk among non-carriers [75]. However, this SNP was only present in 3.7% of individuals, and the results are only generalizable to White women. A recent analysis of White participants in the ASPREE (Aspirin in Reducing Events in the Elderly) trial of aspirin for the primary prevention of CVD in healthy elderly individuals demonstrated similar findings. Carriers of the rs3798220-C variant or individuals with high genetic risk based on a genetic risk score had significantly increased risk of MACE in the placebo group, but not in the aspirin group, again suggesting that aspirin may benefit individuals with increased genetic risk associated with Lp(a) [76]. Further study is needed to evaluate the use of aspirin in association with plasma Lp(a) levels and in a broader population with modern background therapy. In terms of secondary prevention, a study of patients with CAD after PCI demonstrated that prolonged dual anti-platelet therapy (DAPT) >1 year resulted in a significant reduction in CVD events (HR 0.54, 95% CI 0.31–0.92) compared with DAPT $\leq$1 year [77], again suggesting that there is a role for specific considerations related to anti-platelet therapy in this population. Hormone replacement therapy (HRT) has been a source of historical interest as it has previously been shown to lower Lp(a) levels. However, in a recent study of post-menopausal women, HRT resulted in a small reduction in Lp(a) levels, but did not result in a reduction in CHD events [79]. L-carnitine has also been associated with a reduction in Lp(a) levels. In a meta-analysis of randomized controlled trials, L-carnitine was associated with a mean reduction in Lp(a) levels of 8.8 mg/dL (95% CI -10.1, -7.6 mg/dL), particularly with the oral formulation. However, the impact of this modest reduction on clinical events was not evaluated [80]. In addition, L-carnitine is associated with accelerated atherosclerosis and increased CVD risk [81].

Lifestyle interventions, while integral to general cardiovascular health, have not been shown to have a significant impact on Lp(a). A thorough review of non-genetic influences on Lp(a) levels was recently published [93]. In one study, intensive multifactorial lifestyle intervention including diet, exercise, and smoking cessation did not result in a change in Lp(a) levels. [94]. Several studies have observed changes in Lp(a) levels with various diets; however, the changes are almost universally modest. Diet has been shown to modestly influence Lp(a) levels. In general, Lp(a) levels do not vary significantly whether in a fasting or nonfasting state [95]. The composition of macronutrients in diet does appear to influence Lp(a) levels. A low carbohydrate diet resulted in a nearly 15% reduction in Lp(a) in one study [96]. Low and moderate fat diets have also been shown to result in modest reductions in Lp(a) [97]. Carbohydrate intake may have a greater influence on Lp(a) levels than fat intake, as a low-fat, high-carbohydrate diet increased Lp(a) levels compared to a high-fat, low-carbohydrate diet [98]. High-carbohydrate and high-protein diets increase Lp(a) more than high unsaturated-fat diets, but all the absolute increases are small [99]. The type of dietary fat also appears to be relevant. Reducing dietary saturated fat results in a small increase in Lp(a) levels [100], and replacement of saturated fat with monounsaturated fat intake results in an increase in Lp(a) levels (11%), but less so than replacement with carbohydrates (20%) [101]. The data are not entirely consistent, as a Mediterranean-style diet with increased monounsaturated fatty acids decreased trans-fat, increased protein, and decreased carbohydrate intake from baseline resulted in a significant decrease in Lp(a) levels; however, mean levels were not elevated to begin with [102]. In addition, alcohol consumption does not appear to be associated with Lp(a) levels [103]. Finally, physical activity does not appear to have a significant impact on Lp(a) levels [93].

5. Emerging Therapies to Lower Lipoprotein(a)

Targeted therapies to lower lipoprotein(a) are currently under development, with safety and efficacy being testing across phase I-III clinical trials (Table 3). Apo(a), as a key component of Lp(a), is the target of RNA-based therapeutics currently in phase II-III trials. The inhibition of apo(a) synthesis at the RNA level is a highly effective means of potently lowering circulating levels of Lp(a). Two methods of inhibiting the apo(a) mRNA have been Id: anti-sense oligonucleotides (ASO) and small-interfering RNA (siRNA). While different in their mechanism of targeting the apo(a) mRNA and promoting its degradation, both ASO and siRNA molecules are active in hepatocytes where their activity inhibits production of the downstream apo(a) protein and thus assembly of Lp(a) particles. A comprehensive review of the development and mechanism of these RNA-based therapeutics for Lp(a) was recently published elsewhere [92]. Here, we will summarize the key findings with regard to safety and efficacy of these emerging therapies.

Pelacarsen is an ASO targeting apo(a) administered by subcutaneous injection. The molecule has changed over time, for example, with the addition of ligand conjugation with N-acetylgalactosamine (GalNac), improving hepatocyte uptake, and allowing for lower doses of the drug to be administered. In a phase I study of a shorter-acting (second-generation) apo(a) ASO, 47 healthy volunteers with Lp(a) of at least 25 nmol/L were treated with either single dose or multiple (six) doses of the study drug vs. placebo. A single dose did not significantly lower Lp(a) at day 30, but a dose-response effect was observed after multiple doses at 36 days, up to a 77.8% reduction in Lp(a) from baseline ($p = 0.001$). Mild injection site reactions occurred [82]. This second-generation ASO was subsequently studied in a phase II trial of participants with elevated Lp(a), while the next generation ASO (ligand conjugated) entered phase I. The ligand-conjugated form demonstrated significant dose-dependent reductions in Lp(a), at day 30 up to 92% ($p = 0.0007$ vs. placebo) [83]. The safety and efficacy of this ligand-conjugated form of the apo(a) ASO led to its further development and testing in a phase II trial. In phase II, this hepatocyte-directed form of the apo(a) ASO was studied in participants with a history of ASCVD and baseline Lp(a) of at least 150 nmol/L. At 6 months, a dose-dependent reduction in Lp(a) was observed with up to a 80% reduction for 20 mg administered weekly. Injection site reactions were the most common adverse events [84]. The equivalent to this 20 mg/week formulation was chosen for the phase III cardiovascular outcomes trial with pelacarsen, Lp(a) HORIZON, which is currently underway and studying the impact of 80 mg/month of pelacarsen vs. placebo on rates of recurrent ASCVD events in a secondary prevention population with baseline elevated Lp(a) (NCT04023552).

Olpasiran is a GalNac-conjugated siRNA targeting apo(a) administered by subcutaneous injection. In a phase I, single-ascending-dose study of olpasiran vs. placebo in participants with Lp(a) either ≥ 70 and ≤ 199 nmol/L (n = 40) or ≥ 200 nmol/L (n = 24), the maximum mean percent change in Lp(a) from baseline ranged from -71% to -97%. Of note, the maximum reduction in Lp(a) was observed between days 43 and 71. While Lp(a) levels gradually increased, they remained lower compared to the placebo group out to 225 days. Olpasiran was well-tolerated [85]. A phase II clinical trial with olpasiran (OCEAN(a)-DOSE) is currently underway involving participants with Lp(a) > 150 nmol/L and history of ASCVD (NCT04270760). Additional siRNA therapies targeting apo(a) mRNA are under development. In a phase I clinical trial of SLN360 (an siRNA targeting apo(a) mRNA) vs. placebo, participants with Lp(a) $\geq$ 150 nmol/L were treated with single-ascending doses administered by subcutaneous injection. The maximal median percent reduction in Lp(a) was dose-dependent, up to -98%. The drug was generally well-tolerated; however, injection site reactions were reported [86].

Other targeted therapies for Lp(a) are in the early stages of development, including another siRNA, LY3819469, administered subcutaneously (NCT04914546). A phase I study of LY3473329, an oral medication targeting Lp(a), is also underway (NCT04472676). Thus, there is great interest in the continued development of compounds that can safely and potently lower Lp(a).

6. Conclusions and Future Directions

Lp(a) is now well-established as a risk factor for ASCVD and calcific aortic valve disease. However, optimal management of individuals with elevated Lp(a) is not well-established. Several currently available therapies have been evaluated for use in individuals with elevated Lp(a). However, improvement in clinical outcomes has only been shown in post hoc analyses from PCSK9i cardiovascular outcomes trials and in uncontrolled studies involving lipoprotein apheresis. There may also be an expanded role for anti-platelet therapy in both primary and secondary prevention in individuals with elevated Lp(a), but more research is needed. Multiple promising therapies that produce potent Lp(a) lowering are currently under investigation. Representative patient case scenarios are presented (Figure 2) to summarize an approach to management based on currently available evidence and guidelines. There are several areas in which future research is needed.

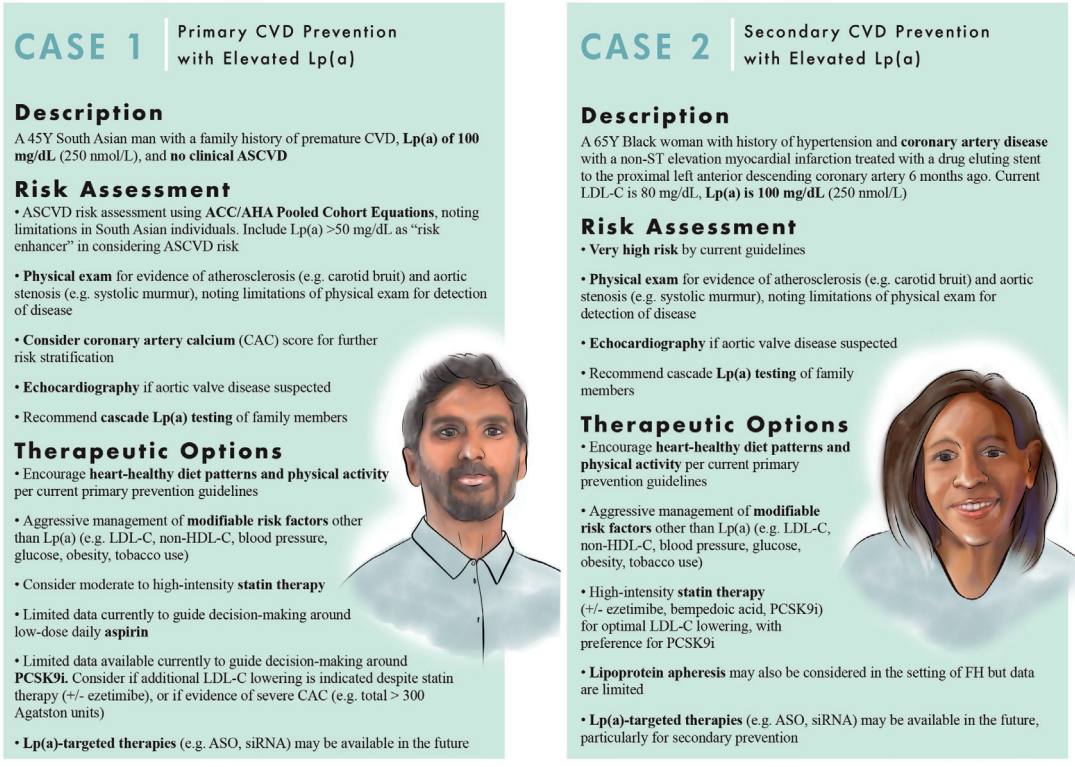

Figure 2. Patient cases: risk assessment and therapeutic options in the setting of elevated Lp(a). Two patient case scenarios are presented above, one for the primary prevention and one for secondary prevention in the setting of elevated Lp(a), with discussion of risk assessment and therapeutic options. **For case 1 (primary prevention),** the patient evaluation starts with risk assessment using the ACC/AHA Pooled Cohort Equations [19]. Lp(a) ≥50 mg/dL is considered a risk enhancer and would be an indication for more aggressive management of risk factors in an individual at borderline or intermediate 10-year risk. A physical exam is important to evaluate for evidence of atherosclerosis or aortic stenosis. If aortic valve disease is suspected, echocardiography would be indicated. CAC scoring can be considered to further risk stratify [20,22]. Cascade Lp(a) testing may be recommended for family members [104,105]. With regards to therapy, a healthy lifestyle should be recommended to all patients [19,106]. In the setting of elevated Lp(a), other modifiable risk factors should be addressed,

and moderate to high-intensity statin therapy should be considered. Low dose daily aspirin may be a consideration, but there is currently limited data to guide this decision. Similarly, there is limited date for PCSK9i, but they may considered, particularly if additional LDL-C lowering is needed despite statin therapy, or there is evidence of severe CAC. Lp(a)-targeted therapies may be available as an option in the future. **For case 2 (secondary prevention),** the patient is considered very high risk by current guidelines [20]. Again, physical exam is important, and echocardiography is indicated if there is suspicion for aortic valve disease. Cascade Lp(a) testing may also be recommended for family members. Regarding therapy, a healthy lifestyle and management of other risk factors are again recommended. High intensity statin therapy should be prescribed, with consideration of PCSK9i if further LDL-C lowering needed [20,22]. Lipoprotein apheresis may be considered in the setting of FH [107]. Lp(a)-targeted therapies may also be an option in the near future, particularly for secondary prevention.

For secondary prevention of CVD, the biggest area of controversy is whether Lp(a)-lowering translates to reduced risk of ASCVD events, and what degree of Lp(a)-lowering is necessary to achieve this effect. Lp(a)HORIZON (NCT04023552) is currently underway and will evaluate the effect of potent Lp(a)-lowering with pelacarsen in the setting of secondary prevention. Another important question is whether prolonged dual anti-platelet therapy after revascularization improves outcomes in individuals with high Lp(a).

For primary prevention, a number of open questions remain. If Lp(a)HORIZON produces positive results, the natural extension may be a large, primary prevention trial to again evaluate if Lp(a)-lowering, and to what degree, will prevent CVD in primary prevention. The use of aspirin for primary prevention, again suggested to have benefit in the Women's Health Study and ASPREE analyses, needs further evaluation. Another open area of investigation is the performance of current risk stratification tools in the context of elevated Lp(a), and whether Lp(a) should be incorporated into these tools.

Another potential area for investigation will be aortic stenosis and whether Lp(a) lowering will prevent or halt the progression of aortic stenosis/CAVD. Finally, Lp(a) may partially explain residual inflammatory ASCVD risk. Further studies may evaluate whether targeting Lp(a)/OxPL reduces this inflammatory risk.

Author Contributions: Conceptualization, data curation, and writing were performed by H.S.B. and M.J.W. All authors have read and agreed to the published version of the manuscript.

Funding: HSB and MJW are supported by the National Institutes of Health, Grant 1KL2TR001444. HSB is supported by the National Institutes of Health, Grant 5T32HL079891.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Schmidt, K.; Noureen, A.; Kronenberg, F.; Utermann, G. Structure, function, and genetics of lipoprotein (a). *J. Lipid Res.* **2016**, *57*, 1339–1359. [CrossRef] [PubMed]
2. Clarke, R.; Peden, J.F.; Hopewell, J.C.; Kyriakou, T.; Goel, A.; Heath, S.; Parish, S.; Barlera, S.; Franzosi, M.G.; Rust, S.; et al. Genetic Variants Associated with Lp(a) Lipoprotein Level and Coronary Disease. *N. Engl. J. Med.* **2009**, *361*, 2518–2528. [CrossRef]
3. The CARDIoGRAMplusC4D Consortium; Deloukas, P.; Kanoni, S.; Willenborg, C.; Farrall, M.; Assimes, T.L.; Thompson, J.R.; Ingelsson, E.; Saleheen, D.; Erdmann, J.; et al. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat. Genet.* **2013**, *45*, 25–33. [CrossRef] [PubMed]
4. Varvel, S.; McConnell, J.P.; Tsimikas, S. Prevalence of Elevated Lp(a) Mass Levels and Patient Thresholds in 532 359 Patients in the United States. *Arter. Thromb. Vasc. Biol.* **2016**, *36*, 2239–2245. [CrossRef] [PubMed]
5. Lee, S.-R.; Prasad, A.; Choi, Y.-S.; Xing, C.; Clopton, P.; Witztum, J.L.; Tsimikas, S. *LPA* Gene, Ethnicity, and Cardiovascular Events. *Circulation* **2017**, *135*, 251–263. [CrossRef]
6. Thanassoulis, G.; Campbell, C.Y.; Owens, D.S.; Smith, J.G.; Smith, A.V.; Peloso, G.M.; Kerr, K.F.; Pechlivanis, S.; Budoff, M.J.; Harris, T.B.; et al. Genetic Associations with Valvular Calcification and Aortic Stenosis. *N. Engl. J. Med.* **2013**, *368*, 503–512. [CrossRef] [PubMed]
7. Langsted, A.; Nordestgaard, B.G.; Kamstrup, P.R. Elevated Lipoprotein(a) and Risk of Ischemic Stroke. *J. Am. Coll. Cardiol.* **2019**, *74*, 54–66. [CrossRef]

8. Colantonio, L.D.; Bittner, V.; Safford, M.M.; Marcovina, S.; Brown, T.M.; Jackson, E.A.; Li, M.; López, J.A.G.; Monda, K.L.; Plante, T.B.; et al. Lipoprotein(a) and the risk for coronary heart disease and ischemic stroke events among black and white adults with cardiovascular disease. *J. Am. Heart Assoc.* **2022**, *11*, e025397. [CrossRef] [PubMed]
9. Kamstrup, P.R.; Nordestgaard, B.G. Elevated Lipoprotein(a) Levels, LPA Risk Genotypes, and Increased Risk of Heart Failure in the General Population. *JACC: Heart Fail.* **2016**, *4*, 78–87. [CrossRef]
10. Mohammadi-Shemirani, P.; Chong, M.; Narula, S.; Perrot, N.; Conen, D.; Roberts, J.D.; Thériault, S.; Bossé, Y.; Lanktree, M.B.; Pigeyre, M.; et al. Elevated Lipoprotein(a) and Risk of Atrial Fibrillation. *J. Am. Coll. Cardiol.* **2022**, *79*, 1579–1590. [CrossRef] [PubMed]
11. Masson, W.; Lobo, M.; Barbagelata, L.; Molinero, G.; Bluro, I.; Nogueira, J.P. Elevated lipoprotein (a) levels and risk of peripheral artery disease outcomes: A systematic review. *Vasc. Med.* **2022**, 1358863X221091320. [CrossRef] [PubMed]
12. Tsimikas, S. A Test in Context: Lipoprotein(a): Diagnosis, prognosis, controversies, and emerging therapies. *J. Am. Coll. Cardiol.* **2017**, *69*, 692–711. [CrossRef]
13. Taleb, A.; Witztum, J.L.; Tsimikas, S. Oxidized phospholipids on apoB-100-containing lipoproteins: A biomarker predicting cardiovascular disease and cardiovascular events. *Biomarkers Med.* **2011**, *5*, 673–694. [CrossRef] [PubMed]
14. Tsimikas, S.; Brilakis, E.S.; Miller, E.R.; McConnell, J.P.; Lennon, R.J.; Kornman, K.S.; Witztum, J.L.; Berger, P.B. Oxidized Phospholipids, Lp(a) Lipoprotein, and Coronary Artery Disease. *N. Engl. J. Med.* **2005**, *353*, 46–57. [CrossRef] [PubMed]
15. Schnitzler, J.G.; Hoogeveen, R.M.; Ali, L.; Prange, K.H.; Waissi, F.; Van Weeghel, M.; Bachmann, J.C.; Versloot, M.; Borrelli, M.J.; Yeang, C.; et al. Atherogenic Lipoprotein(a) Increases Vascular Glycolysis, Thereby Facilitating Inflammation and Leukocyte Extravasation. *Circ. Res.* **2020**, *126*, 1346–1359. [CrossRef]
16. Van Der Valk, F.M.; Bekkering, S.; Kroon, J.; Yeang, C.; Van den Bossche, J.; Van Buul, J.D.; Ravandi, A.; Nederveen, A.J.; Verberne, H.J.; Scipione, C.; et al. Oxidized Phospholipids on Lipoprotein(a) Elicit Arterial Wall Inflammation and an Inflammatory Monocyte Response in Humans. *Circulation* **2016**, *134*, 611–624. [CrossRef] [PubMed]
17. Boffa, M.B.; Koschinsky, M.L. Lipoprotein (a): Truly a direct prothrombotic factor in cardiovascular disease? *J. Lipid Res.* **2016**, *57*, 745–757. [CrossRef] [PubMed]
18. Yeang, C.; Wilkinson, M.J.; Tsimikas, S. Lipoprotein(a) and oxidized phospholipids in calcific aortic valve stenosis. *Curr. Opin. Cardiol.* **2016**, *31*, 440–450. [CrossRef] [PubMed]
19. Arnett, D.K.; Blumenthal, R.S.; Albert, M.A.; Buroker, A.B.; Goldberger, Z.D.; Hahn, E.J.; Himmelfarb, C.D.; Khera, A.; Lloyd-Jones, D.; McEvoy, J.W.; et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J. Am. Coll. Cardiol.* **2019**, *74*, e177–e232. [CrossRef]
20. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; De Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/AdA/AGS/AphA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2019**, *73*, e285–e350. [CrossRef] [PubMed]
21. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur. Heart J.* **2020**, *41*, 111–188. [CrossRef] [PubMed]
22. Pearson, G.J.; Thanassoulis, G.; Anderson, T.J.; Barry, A.R.; Couture, P.; Dayan, N.; Francis, G.A.; Genest, J.; Grégoire, J.; Grover, S.A.; et al. 2021 canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. *Can. J. Cardiol.* **2021**, *37*, 1129–1150. [CrossRef] [PubMed]
23. Tsimikas, S.; Fazio, S.; Ferdinand, K.C.; Ginsberg, H.N.; Koschinsky, M.L.; Marcovina, S.M.; Moriarty, P.M.; Rader, D.J.; Remaley, A.T.; Reyes-Soffer, G.; et al. NHLBI Working Group Recommendations to Reduce Lipoprotein(a)-Mediated Risk of Cardiovascular Disease and Aortic Stenosis. *J. Am. Coll. Cardiol.* **2018**, *71*, 177–192. [CrossRef] [PubMed]
24. Reyes-Soffer, G.; Ginsberg, H.N.; Berglund, L.; Duell, P.B.; Heffron, S.P.; Kamstrup, P.R.; Lloyd-Jones, D.M.; Marcovina, S.M.; Yeang, C.; Koschinsky, M.L. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Arter. Thromb. Vasc. Biol.* **2022**, *42*, e48–e60. [CrossRef] [PubMed]
25. Yeang, C.; Witztum, J.L.; Tsimikas, S. Novel method for quantification of lipoprotein(a)-cholesterol: Implications for improving accuracy of LDL-C measurements. *J. Lipid Res.* **2021**, *62*, 100053. [CrossRef] [PubMed]
26. Emerging Risk Factors Collaboration; Sebhat Erqou, S.; Kaptoge, S.; Perry, P.L.; Di Angelantonio, E.; Thompson, A.; White, I.R.; Marcovina, S.M.; Collins, R.; Thompson, S.G.; et al. Lipoprotein(a) Concentration and the Risk of Coronary Heart Disease, Stroke, and Nonvascular Mortality. *JAMA* **2009**, *302*, 412–423.
27. O'Donoghue, M.L.; Morrow, D.A.; Tsimikas, S.; Sloan, S.; Ren, A.F.; Hoffman, E.B.; Desai, N.R.; Solomon, S.D.; Domanski, M.; Arai, K.; et al. Lipoprotein(a) for Risk Assessment in Patients With Established Coronary Artery Disease. *J. Am. Coll. Cardiol.* **2014**, *63*, 520–527. [CrossRef]
28. Willeit, P.; Ridker, P.M.; Nestel, P.J.; Simes, J.; Tonkin, A.M.; Pedersen, T.R.; Schwartz, G.G.; Olsson, A.G.; Colhoun, H.M.; Kronenberg, F.; et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: Individual patient-data meta-analysis of statin outcome trials. *Lancet* **2018**, *392*, 1311–1320. [CrossRef]

29. Bennet, A.; Di Angelantonio, E.; Erqou, S.; Eiriksdottir, G.; Sigurdsson, G.; Woodward, M.; Rumley, A.; Lowe, G.D.O.; Danesh, J.; Gudnason, V. Lipoprotein(a) Levels and Risk of Future Coronary Heart DiseaseLarge-Scale Prospective Data. *Arch. Intern. Med.* **2008**, *168*, 598–608. [CrossRef]
30. Kamstrup, P.R.; Benn, M.; Tybjærg-Hansen, A.; Nordestgaard, B.G. Extreme Lipoprotein(a) Levels and Risk of Myocardial Infarction in the General Population. *Circulation* **2008**, *117*, 176–184. [CrossRef]
31. Virani, S.; Brautbar, A.; Davis, B.C.; Nambi, V.; Hoogeveen, R.; Sharrett, A.R.; Coresh, J.; Mosley, T.H.; Morrisett, J.D.; Catellier, D.J.; et al. Associations Between Lipoprotein(a) Levels and Cardiovascular Outcomes in Black and White Subjects. *Circulation* **2012**, *125*, 241–249. [CrossRef] [PubMed]
32. Paré, G.; Çaku, A.; McQueen, M.; Anand, S.S.; Enas, E.; Clarke, R.; Boffa, M.B.; Koschinsky, M.; Wang, X.; Yusuf, S.; et al. Lipoprotein(a) Levels and the Risk of Myocardial Infarction Among 7 Ethnic Groups. *Circulation* **2019**, *139*, 1472–1482. [CrossRef] [PubMed]
33. Jin, J.-L.; Cao, Y.-X.; Zhang, H.-W.; Sun, D.; Hua, Q.; Li, Y.-F.; Guo, Y.-L.; Wu, N.-Q.; Zhu, C.-G.; Gao, Y.; et al. Lipoprotein(a) and Cardiovascular Outcomes in Patients With Coronary Artery Disease and Prediabetes or Diabetes. *Diabetes Care* **2019**, *42*, 1312–1318. [CrossRef] [PubMed]
34. Patel, A.P.; Wang, M.; Pirruccello, J.P.; Ellinor, P.T.; Ng, K.; Kathiresan, S.; Khera, A.V. Lp(a) (Lipoprotein[a]) Concentrations and Incident Atherosclerotic Cardiovascular Disease: New insights from a large national biobank. *Arter. Thromb. Vasc. Biol.* **2020**, *41*, 465–474. [CrossRef]
35. Kamstrup, P.R.; Tybjaerg-Hansen, A.; Steffensen, R.; Nordestgaard, B.G. Genetically Elevated Lipoprotein(a) and Increased Risk of Myocardial Infarction. *JAMA* **2009**, *301*, 2331–2339. [CrossRef] [PubMed]
36. Kamstrup, P.R.; Tybjærg-Hansen, A.; Nordestgaard, B.G. Extreme Lipoprotein(a) Levels and Improved Cardiovascular Risk Prediction. *J. Am. Coll. Cardiol.* **2013**, *61*, 1146–1156. [CrossRef]
37. Kyriakou, T.; Seedorf, U.; Goel, A.; Hopewell, J.C.; Clarke, R.; Watkins, H.; Farrall, M. A Common *LPA* Null Allele Associates With Lower Lipoprotein(a) Levels and Coronary Artery Disease Risk. *Arter. Thromb. Vasc. Biol.* **2014**, *34*, 2095–2099. [CrossRef]
38. Lim, T.T.; Würtz, P.; Havulinna, A.S.; Palta, P.; Tukiainen, T.; Rehnström, K.; Esko, T.; Mägi, R.; Inouye, M.; Lappalainen, T.; et al. Distribution and Medical Impact of Loss-of-Function Variants in the Finnish Founder Population. *PloS Genet.* **2014**, *10*, e1004494. [CrossRef]
39. Saleheen, D.; Haycock, P.C.; Zhao, W.; Rasheed, A.; Taleb, A.; Imran, A.; Abbas, S.; Majeed, F.; Akhtar, S.; Qamar, N.; et al. Apolipoprotein(a) isoform size, lipoprotein(a) concentration, and coronary artery disease: A mendelian randomisation analysis. *Lancet Diabetes Endocrinol.* **2017**, *5*, 524–533. [CrossRef]
40. Mehta, A.; Virani, S.S.; Ayers, C.R.; Sun, W.; Hoogeveen, R.C.; Rohatgi, A.; Berry, J.D.; Joshi, P.H.; Ballantyne, C.M.; Khera, A. Lipoprotein(a) and Family History Predict Cardiovascular Disease Risk. *J. Am. Coll. Cardiol.* **2020**, *76*, 781–793. [CrossRef]
41. Trinder, M.; Zekavat, S.M.; Uddin, M.; Pampana, A.; Natarajan, P. Apolipoprotein B is an insufficient explanation for the risk of coronary disease associated with lipoprotein(a). *Cardiovasc. Res.* **2021**, *117*, 1245–1247. [CrossRef] [PubMed]
42. Zhang, W.; Speiser, J.L.; Ye, F.; Tsai, M.Y.; Cainzos-Achirica, M.; Nasir, K.; Herrington, D.M.; Shapiro, M.D. High-Sensitivity C-Reactive Protein Modifies the Cardiovascular Risk of Lipoprotein(a). *J. Am. Coll. Cardiol.* **2021**, *78*, 1083–1094. [CrossRef] [PubMed]
43. Gotoh, T.; Kuroda, T.; Yamasawa, M.; Nishinaga, M.; Mitsuhashi, T.; Seino, Y.; Nagoh, N.; Kayaba, K.; Yamada, S.; Matsuo, H.; et al. Correlation between lipoprotein(a) and aortic valve sclerosis assessed by echocardiography (the JMS Cardiac Echo and Cohort Study). *Am. J. Cardiol.* **1995**, *76*, 928–932. [CrossRef]
44. Stewart, B.; Siscovick, D.; Lind, B.K.; Gardin, J.M.; Gottdiener, J.S.; Smith, V.E.; Kitzman, D.W.; Otto, C.M. Clinical Factors Associated With Calcific Aortic Valve Disease. *J. Am. Coll. Cardiol.* **1997**, *29*, 630–634. [CrossRef]
45. Torzewski, M.; Ravandi, A.; Yeang, C.; Edel, A.; Bhindi, R.; Kath, S.; Twardowski, L.; Schmid, J.; Yang, X.; Franke, U.F.; et al. Lipoprotein(a)-Associated Molecules Are Prominent Components in Plasma and Valve Leaflets in Calcific Aortic Valve Stenosis. *JACC: Basic Transl. Sci.* **2017**, *2*, 229–240. [CrossRef]
46. Bozbas, H.; Yildirir, A.; Atar, I.; Pirat, B.; Eroglu, S.; Aydinalp, A.; Ozin, B.; Muderrisoglu, H. Effects of serum levels of novel atherosclerotic risk factors on aortic valve calcification. *J. Heart Valve Dis.* **2007**, *16*, 387–393.
47. Vongpromek, R.; Bos, S.; Kate, G.-J.R.T.; Yahya, R.; Verhoeven, A.J.M.; de Feyter, P.J.; Kronenberg, F.; van Lennep, J.E.R.; Sijbrands, E.J.G.; Mulder, M.T. Lipoprotein(a) levels are associated with aortic valve calcification in asymptomatic patients with familial hypercholesterolaemia. *J. Intern. Med.* **2014**, *278*, 166–173. [CrossRef]
48. Bouchareb, R.; Mahmut, A.; Nsaibia, M.J.; Boulanger, M.-C.; Dahou, A.; Lépine, J.-L.; Laflamme, M.-H.; Hadji, F.; Couture, C.; Trahan, S.; et al. Autotaxin Derived From Lipoprotein(a) and Valve Interstitial Cells Promotes Inflammation and Mineralization of the Aortic Valve. *Circulation* **2015**, *132*, 677–690. [CrossRef]
49. Després, A.-A.; Perrot, N.; Poulin, A.; Tastet, L.; Shen, M.; Chen, H.Y.; Bourgeois, R.; Trottier, M.; Tessier, M.; Guimond, J.; et al. Lipoprotein(a), Oxidized Phospholipids, and Aortic Valve Microcalcification Assessed by 18F-Sodium Fluoride Positron Emission Tomography and Computed Tomography. *CJC Open* **2019**, *1*, 131–140. [CrossRef]
50. Zheng, K.H.; Tsimikas, S.; Pawade, T.; Kroon, J.; Jenkins, W.S.; Doris, M.K.; White, A.C.; Timmers, N.K.; Hjortnaes, J.; Rogers, M.A.; et al. Lipoprotein(a) and Oxidized Phospholipids Promote Valve Calcification in Patients With Aortic Stenosis. *J. Am. Coll. Cardiol.* **2019**, *73*, 2150–2162. [CrossRef]

51. Glader, C.; Birgander, L.; Söderberg, S.; Ildgruben, H.; Saikku, P.; Waldenström, A.; Dahlén, G. Lipoprotein(a), Chlamydia pneumoniae, leptin and tissue plasminogen activator as risk markers for valvular aortic stenosis. *Eur. Heart J.* **2003**, *24*, 198–208. [CrossRef]
52. Kamstrup, P.R.; Tybjærg-Hansen, A.; Nordestgaard, B.G. Elevated Lipoprotein(a) and Risk of Aortic Valve Stenosis in the General Population. *J. Am. Coll. Cardiol.* **2014**, *63*, 470–477. [CrossRef] [PubMed]
53. Arsenault, B.J.; Boekholdt, M.; Dubé, M.-P.; Rhéaume, E.; Wareham, N.J.; Khaw, K.-T.; Sandhu, M.S.; Tardif, J.-C. Lipoprotein(a) Levels, Genotype, and Incident Aortic Valve Stenosis. *Circ. Cardiovasc. Genet.* **2014**, *7*, 304–310. [CrossRef] [PubMed]
54. Langsted, A.; Varbo, A.; Kamstrup, P.R.; Nordestgaard, B.G. Elevated Lipoprotein(a) Does Not Cause Low-Grade Inflammation Despite Causal Association With Aortic Valve Stenosis and Myocardial Infarction: A Study of 100 578 Individuals from the General Population. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 2690–2699. [CrossRef] [PubMed]
55. Kamstrup, P.R.; Hung, M.-Y.; Witztum, J.L.; Tsimikas, S.; Nordestgaard, B.G. Oxidized Phospholipids and Risk of Calcific Aortic Valve Disease. *Arter. Thromb. Vasc. Biol.* **2017**, *37*, 1570–1578. [CrossRef]
56. Que, X.; Hung, M.-Y.; Yeang, C.; Gonen, A.; Prohaska, T.A.; Sun, X.; Diehl, C.; Määttä, A.; Gaddis, D.E.; Bowden, K.; et al. Oxidized phospholipids are proinflammatory and proatherogenic in hypercholesterolaemic mice. *Nature* **2018**, *558*, 301–306. [CrossRef]
57. Capoulade, R.; Chan, K.L.; Yeang, C.; Mathieu, P.; Bossé, Y.; Dumesnil, J.G.; Tam, J.W.; Teo, K.K.; Mahmut, A.; Yang, X.; et al. Oxidized Phospholipids, Lipoprotein(a), and Progression of Calcific Aortic Valve Stenosis. *J. Am. Coll. Cardiol.* **2015**, *66*, 1236–1246. [CrossRef]
58. Capoulade, R.; Yeang, C.; Chan, K.L.; Pibarot, P.; Tsimikas, S. Association of Mild to Moderate Aortic Valve Stenosis Progression With Higher Lipoprotein(a) and Oxidized Phospholipid Levels. *JAMA Cardiol.* **2018**, *3*, 1212–1217. [CrossRef]
59. Tsimikas, S.; Gordts, P.L.S.M.; Nora, C.; Yeang, C.; Witztum, J.L. Statin therapy increases lipoprotein(a) levels. *Eur. Heart J.* **2020**, *41*, 2275–2284. [CrossRef]
60. Chan, K.L.; Teo, K.; Dumesnil, J.G.; Ni, A.; Tam, J.; ASTRONOMER Investigators. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: Results of the aortic stenosis progression observation: Measuring effects of rosuvastatin (ASTRONOMER) trial. *Circulation* **2010**, *121*, 306–314. [CrossRef]
61. Samaha, F.F.; McKenney, J.; Bloedon, L.T.; Sasiela, W.J.; Rader, D.J. Inhibition of microsomal triglyceride transfer protein alone or with ezetimibe in patients with moderate hypercholesterolemia. *Nat. Clin. Pr. Cardiovasc. Med.* **2008**, *5*, 497–505. [CrossRef] [PubMed]
62. Nozue, T.; Michishita, I.; Mizuguchi, I. Effects of Ezetimibe on Remnant-Like Particle Cholesterol, Lipoprotein (a), and Oxidized Low-Density Lipoprotein in Patients with Dyslipidemia. *J. Atheroscler. Thromb.* **2010**, *17*, 37–44. [CrossRef] [PubMed]
63. Boffa, M.B.; Koschinsky, M.L. Therapeutic Lowering of Lipoprotein(a). *Circ. Genom. Precis. Med.* **2018**, *11*, e002052. [CrossRef] [PubMed]
64. Albers, J.J.; Sle', A.; O'Brien, K.D.; Robinson, J.G.; Kashyap, M.L.; Kwiterovich, P.O.; Xu, P.; Marcovina, S.M. Relationship of Apolipoproteins A-1 and B, and Lipoprotein(a) to Cardiovascular Outcomes. *J. Am. Coll. Cardiol.* **2013**, *62*, 1575–1579. [CrossRef] [PubMed]
65. The HPS2-THRIVE Collaborative Group Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients. *N. Engl. J. Med.* **2014**, *371*, 203–212. [CrossRef] [PubMed]
66. Santos, R.D.; Raal, F.J.; Catapano, A.L.; Witztum, J.L.; Steinhagen-Thiessen, E.; Tsimikas, S. Mipomersen, an Antisense Oligonucleotide to Apolipoprotein B-100, Reduces Lipoprotein(a) in Various Populations With Hypercholesterolemia. *Arter. Thromb. Vasc. Biol.* **2015**, *35*, 689–699. [CrossRef]
67. O'Donoghue, M.L.; Fazio, S.; Giugliano, R.P.; Stroes, E.S.; Kanevsky, E.; Gouni-Berthold, I.; Im, K.; Pineda, A.L.; Wasserman, S.M.; Češka, R.; et al. Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. *Circulation* **2019**, *139*, 1483–1492. [CrossRef]
68. Bittner, V.A.; Szarek, M.; Aylward, P.E.; Bhatt, D.L.; Diaz, R.; Edelberg, J.M.; Fras, Z.; Goodman, S.G.; Halvorsen, S.; Hanotin, C.; et al. Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome. *J. Am. Coll. Cardiol.* **2020**, *75*, 133–144. [CrossRef] [PubMed]
69. Ray, K.K.; Wright, R.S.; Kallend, D.; Koenig, W.; Leiter, L.A.; Raal, F.J.; Bisch, J.A.; Richardson, T.; Jaros, M.; Wijngaard, P.L.; et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N. Engl. J. Med.* **2020**, *382*, 1507–1519. [CrossRef]
70. Bhatia, H.S.; Yeang, C.; Baruch, A.; Yang, X.; Stroes, E.S.; Tsimikas, S. PCSK9 Inhibition and Oxidized Phospholipids. *J. Am. Coll. Cardiol.* **2021**, *78*, 1288–1289. [CrossRef]
71. Waldmann, E.; Parhofer, K.G. Lipoprotein apheresis to treat elevated lipoprotein (a). *J. Lipid Res.* **2016**, *57*, 1751–1757. [CrossRef] [PubMed]
72. Moriarty, P.M.; Gray, J.V.; Gorby, L.K. Lipoprotein apheresis for lipoprotein(a) and cardiovascular disease. *J. Clin. Lipidol.* **2019**, *13*, 894–900. [CrossRef] [PubMed]
73. Roeseler, E.; Julius, U.; Heigl, F.; Spitthoever, R.; Heutling, D.; Breitenberger, P.; Leebmann, J.; Lehmacher, W.; Kamstrup, P.R.; Nordestgaard, B.G.; et al. Lipoprotein Apheresis for Lipoprotein(a)-Associated Cardiovascular Disease. *Arter. Thromb. Vasc. Biol.* **2016**, *36*, 2019–2027. [CrossRef] [PubMed]
74. Hohenstein, B.; Julius, U.; Lansberg, P.; Jaeger, B.; Mellwig, K.-P.; Weiss, N.; Graehlert, X.; Roeder, I.; Ramlow, W. Rationale and design of MultiSELECt: A European Multi center S tudy on the E ffect of L ipoprotein(a) E limination by lipoprotein apheresis on C ardiovascular ou t comes. *Atheroscler. Suppl.* **2017**, *30*, 180–186. [CrossRef] [PubMed]

75. Chasman, D.I.; Shiffman, D.; Zee, R.Y.; Louie, J.Z.; Luke, M.M.; Rowland, C.M.; Catanese, J.J.; Buring, J.E.; Devlin, J.J.; Ridker, P.M. Polymorphism in the apolipoprotein(a) gene, plasma lipoprotein(a), cardiovascular disease, and low-dose aspirin therapy. *Atherosclerosis* **2009**, *203*, 371–376. [CrossRef]
76. Lacaze, P.; Bakshi, A.; Riaz, M.; Polekhina, G.; Owen, A.; Bhatia, H.S.; Natarajan, P.; Wolfe, R.; Beilin, L.; Nicholls, S.J.; et al. Aspirin for primary prevention of cardiovascular events in relation to lipoprotein(a) genotypes. *J. Am. Coll. Cardiol.* **2022**, *80*, 1287–1298. [CrossRef] [PubMed]
77. Cui, K.; Yin, D.; Zhu, C.; Song, W.; Wang, H.; Jia, L.; Zhang, R.; Wang, H.; Cai, Z.; Feng, L.; et al. How do lipoprotein(a) concentrations affect clinical outcomes for patients with stable coronary artery disease who underwent different dual antiplatelet therapy after percutaneous coronary intervention? *J. Am. Heart Assoc.* **2022**, *11*, e023578. [CrossRef] [PubMed]
78. Danik, J.S.; Rifai, N.; Buring, J.E.; Ridker, P.M. Lipoprotein(a), Hormone Replacement Therapy, and Risk of Future Cardiovascular Events. *J. Am. Coll. Cardiol.* **2008**, *52*, 124–131. [CrossRef]
79. Honigberg, M.C.; Trinder, M.; Natarajan, P. Lipoprotein(a), Menopausal Hormone Therapy, and Risk of Coronary Heart Disease in Postmenopausal Individuals. *JAMA Cardiol.* **2022**, *7*, 565. [CrossRef]
80. Serban, M.-C.; Sahebkar, A.; Mikhailidis, D.P.; Toth, P.P.; Jones, S.R.; Muntner, P.; Blaha, M.J.; Andrica, F.; Martin, S.S.; Borza, C.; et al. Impact of L-carnitine on plasma lipoprotein(a) concentrations: A systematic review and meta-analysis of randomized controlled trials. *Sci. Rep.* **2016**, *6*, 19188. [CrossRef] [PubMed]
81. Witkowski, M.; Weeks, T.L.; Hazen, S.L. Gut Microbiota and Cardiovascular Disease. *Circ. Res.* **2020**, *127*, 553–570. [CrossRef]
82. Tsimikas, S.; Viney, N.J.; Hughes, S.G.; Singleton, W.; Graham, M.J.; Baker, B.F.; Burkey, J.L.; Yang, Q.; Marcovina, S.M.; Geary, R.S.; et al. Antisense therapy targeting apolipoprotein(a): A randomised, double-blind, placebo-controlled phase 1 studyy. *Lancet* **2015**, *386*, 1472–1483. [CrossRef]
83. Viney, N.J.; van Capelleveen, J.C.; Geary, R.S.; Xia, S.; A Tami, J.; Yu, R.Z.; Marcovina, S.M.; Hughes, S.G.; Graham, M.J.; Crooke, R.M.; et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): Two randomised, double-blind, placebo-controlled, dose-ranging trials. *Lancet* **2016**, *388*, 2239–2253. [CrossRef]
84. Tsimikas, S.; Karwatowska-Prokopczuk, E.; Gouni-Berthold, I.; Tardif, J.-C.; Baum, S.J.; Steinhagen-Thiessen, E.; Shapiro, M.D.; Stroes, E.S.; Moriarty, P.M.; Nordestgaard, B.G.; et al. Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. *N. Engl. J. Med.* **2020**, *382*, 244–255. [CrossRef] [PubMed]
85. Koren, M.J.; Moriarty, P.M.; Baum, S.J.; Neutel, J.; Hernandez-Illas, M.; Weintraub, H.S.; Florio, M.; Kassahun, H.; Melquist, S.; Varrieur, T.; et al. Preclinical development and phase 1 trial of a novel siRNA targeting lipoprotein(a). *Nat. Med.* **2022**, *28*, 96–103. [CrossRef] [PubMed]
86. Nissen, S.E.; Wolski, K.; Balog, C.; Swerdlow, D.I.; Scrimgeour, A.C.; Rambaran, C.; Wilson, R.J.; Boyce, M.; Ray, K.K.; Cho, L.; et al. Single Ascending Dose Study of a Short Interfering RNA Targeting Lipoprotein(a) Production in Individuals With Elevated Plasma Lipoprotein(a) Levels. *JAMA* **2022**, *327*, 1679. [CrossRef] [PubMed]
87. Silence Therapeutics Announces Detailed Results from sln360 Phase 1 Study in High Lipoprotein(a) Presented in Late Breaker at the American College of Cardiology (acc.22) Annual Meeting. 2022. Available online: https://silence-therapeutics.com/investors/press-releases/press-releases-details/2022/Silence-Therapeutics-Announces-Detailed-Results-From-SLN360-Phase-1-Study-in-High-Lipoproteina-Presented-in-Late-Breaker-at-the-American-College-of-Cardiology-ACC.22-Annual-Meeting/default.aspx (accessed on 11 August 2022).
88. Szarek, M.; A Bittner, V.; Aylward, P.; Baccara-Dinet, M.; Bhatt, D.L.; Diaz, R.; Fras, Z.; Goodman, S.G.; Halvorsen, S.; A Harrington, R.; et al. Lipoprotein(a) lowering by alirocumab reduces the total burden of cardiovascular events independent of low-density lipoprotein cholesterol lowering: ODYSSEY OUTCOMES trial. *Eur. Heart J.* **2020**, *41*, 4245–4255. [CrossRef]
89. Warden, B.; Minnier, J.; Watts, G.; Fazio, S.; Shapiro, M.D. Impact of PCSK9 inhibitors on plasma lipoprotein(a) concentrations with or without a background of niacin therapy. *J. Clin. Lipidol.* **2019**, *13*, 580–585. [CrossRef]
90. A Stiekema, L.C.; Stroes, E.S.G.; Verweij, S.L.; Kassahun, H.; Chen, L.; Wasserman, S.M.; Sabatine, M.S.; Mani, V.; A Fayad, Z. Persistent arterial wall inflammation in patients with elevated lipoprotein(a) despite strong low-density lipoprotein cholesterol reduction by proprotein convertase subtilisin/kexin type 9 antibody treatment. *Eur. Heart J.* **2019**, *40*, 2775–2781. [CrossRef]
91. Merki, E.; Graham, M.J.; Mullick, A.; Miller, E.R.; Crooke, R.M.; Pitas, R.E.; Witztum, J.L.; Tsimikas, S. Antisense Oligonucleotide Directed to Human Apolipoprotein B-100 Reduces Lipoprotein(a) Levels and Oxidized Phospholipids on Human Apolipoprotein B-100 Particles in Lipoprotein(a) Transgenic Mice. *Circulation* **2008**, *118*, 743–753. [CrossRef] [PubMed]
92. Tsimikas, S.; Moriarty, P.M.; Stroes, E.S. Emerging RNA Therapeutics to Lower Blood Levels of Lp(a). *J. Am. Coll. Cardiol.* **2021**, *77*, 1576–1589. [CrossRef] [PubMed]
93. Enkhmaa, B.; Berglund, L. Non-genetic influences on lipoprotein(a) concentrations. *Atherosclerosis* **2022**, *349*, 53–62. [CrossRef]
94. Haskell, W.L.; Alderman, E.L.; Fair, J.M.; Maron, D.J.; Mackey, S.F.; Superko, H.R.; Williams, P.T.; Johnstone, I.M.; A Champagne, M.; Krauss, R.M. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). *Circulation* **1994**, *89*, 975–990. [CrossRef] [PubMed]
95. Langsted, A.; Kamstrup, P.R.; Nordestgaard, B.G. Lipoprotein(a): Fasting and nonfasting levels, inflammation, and cardiovascular risk. *Atherosclerosis* **2014**, *234*, 95–101. [CrossRef] [PubMed]

96. Ebbeling, C.B.; Knapp, A.; Johnson, A.; Wong, J.M.W.; Greco, K.F.; Ma, C.; Mora, S.; Ludwig, D.S. Effects of a low-carbohydrate diet on insulin-resistant dyslipoproteinemia—a randomized controlled feeding trial. *Am. J. Clin. Nutr.* **2021**, *115*, 154–162. [CrossRef] [PubMed]
97. Wang, L.; Bordi, P.L.; Fleming, J.A.; Hill, A.M.; Kris-Etherton, P. Effect of a Moderate Fat Diet With and Without Avocados on Lipoprotein Particle Number, Size and Subclasses in Overweight and Obese Adults: A Randomized, Controlled Trial. *J. Am. Heart Assoc.* **2015**, *4*, e001355. [CrossRef] [PubMed]
98. Faghihnia, N.; Tsimikas, S.; Miller, E.R.; Witztum, J.L.; Krauss, R.M. Changes in lipoprotein(a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. *J. Lipid Res.* **2010**, *51*, 3324–3330. [CrossRef]
99. Haring, B.; von Ballmoos, M.C.W.; Appel, L.J.; Sacks, F.M. Healthy Dietary Interventions and Lipoprotein (a) Plasma Levels: Results from the Omni Heart Trial. *PloS ONE* **2014**, *9*, e114859. [CrossRef]
100. Ginsberg, H.N.; Kris-Etherton, P.; Dennis, B.; Elmer, P.J.; Ershow, A.; Lefevre, M.; Pearson, T.; Roheim, P.; Ramakrishnan, R.; Reed, R.; et al. Effects of Reducing Dietary Saturated Fatty Acids on Plasma Lipids and Lipoproteins in Healthy Subjects. *Arter. Thromb. Vasc. Biol.* **1998**, *18*, 441–449. [CrossRef]
101. Berglund, L.; Lefevre, M.; Ginsberg, H.N.; Kris-Etherton, P.M.; Elmer, P.J.; Stewart, P.W.; Ershow, A.; A Pearson, T.; Dennis, B.H.; Roheim, P.S.; et al. Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: Studies in the fasting and postprandial states. *Am. J. Clin. Nutr.* **2007**, *86*, 1611–1620. [CrossRef]
102. Jones, J.L.; Comperatore, M.; Barona, J.; Calle, M.C.; Andersen, C.; McIntosh, M.; Najm, W.; Lerman, R.H.; Fernandez, M.L. A Mediterranean-style, low–glycemic-load diet decreases atherogenic lipoproteins and reduces lipoprotein (a) and oxidized low-density lipoprotein in women with metabolic syndrome. *Metabolism* **2012**, *61*, 366–372. [CrossRef]
103. Vu, K.N.; Ballantyne, C.M.; Hoogeveen, R.C.; Nambi, V.; Volcik, K.A.; Boerwinkle, E.; Morrison, A.C. Causal Role of Alcohol Consumption in an Improved Lipid Profile: The Atherosclerosis Risk in Communities (ARIC) Study. *PLoS ONE* **2016**, *11*, e0148765. [CrossRef]
104. Ellis, K.L.; de Isla, L.P.; Alonso, R.; Fuentes, F.; Watts, G.; Mata, P. Value of Measuring Lipoprotein(a) During Cascade Testing for Familial Hypercholesterolemia. *J. Am. Coll. Cardiol.* **2019**, *73*, 1029–1039. [CrossRef]
105. Chakraborty, A.; Chan, D.C.; Ellis, K.L.; Pang, J.; Barnett, W.; Woodward, A.M.; Vorster, M.; Norman, R.; Moses, E.K.; Watts, G.F. Cascade testing for elevated lipoprotein(a) in relatives of probands with high lipoprotein(a). *Am. J. Prev. Cardiol.* **2022**, *10*, 100343. [CrossRef]
106. Piercy, K.L.; Troiano, R.P.; Ballard, R.M.; Carlson, S.A.; Fulton, J.E.; Galuska, D.A.; George, S.M.; Olson, R.D. The Physical Activity Guidelines for Americans. *JAMA* **2018**, *320*, 2020–2028. [CrossRef]
107. Kayikcioglu, M. LDL Apheresis and Lp (a) Apheresis: A Clinician's Perspective. *Curr. Atheroscler. Rep.* **2021**, *23*, 15. [CrossRef]

Journal of
Clinical Medicine

MDPI

Review

Newer and Emerging LDL-C Lowering Agents and Implications for ASCVD Residual Risk

Rishi Rikhi and Michael D. Shapiro *

Center for Prevention of Cardiovascular Disease, Section of Cardiovascular Medicine, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27101, USA
* Correspondence: mdshapir@wakehealth.edu

Abstract: Multiple lines of evidence demonstrate that low-density lipoprotein-cholesterol causes atherosclerotic cardiovascular disease. Thus, targeting and lowering low-density lipoprotein-cholesterol is the principal strategy to reduce cardiovascular disease risk in primary and secondary prevention. Statin therapy is the foundation of lipid-lowering treatment, but adherence rates are low, and many individuals do not attain target low-density lipoprotein-cholesterol values. Additionally, most statin-treated patients are still at considerable atherosclerotic cardiovascular disease risk, emphasizing the need for more aggressive low-density lipoprotein-cholesterol-lowering therapies. The purpose of this review is to discuss new and emerging approaches to further lower low-density lipoprotein-cholesterol, including inhibition of ATP-citrate lyase, proprotein convertase subtilisin-kexin type 9, angiopoietin-related protein 3, and cholesteryl ester transfer protein.

Keywords: dyslipidemia; cardiovascular disease; prevention; treatment; risk factors

Citation: Rikhi, R.; Shapiro, M.D. Newer and Emerging LDL-C Lowering Agents and Implications for ASCVD Residual Risk. *J. Clin. Med.* **2022**, *11*, 4611. https://doi.org/10.3390/jcm11154611

Academic Editor: Alessandro Delitala

Received: 2 July 2022
Accepted: 3 August 2022
Published: 8 August 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

For the past three decades, statin therapy has been the cornerstone for reducing atherosclerotic cardiovascular disease (ASCVD) risk [1,2]. During this time, numerous studies have demonstrated an indisputable causal role between low-density lipoprotein-cholesterol (LDL-C) and ASCVD [2]. Thus, therapies that decrease cumulative lifetime exposure to LDL-C have been efficacious in lowering ASCVD risk [2,3]. However, despite the efficacy and cost-effectiveness of statin therapy, ASCVD remains the leading cause of death globally [4–6]. Importantly, many of those on statin therapy continue to have residual ASCVD risk and are unable to achieve target LDL-C goals [1].

More recently, newer non-statin lipid-lowering therapies have surfaced with high efficacy in lowering LDL-C. The purpose of this review is to discuss mainstay LDL-C-lowering treatments, as well as emerging therapies that show promise in further reducing ASCVD risk (Table 1).

Table 1. Current, new, and emerging LDL-C lowering therapies.

Drug	Target	LDL-C Impact	Clinical Use or Status
Statins [7,8]	(HMG)-CoA reductase	~50%	DM Severe hypercholesterolemia ASCVD PCE $\geq$ 7.5%
Ezetimibe [7]	NPC1L1	~20%	Add-on to statin therapy for: ASCVD and LDL-C $\geq$ 70 mg/dL Severe hypercholesterolemia and LDL-C $\geq$ 100 mg/dL
Bempedoic acid [9–11]	ATP-citrate lyase	~20–25%	Add-on therapy (FDA 2/2020): ASCVD Heterozygous familial hypercholesterolemia
Alirocumab and Evolocumab [7]	Plasma PCSK9	~60%	Add-on to statin and ezetimibe therapy (FDA 7/2015): ASCVD and LDL-C $\geq$ 70 mg/dL Severe hypercholesterolemia and LDL-C $\geq$ 100 mg/dL
Inclisiran [12,13]	PCSK9 mRNA	~50%	Add-on therapy (FDA 12/2021): ASCVD Heterozygous familial hypercholesterolemia
MK-0616 [14–16]	Plasma PCSK9	~65%	Phase 2 upcoming
AZD8233 [17]	PCSK9 mRNA	~45–50%	Non-human primate data
VERVE-101 [18]	*PCSK9*	~60%	Non-human primate data
Evinacumab [19,20]	ANGPTL3	~50%	Add-on therapy (FDA 2/2021): Homozygous familial hypercholesterolemia
ANGPTL3-L_{RX} [21]	ANGPTL3 mRNA	~50%	Development Terminated
ARO-ANG3 [22–25]	ANGPTL3 mRNA	~50%	Phase 2, actively recruiting
Evacetrapib [26]	CETP	~40%	Development Terminated
Anacetrapib [27]	CETP	~40%	Development Terminated
Obicetrapib [28,29]	CETP	~45%	Phase 3, actively recruiting

HMG-CoA = β-hydroxy β-methylglutaryl-coenzyme A, DM = diabetes mellitus; ASCVD = atherosclerotic cardiovascular disease; PCE = pooled cohort equations; NPC1L1 = Niemann-Pick C1-Like 1; LDL-C = low-density lipoprotein-cholesterol; PCSK9 = Proprotein convertase subtilisin-kexin type 9, ANGPTL3 = Angiopoietin-related protein 3; CETP = Cholesteryl ester transfer protein.

2. Statins

Statins, originally derived from fungus, decrease LDL-C by inhibiting the rate-limiting enzyme, β-hydroxy β-methylglutaryl-coenzyme A (HMG)-CoA reductase, in the cholesterol synthesis pathway [30]. This results in increased expression of LDL receptors in the liver and, therefore, higher uptake of LDL-C from circulation, driving down plasma LDL-C [30]. Although discovered in the 1970s, it was not until 1987 when the first statin, lovastatin, became commercially available [30,31]. In 1997, statins gained significant notoriety as they were shown to decrease CVD risk (HR 0.70, 95% CI 0.58, 0.85) in the landmark Scandinavian Simvastatin Survival Study [32]. Subsequently, several more statin compounds have been commercialized, with different LDL-C-lowering efficacies [31].

Since their discovery, statins have been extensively studied in randomized clinical trials and are the first-line therapy in primary and secondary prevention of ASCVD [1,7]. The most important evidence for statin efficacy comes from the 2010 meta-analyses of 26 randomized controlled trials from the Cholesterol Treatment Trialists' Collaboration that included individual data from 169,138 participants, showing that a reduction in LDL-C by approximately 39 mg/dL led to a 22% reduction in major vascular events over the span of 5 years, even when LDL-C was low [8]. Despite the efficacy and excellent side-effect profile, where myopathy is expected to occur in 1 out of every 10,000 patient-years, adherence rates are poor and many individuals on statin therapy develop ASCVD events [1,4,33]. Thus, non-statin lipid-lowering therapies are under investigation and currently in use to reduce residual risk in certain patient populations.

3. Ezetimibe

Cholesterol homeostasis in the body is governed by the liver and intestine, of which the latter is the target for ezetimibe, the most used non-statin lipid-lowering therapy [7,34]. Ezetimibe targets the Niemann-Pick C1-Like 1 (NPC1L1) transporter found in the jejunal brush border, decreasing cholesterol absorption by 50% [1,33,35]. By doing so, less cholesterol makes its way to the liver, resulting in increased expression of LDL receptors and, therefore, reduced plasma LDL-C, by approximately 20% [1,4]. The most convincing evidence of the cardiovascular benefit of adding ezetimibe to statin therapy comes from The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [36]. Here, 18,144 patients at least 50 years of age with recent acute coronary syndrome were randomly assigned to receive simvastatin 40 mg plus placebo daily (n = 9077) or simvastatin 40 mg plus ezetimibe 10 mg daily (n = 9067) [36]. After 7 years of follow up, the group with ezetimibe had decreased risk of the primary composite endpoint (HR 0.936, 95% CI 0.89, 0.99) and 24% lower LDL-C [36]. The decreased risk was notable early at approximately 1 year and seems to be driven predominately by reduced incidence of myocardial infarction and stroke [36]. These findings were confirmed in a large meta-analysis of 21,727 individuals, where the authors found reduced risk of major cardiovascular events with the addition of ezetimibe to statin therapy (HR 0.94, 95% CI 0.90, 0.98) [37]. It is worth mentioning that the cardiovascular risk reduction was primarily in those with established ASCVD and there was no benefit in fatal outcomes with the addition of ezetimibe [37].

These findings illustrate the cardiovascular benefit of LDL-C-lowering and how it is not intrinsic to only statin therapy [1,36]. Based on this evidence, ezetimibe is recommended as add-on therapy in secondary prevention for those who have an LDL-C $\geq$ 70 mg/dL while on the highest tolerated statin dose [7]. Additionally, ezetimibe can be added to maximally tolerated statin therapy in those with severe primary hypercholesterolemia who have an LDL-C $\geq$ 100 mg/dL [7]. Although effective in reducing cardiovascular risk, the added LDL-C lowering impact of ezetimibe is modest; thus, newer therapies to further drive down plasma LDL-C and cardiovascular risk are needed [4,36].

4. Bempedoic Acid

The non-statin lipid lowering prodrug, 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic (bempedoic) acid, is metabolized in the liver and targets ATP-citrate lyase in the cholesterol synthesis pathway, upstream from HMG-CoA reductase [1,4,10]. As a prodrug, bempedoic acid requires enzymatic activation in the liver, minimizing off target effects, including skeletal muscle, and thus, may be of value in those who experience myopathy symptoms associated with statin use [1,4,10]. The safety and efficacy of bempedoic acid has been described in recent phase 3 Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) trials [9,11,38,39].

Clear Serenity, a phase 3 trial, randomized 345 participants with statin intolerance and an LDL-C $\geq$ 130 mg/dL for primary prevention or an LDL-C $\geq$ 100 mg/dL in those with heterozygous familial hypercholesteremia or history of ASCVD, to receive bempedoic acid or placebo [39]. The study found that bempedoic acid was effective at reducing LDL-C by 21.4% and caused less myalgias than the placebo group at 12 weeks [39]. Even more pronounced LDL-C-lowering was seen in CLEAR Tranquility, which randomized 269 participants with an LDL-C $\geq$ 100 mg/dL on ezetimibe therapy to bempedoic acid versus placebo [38]. After 12 weeks, bempedoic acid was able to reduce LDL-C by 28.5% with similar adverse events compared to placebo [38]. More long-term follow up was completed in the CLEAR Harmony trial, where 2230 participants with a history of ASCVD and/or heterozygous familial hypercholesterolemia on maximally tolerated statin therapy with an LDL-C $\geq$ 70 mg/dL were randomized to bempedoic acid or placebo [11]. The bempedoic acid group had significantly lower LDL-C at 52 weeks, with the highest LDL-C reduction, 18.1%, compared to placebo, occurring at 12 weeks [11]. Additionally, adverse events in the bempedoic acid and placebo group were comparable at 52 weeks; although, the bempedoic acid group had higher uric acid levels and gout events [11]. In a

very similar designed randomized trial, CLEAR Wisdom, 779 participants with an initial LDL-C $\geq$ 100 mg/dL were included [9]. After 12 weeks, the bempedoic acid group had an LDL-C reduction of 17.4% compared to the placebo that was largely sustained through 52 weeks [9]. A more recent randomized controlled trial investigated the use of a fixed-dose combination of bempedoic acid and ezetimibe in 301 participants with elevated CVD risk [40]. The group receiving the fixed-dose combination had an LDL-C reduction of 38.0% compared to the placebo at 12 weeks [40]. These trials indicate a promising role for bempedoic acid; although, cardiovascular outcome data are not yet available, but are currently being investigated in the fully recruited CLEAR Outcomes trial (ClinicalTrials.gov Identified NCT02993406) [40]. In February 2020, the FDA approved bempedoic acid and the fixed-dose combination with ezetimibe for use in those with a history of ASCVD or heterozygous familial hypercholesterolemia who are on maximally tolerated lipid-lowering therapy and in need of further LDL-C reduction [10].

5. Proprotein Convertase Subtilisin-Kexin Type 9 (PCSK9) Inhibition

Over the past 20 years, much has been learned about the PCSK9 pathway, stemming from the breakthrough finding in 2003 where gain of function mutations in *PCSK9* were shown to be the third locus of familial hypercholesterolemia [41,42]. PCSK9 is a serine protease secreted from hepatocytes into circulation and targets the extracellular surface of the LDL receptor, signaling it for lysosomal degradation [41,43]. This destruction of the LDL receptor results in decreased quantity of LDL receptors on the hepatic surface, and thus, less LDL particle clearance [41,43]. Moreover, loss of function in *PCSK9* is associated with significantly lower LDL-C and cardioprotection, highlighting the potential of PCSK9 as a therapeutic target [41,43,44].

One of the methods for inhibiting PCSK9 is with fully human monoclonal antibodies, of which alirocumab and evolocumab have been well studied in secondary prevention trials, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES) and Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER), respectively, capable of lowering LDL-C by approximately 60% [1,45,46]. In ODYSSEY OUTCOMES, 18,924 individuals with recent acute coronary syndrome on maximally tolerated statin therapy were randomized to receive alirocumab versus placebo [45]. After a median of 2.8 years, the investigators found decreased risk in the primary composite outcome in the alirocumab group (HR 0.85, 95% CI 0.78, 0.93) [45]. A similar reduction in cardiovascular risk was seen in FOURIER, which randomized 27,564 participants with a history of ASCVD and elevated cardiovascular risk, on maximally tolerated statin therapy, to evolocumab versus placebo [47]. After a median of 2.2 years, the group treated with evolocumab had lower risk of the primary composite outcome (HR 0.85, 95% 0.79, 0.92) [47]. In both ODYSSEY OUTCOMES and FOURIER, therapy was well tolerated with no major differences in adverse events between treatment versus placebo groups, despite dramatic reductions in LDL-C [45,47]. These trial results highlight the LDL-C-lowering potential and cardioprotective impact of alirocumab and evolocumab; however, these medications are currently much more expensive than ezetimibe and statin therapy, at approximately USD $6000 a year [45–47]. Thus, current recommendations are to use alirocumab and evolocumab as add-on therapy to maximally tolerated statin and ezetimibe treatment, when LDL-C is $\geq$70 mg/dL in secondary prevention or $\geq$100 mg/dL for those with severe primary hypercholesterolemia [7].

Another method to target PCSK9 is with inclisiran, a small interfering RNA (siRNA) therapy that inhibits translation of messenger-RNA (mRNA) [48,49]. Inclisiran has two strands, each 21–23 nucleotides in length, that interacts with the RNA-induced silencing complex (RISC), which then binds with PCSK9 mRNA, preventing translation of the PCSK9 protein [48,49]. During drug development, several chemical modifications occur to increase the compound's potency and duration of action [48,49]. Additionally, N-acetylgalactosamine is added to the sense strand, targeting inclisiran to the liver, mini-

mizing systemic adverse effects [48,49]. Although the half-life of inclisiran is only 9 h, the guide strand and RISC remain active and capable of interacting with PCSK9 mRNA multiple times, prolonging the clinical efficacy duration [48,49]. Much of the pharmacology and efficacy surrounding inclisiran comes from the phase 1, 2, and 3 ORION clinical trials [50].

ORION-1 randomly assigned 501 participants with an LDL $\geq$ 70 mg/dL and a history of ASCVD or LDL-C $\geq$ 100 mg/dL and no history of ASCVD to inclisiran versus placebo in a multiple-ascending dose phase 2 trial [51]. The authors found a significant and sustained reduction in LDL-C at 6 months in those who received one dose of inclisiran compared to placebo (30–44%) [51]. This reduction was even higher in those who received two injections of inclisiran, at day 1 and day 90, compared to placebo (37.3–54.4%), signifying a dose-dependent response [51]. This profound and sustained reduction in LDL-C was also seen in three phase 3 inclisiran trials, ORION-9, -10 and -11, all of which included patients with elevated cardiovascular risk, with LDL-C not at the goal on maximally tolerated statin therapy [52]. Additionally, the intervention group in all three trials received inclisiran sodium (300 mg) at day 1, 90, and every six months thereafter [52,53]. In ORION-10 and -11, at 510 days, LDL-C was 52.3% and 49.9% lower in the inclisiran group, respectively, compared to placebo [52]. Although long term safety data are not available, the analysis of the ORION-10 and -11 trials included data on a total of 2166 person-years, which did not show significant differences in adverse events between inclisiran and placebo groups [52]. Similar results were seen in ORION-9, which included 482 individuals with heterozygous familial hypercholesterolemia [53]. After 510 days, the inclisiran group had a reduction in LDL-C of 47.9%, with similar adverse events, compared to placebo [53]. In a recent meta-analysis of 3660 participants from ORION-9, -10, and -11, the authors found that inclisiran reduces LDL-C by 51% and major adverse cardiac events by 24%; however, these trials were not powered to assess clinical outcomes [12]. Fortunately, several other inclisiran clinical trials are underway, with the ORION-4 trial assessing major adverse cardiac event outcomes (ClinicalTrials.gov Identified NCT03705234) [50]. Based on the available evidence, the FDA approved use of inclisiran in the United States on 22 December 2021 as additional lipid-lowering therapy for those with a history of ASCVD or heterozygous familial hypercholesterolemia [13].

An emerging method of targeting PCSK9 is with oral therapy, avoiding the need for injections. MK-0616 is a macrocyclic peptide that was recently investigated in two phase 1 studies and found to lower LDL-C by 65%, with no significant adverse events [14,15]. Given these promising phase 1 results, there are plans for a phase 2 trial later this year [16]. Another oral therapy in development is a highly potent ASO, AZD8233, which was found to reduce LDL-C by 45–50% in cynomolgus monkeys and was mostly well tolerated [17].

A permanent approach to gene silencing is underway with Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) base editing of *PCSK9* [18]. Recently, *PCSK9* loss of function mutation was delivered via CRISPR adenine base editing therapy, VERVE-101, to non-human primates, resulting in a 90% reduction in circulating PCSK9 and 60% lowering of LDL-C [18]. This type of technology offers a paradigm shift in cholesterol management, omitting oral medications and frequent injections; however, long-term studies will be needed to assess the safety of permanent silencing of *PCSK9* and possible off target effects [18].

6. Angiopoietin-Related Protein 3 (ANGPTL3)

ANGPTL3 is a polypeptide hepatokine that inhibits lipoprotein lipase, an enzyme involved in the hydrolysis of triglycerides that plays a key role in the metabolism of very-low-density lipoprotein-cholesterol (VLDL-C) to LDL-C [54]. Additionally, ANGPTL3 inhibits endothelial lipase, a phospholipase pivotal to HDL-C metabolism [54]. There has been significant interest in the role of ANGPTL3 in the lipid metabolism pathway, as individuals with loss of function of *ANGPTL3* have hypobetalipoproteinemia, including 70% lower LDL-C levels [21]. While the mechanism of lowering LDL-C is not completely

understood, it is thought that blocking ANGPTL3 increases the clearance of remnant lipoproteins, preventing the formation of LDL-C [54].

One method of blocking ANGPTL3 is with evinacumab, a fully human monoclonal antibody that was shown in a phase 1 study of 83 healthy volunteers to reduce LDL-C by 23.2% [55]. In a phase 2 trial involving nine participants with homozygous familial hypercholesterolemia with a mean LDL-C of 376 mg/dL, evinacumab was able to reduce LDL-C by 49% after 1 month [56]. Similar results were seen in another phase 2 randomized controlled trial of 272 participants with primary hypercholesterolemia on maximally tolerated lipid lowering therapy, where LDL-C was reduced by 56% and 50.5% by subcutaneous and intravenous evinacumab at 16 weeks, respectively [57]. More recently, a phase 3 trial randomized 65 patients with homozygous familial hypercholesterolemia on maximally tolerated lipid lowering therapy with a mean LDL-C of 255.1 mg/dL to evinacumab versus placebo [19]. The study found a decrease in LDL-C of 49% compared to placebo at 24 weeks with no major differences in adverse events [19]. While safety data from these trials are promising, long-term safety data of evinacumab are unknown, but will be addressed in a fully recruited phase 3 trial (ClinicalTrials.gov Identified NCT03409744) [58]. In 2021, the FDA approved evinacumab for individuals with homozygous familial hypercholesterolemia and at least 12 years of age [20].

ANGPTL3 can also be targeted via gene-silencing mechanisms, including antisense oligonucleotide (ASO) and siRNA techniques. Compared to siRNA therapies, such as inclisiran, ASOs are single stranded and independently target mRNA, without interacting with RISC [25]. In 2017, Graham et al. conducted a preclinical study and a phase 1 trial in healthy participants of an ASO targeting ANGPTL3 mRNA, ANGPTL3-L_{RX} [21]. In the preclinical study, the authors found lowering of LDL-C and triglycerides in all the mice treated with ANGPTL3 ASO therapy, as well as reduced hepatic triglyceride content [21]. Similar results were seen in the phase 1 trial, with maximal reductions in LDL-C, triglycerides, and apolipoprotein B by 46.5%, 51.7%, and 36.7%, respectively, compared to placebo, with no significant adverse events [21]. However, phase 2a and phase 2b trials had only modest LDL-C reductions, despite using higher doses of ANGPTL3 ASO therapy; although, the phase 2 study participants had lower baseline LDL-C values [21,59,60]. Additionally, in the phase 2 studies, there were concerning increases in liver enzymes and hepatic fat content, especially at higher doses, leading to its discontinuation in development [59–61].

The second approach to gene silencing ANGPTL3 is with ARO-ANG3, a siRNA-based therapy. In a phase 1 trial, 12 healthy volunteers received ARO-ANG3 at day 1 and a repeat dose at day 29 and had maximal reductions in LDL-C of 45–54% at around 5 weeks that was largely sustained to 16 weeks [24]. Similar preliminary results were seen in 17 patients with heterozygous familial hypercholesterolemia and an LDL-C $\geq$ 130 mg/dL despite maximally tolerated statin therapy, where after 16 weeks, LDL-C levels were reduced 23–37%, with no severe adverse events [62]. Further knowledge regarding ARO-ANG3 and safety information will be obtained from actively recruiting phase 2 trials (ClinicalTrials.gov Identified NCT05217667 and NCT04832971) [22,23].

7. Cholesteryl Ester Transfer Protein (CETP) Inhibitors

Observational studies have shown that loss of function of *CETP* is associated with an increase in high-density lipoprotein-cholesterol (HDL-C) and decrease in LDL-C [63]. CETP is involved in transferring triglycerides from atherogenic lipoprotein particles to HDL-C and cholesterol esters from HDL-C to atherogenic lipoproteins [63]. The original CETP inhibitors predominantly increased HDL-C, with minimal impact on LDL-C, but were terminated in development due to safety concerns and futility [63]. The newer CETP inhibitors, anacetrapib and evacetrapib, have been shown to not only increase HDL-C, but also decrease LDL-C [26]. In a phase 3 randomized control trial including 12,092 participants with elevated ASCVD risk, evacetrapib was found to increase HDL-C by 134.8% and decrease LDL-C by 37.1% compared to placebo [26]. Despite these favorable lipid profile results, treatment with evacetrapib did not result in lower cardiovascular risk, which is

surprising as the LDL-C reduction achieved was similar to that of moderate intensity statin therapy [26]. A possible explanation for this negative result could be inadequate follow up time to demonstrate a cardiovascular benefit, as participants were only followed for slightly over 2 years [26]. Anacetrapib was also studied in a phase 3 trial that included adults over the age of 50 years with a history of ASCVD and was shown to increase HDL-C by 104% and reduce LDL-C by 41% compared to placebo [27]. Even more, after four years, the group treated with anacetrapib was found to have reduced cardiovascular risk (HR 0.91, 95% CI 0.85, 0.97) compared to the placebo group [27]. Although there were no major safety events, anacetrapib was found to persist in adipose tissue, providing concerns for prolonged duration of action [27]. Given the negative phase 3 trial for evacetrapib and concerns for drug accumulation in adipose tissue for anacetrapib, the development of both therapies has been discontinued [64].

Obicetrapib is the newest member of the CETP inhibitor class of medications [63]. Compared to the older CETP inhibitors, obicetrapib was created as a tetrahydroquinoline derivative, improving its oral absorption and potency [63]. In a phase 2 trial, 364 patients were randomized to obicetrapib or placebo, and after 12 weeks, LDL-C values were reduced by 26.6–44.5% compared to placebo [28]. Even more, combination therapy of obicetrapib and atorvastatin 20 mg led to an additional reduction in LDL-C by 50.2% compared to atorvastatin alone [28]. Currently, there is an actively recruiting randomized controlled cardiovascular outcomes trial, PREVAIL, studying if 10 mg of obicetrapib in secondary prevention lowers risk of major adverse cardiac events (ClinicalTrials.gov Identified NCT05202509) [29].

8. Discussion

An unmet need exists to appropriately lower LDL-C to reduce residual cardiovascular risk in primary and secondary prevention for individuals on maximally tolerated statin therapy who have not met LDL-C goals [1,2,4]. Despite the efficacy and safety of statin therapy, adherence rates remain low in primary and secondary prevention, at approximately 37% and 64%, respectively, with many not able to achieve LDL-C targets [65]. Currently, new therapies exist to lower residual cardiovascular risk in those with a history of ASCVD who have an LDL-C $\geq$ 70 mg/dL or severe primary hypercholesterolemia with an LDL-C $\geq$ 100 mg/dL while on the maximally tolerate statin therapy [7].

Ezetimibe is recommended for this patient population as a first-line add-on therapy given its low cost; although, its LDL-C lowering ability is modest at only 20% [1,4]. Thus, further LDL-C-lowering may be needed, which can be achieved with alirocumab and evolocumab; however, these monoclonal antibodies against PCSK9 are expensive and require injections every two weeks, limiting widespread use [45–47]. Recently, the FDA approved inclisiran, an siRNA therapy silencing PCSK9 expression capable of reducing LDL-C by 51%, requiring only twice-yearly injections [12,13]. Another medication that can be used in this population to lower residual risk is bempedoic acid, a prodrug targeting ATP-citrate lyase in the cholesterol synthesis pathway [1,4,10]. While not as effective as PCSK9 inhibitors in lowering LDL-C, bempedoic acid is cost-effective and oral; even more, the combination of bempedoic acid and ezetimibe lowers LDL-C by only a third less than PCSK9 inhibitors [40].

In addition to these new therapies to lower LDL-C, emerging therapies are underway that show promise if they further reduce residual ASCVD risk [18,19,24,62]. One promising avenue is with oral therapy targeting plasma PCSK9, MK-0616, and PCSK9 mRNA, AZD8233, capable of reducing LDL-C by 65% in a phase 1 study and 45–50% in cynomolgus monkeys, respectively [14–17,66]. Another target is ANGPTL3, which can be inhibited with fully human monoclonal antibodies or gene-silencing technology [19,24,62]. The monoclonal antibody against ANGPTL3, evinacumab, has been shown to reduce LDL-C by approximately 50% in individuals with homozygous familial hypercholesterolemia on maximally tolerated lipid-lowering therapy [19]. Additionally, ARO-ANG3, an siRNA targeting ANGPTL3, also shows promise, although more data are needed, which will be obtained in actively recruiting phase 2 trials [22,23]. Another emerging therapy is obicetrapib, the

newest and most potent CETP inhibitor, shown to reduce LDL-C by 26.6–44.5% in a phase 2 study, with an actively recruiting cardiovascular outcomes trial underway [28]. Lastly, CRISPR adenine base editing therapy causes permanent loss of function of *PCSK9*, which has been shown to reduce LDL-C by 60% in non-human primates [18]. The advantages and disadvantages of these new and emerging therapies that have been FDA approved are seen in Table 2.

Table 2. Advantages and disadvantages of LDL-C-lowering therapies.

Drug	Advantages	Disadvantages
Statins [7,8]	Excellent LDL-C lowering Strong evidence reducing ASCVD risk Six of the seven statins are generic	Low adherence
Ezetimibe [7]	Well tolerated Moderate evidence in secondary prevention	Modest LDL-C lowering
Bempedoic acid [9–11]	Well tolerated in those with statin associated side effects	Modest LDL-C lowering
Alirocumab and Evolocumab [7]	Excellent LDL-C lowering Well tolerated Strong evidence reducing ASCVD risk	Cost Injection
Inclisiran [12,13]	Excellent LDL-C lowering Durability (only 3 injections first year)	No ASCVD outcome data
Evinacumab [19,20]	Excellent LDL-C lowering (Use in homozygous familial hypercholesterolemia)	Cost Injection

LDL-C = low-density lipoprotein-cholesterol; ASCVD = atherosclerotic cardiovascular disease.

In conclusion, there has been tremendous innovation regarding targets and drug delivery techniques to lower LDL-C. Although statin therapy is the cornerstone to reducing cardiovascular disease risk in primary and secondary prevention, several individuals require additional LDL-C-lowering therapy. These new and emerging therapies show promise in reducing residual cardiovascular disease risk.

Author Contributions: All authors have read and agreed to the published version of the manuscript.

Funding: Rikhi is supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number T32HL076132. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: Rikhi declares no conflict of interest. Shapiro has participated in scientific advisory boards with the following entities: Amgen, Novartis, and Novo Nordisk; and has served as a consultant for Regeneron.

References

1. Shapiro, M.D.; Fazio, S. From Lipids to Inflammation: New Approaches to Reducing Atherosclerotic Risk. *Circ. Res.* **2016**, *118*, 732–749. [CrossRef]
2. Ference, B.A.; Ginsberg, H.N.; Graham, I.; Ray, K.K.; Packard, C.J.; Bruckert, E.; Hegele, R.A.; Krauss, R.M.; Raal, F.J.; Schunkert, H.; et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur. Heart J.* **2017**, *38*, 2459–2472. [CrossRef]
3. Shapiro, M.D.; Bhatt, D.L. "Cholesterol-Years" for ASCVD Risk Prediction and Treatment. *J. Am. Coll. Cardiol.* **2020**, *76*, 1517–1520. [CrossRef]
4. Nurmohamed, N.S.; Navar, A.M.; Kastelein, J.J.P. New and Emerging Therapies for Reduction of LDL-Cholesterol and Apolipoprotein B: JACC Focus Seminar 1/4. *J. Am. Coll. Cardiol.* **2021**, *77*, 1564–1575. [CrossRef]
5. Roth, G.A.; Mensah, G.A.; Johnson, C.O.; Addolorato, G.; Ammirati, E.; Baddour, L.M.; Barengo, N.C.; Beaton, A.Z.; Benjamin, E.J.; Benziger, C.P.; et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J. Am. Coll. Cardiol.* **2020**, *76*, 2982–3021. [CrossRef]
6. Silverman, M.G.; Ference, B.A.; Im, K.; Wiviott, S.D.; Giugliano, R.P.; Grundy, S.M.; Braunwald, E.; Sabatine, M.S. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. *JAMA* **2016**, *316*, 1289–1297. [CrossRef]

7. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **2019**, *139*, e1082–e1143. [CrossRef]
8. Cholesterol Treatment Trialists, C.; Baigent, C.; Blackwell, L.; Emberson, J.; Holland, L.E.; Reith, C.; Bhala, N.; Peto, R.; Barnes, E.H.; Keech, A.; et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* **2010**, *376*, 1670–1681. [CrossRef]
9. Goldberg, A.C.; Leiter, L.A.; Stroes, E.S.G.; Baum, S.J.; Hanselman, J.C.; Bloedon, L.T.; Lalwani, N.D.; Patel, P.M.; Zhao, X.; Duell, P.B. Effect of Bempedoic Acid vs. Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial. *JAMA* **2019**, *322*, 1780–1788. [CrossRef]
10. Markham, A. Bempedoic Acid: First Approval. *Drugs* **2020**, *80*, 747–753. [CrossRef]
11. Ray, K.K.; Bays, H.E.; Catapano, A.L.; Lalwani, N.D.; Bloedon, L.T.; Sterling, L.R.; Robinson, P.L.; Ballantyne, C.M.; Trial, C.H. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. *N. Engl. J. Med.* **2019**, *380*, 1022–1032. [CrossRef]
12. Khan, S.A.; Naz, A.; Qamar Masood, M.; Shah, R. Meta-Analysis of Inclisiran for the Treatment of Hypercholesterolemia. *Am. J. Cardiol.* **2020**, *134*, 69–73. [CrossRef]
13. NOVARTIS FDA Approves Novartis Leqvio®(inclisiran), First-in-Class siRNA to Lower Cholesterol and Keep It Low with Two Doses a Year. Available online: https://www.novartis.com/news/media-releases/fda-approves-novartis-leqvio-inclisiran-first-class-sirna-lower-cholesterol-and-keep-it-low-two-doses-year (accessed on 9 June 2022).
14. Late-Breaking Science Abstracts and Featured Science Abstracts From the American Heart Association's Scientific Sessions 2021 and Late-Breaking Abstracts in Resuscitation Science From the Resuscitation Science Symposium 2021. *Circulation* **2021**, *144*, e564–e593. [CrossRef]
15. American Heart Association. Oral PCSK9 Inhibitor Found to Be Safe, Effective to Lower Cholesterol, in First Human Trial. Available online: https://newsroom.heart.org/news/oral-pcsk9-inhibitor-found-to-be-safe-effective-to-lower-cholesterol-in-first-human-trial (accessed on 30 June 2022).
16. Mullard, A. Merck readies oral, macrocyclic PCSK9 inhibitor for phase II test. *Nat. Rev. Drug Discov.* **2022**, *21*, 9. [CrossRef]
17. Gennemark, P.; Walter, K.; Clemmensen, N.; Rekic, D.; Nilsson, C.A.M.; Knochel, J.; Holtta, M.; Wernevik, L.; Rosengren, B.; Kakol-Palm, D.; et al. An oral antisense oligonucleotide for PCSK9 inhibition. *Sci. Transl. Med.* **2021**, *13*, eabe9117. [CrossRef]
18. Musunuru, K.; Chadwick, A.C.; Mizoguchi, T.; Garcia, S.P.; DeNizio, J.E.; Reiss, C.W.; Wang, K.; Iyer, S.; Dutta, C.; Clendaniel, V.; et al. In vivo CRISPR base editing of PCSK9 durably lowers cholesterol in primates. *Nature* **2021**, *593*, 429–434. [CrossRef]
19. Raal, F.J.; Rosenson, R.S.; Reeskamp, L.F.; Hovingh, G.K.; Kastelein, J.J.P.; Rubba, P.; Ali, S.; Banerjee, P.; Chan, K.C.; Gipe, D.A.; et al. Evinacumab for Homozygous Familial Hypercholesterolemia. *N. Engl. J. Med.* **2020**, *383*, 711–720. [CrossRef]
20. U.S. Food & Drug Administration. FDA Approves Add-on Therapy for Patients with Genetic Form of Severely High Cholesterol. Available online: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-add-therapy-patients-genetic-form-severely-high-cholesterol-0 (accessed on 2 July 2022).
21. Graham, M.J.; Lee, R.G.; Brandt, T.A.; Tai, L.J.; Fu, W.; Peralta, R.; Yu, R.; Hurh, E.; Paz, E.; McEvoy, B.W.; et al. Cardiovascular and Metabolic Effects of ANGPTL3 Antisense Oligonucleotides. *N. Engl. J. Med.* **2017**, *377*, 222–232. [CrossRef]
22. Arrowhead Pharmaceuticals. Study of ARO-ANG3 in Adults with Mixed Dyslipidemia (ARCHES-2). Available online: https://clinicaltrials.gov/ct2/show/NCT04832971 (accessed on 14 June 2022).
23. Arrowhead Pharmaceuticals. Study of ARO-ANG3 in Participants with Homozygous Familial Hypercholesterolemia (HOFH) (Gateway). Available online: https://clinicaltrials.gov/ct2/show/NCT05217667?term=NCT05217667&draw=2&rank=1 (accessed on 14 June 2022).
24. Watts, G.F.; Schwabe, C.; Scott, R.; Gladding, P.; Sullivan, D.; Baker, J.; Clifton, P.; Hamilton, J.; Given, B.; San Martin, J.; et al. RNAi inhibition of angiopoietin-like protein 3 (ANGPTL3) with ARO-ANG3 mimics the lipid and lipoprotein profile of familial combined hypolipidemia. *Eur. Heart J.* **2020**, *41*, 3331. [CrossRef]
25. Watts, J.K.; Corey, D.R. Silencing disease genes in the laboratory and the clinic. *J. Pathol.* **2012**, *226*, 365–379. [CrossRef]
26. Lincoff, A.M.; Nicholls, S.J.; Riesmeyer, J.S.; Barter, P.J.; Brewer, H.B.; Fox, K.A.A.; Gibson, C.M.; Granger, C.; Menon, V.; Montalescot, G.; et al. Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. *N. Engl. J. Med.* **2017**, *376*, 1933–1942. [CrossRef]
27. Group, H.T.R.C.; Bowman, L.; Hopewell, J.C.; Chen, F.; Wallendszus, K.; Stevens, W.; Collins, R.; Wiviott, S.D.; Cannon, C.P.; Braunwald, E.; et al. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. *N. Engl. J. Med.* **2017**, *377*, 1217–1227. [CrossRef]
28. Hovingh, G.K.; Kastelein, J.J.; van Deventer, S.J.; Round, P.; Ford, J.; Saleheen, D.; Rader, D.J.; Brewer, H.B.; Barter, P.J. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): A randomised, double-blind, placebo-controlled phase 2 trial. *Lancet* **2015**, *386*, 452–460. [CrossRef]
29. New Amsterdam Pharma. Cardiovascular Outcome Study to Evaluate the Effect of Obicetrapib in Patients with Cardiovascular Disease (PREVAIL). Available online: https://clinicaltrials.gov/ct2/show/NCT05202509 (accessed on 16 June 2022).
30. Sirtori, C.R. The pharmacology of statins. *Pharm. Res.* **2014**, *88*, 3–11. [CrossRef]
31. Hajar, R. Statins: Past and present. *Heart Views* **2011**, *12*, 121–127. [CrossRef]

32. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* **1994**, *344*, 1383–1389.
33. Reith, C.; Armitage, J. Management of residual risk after statin therapy. *Atherosclerosis* **2016**, *245*, 161–170. [CrossRef]
34. Earl, J.; Kirkpatrick, P. Fresh from the pipeline. Ezetimibe. *Nat. Rev. Drug Discov.* **2003**, *2*, 97–98. [CrossRef]
35. Altmann, S.W.; Davis, H.R., Jr.; Zhu, L.J.; Yao, X.; Hoos, L.M.; Tetzloff, G.; Iyer, S.P.; Maguire, M.; Golovko, A.; Zeng, M.; et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science* **2004**, *303*, 1201–1204. [CrossRef]
36. Cannon, C.P.; Blazing, M.A.; Giugliano, R.P.; McCagg, A.; White, J.A.; Theroux, P.; Darius, H.; Lewis, B.S.; Ophuis, T.O.; Jukema, J.W.; et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N. Engl. J. Med.* **2015**, *372*, 2387–2397. [CrossRef]
37. Zhan, S.; Tang, M.; Liu, F.; Xia, P.; Shu, M.; Wu, X. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. *Cochrane Database Syst. Rev.* **2018**, *11*, CD012502. [CrossRef] [PubMed]
38. Ballantyne, C.M.; Banach, M.; Mancini, G.B.J.; Lepor, N.E.; Hanselman, J.C.; Zhao, X.; Leiter, L.A. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. *Atherosclerosis* **2018**, *277*, 195–203. [CrossRef] [PubMed]
39. Laufs, U.; Banach, M.; Mancini, G.B.J.; Gaudet, D.; Bloedon, L.T.; Sterling, L.R.; Kelly, S.; Stroes, E.S.G. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. *J. Am. Heart Assoc.* **2019**, *8*, e011662. [CrossRef] [PubMed]
40. Ballantyne, C.M.; Laufs, U.; Ray, K.K.; Leiter, L.A.; Bays, H.E.; Goldberg, A.C.; Stroes, E.S.; MacDougall, D.; Zhao, X.; Catapano, A.L. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur. J. Prev. Cardiol.* **2020**, *27*, 593–603. [CrossRef]
41. Dullaart, R.P.F. PCSK9 Inhibition to Reduce Cardiovascular Events. *N. Engl. J. Med.* **2017**, *376*, 1790–1791. [CrossRef]
42. Shapiro, M.D.; Tavori, H.; Fazio, S. PCSK9: From Basic Science Discoveries to Clinical Trials. *Circ. Res.* **2018**, *122*, 1420–1438. [CrossRef]
43. Handelsman, Y.; Lepor, N.E. PCSK9 Inhibitors in Lipid Management of Patients With Diabetes Mellitus and High Cardiovascular Risk: A Review. *J. Am. Heart Assoc.* **2018**, *7*, e008953. [CrossRef]
44. Cohen, J.C.; Boerwinkle, E.; Mosley, T.H., Jr.; Hobbs, H.H. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N. Engl. J. Med.* **2006**, *354*, 1264–1272. [CrossRef]
45. Schwartz, G.G.; Steg, P.G.; Szarek, M.; Bhatt, D.L.; Bittner, V.A.; Diaz, R.; Edelberg, J.M.; Goodman, S.G.; Hanotin, C.; Harrington, R.A.; et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N. Engl. J. Med.* **2018**, *379*, 2097–2107. [CrossRef]
46. Rifai, M.A.; Ballantyne, C.M. PCSK9-targeted therapies: Present and future approaches. *Nat. Rev. Cardiol.* **2021**, *18*, 805–806. [CrossRef]
47. Sabatine, M.S.; Giugliano, R.P.; Keech, A.C.; Honarpour, N.; Wiviott, S.D.; Murphy, S.A.; Kuder, J.F.; Wang, H.; Liu, T.; Wasserman, S.M.; et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N. Engl. J. Med.* **2017**, *376*, 1713–1722. [CrossRef] [PubMed]
48. Scicchitano, P.; Milo, M.; Mallamaci, R.; De Palo, M.; Caldarola, P.; Massari, F.; Gabrielli, D.; Colivicchi, F.; Ciccone, M.M. Inclisiran in lipid management: A Literature overview and future perspectives. *Biomed. Pharm.* **2021**, *143*, 112227. [CrossRef] [PubMed]
49. German, C.A.; Shapiro, M.D. Small Interfering RNA Therapeutic Inclisiran: A New Approach to Targeting PCSK9. *BioDrugs* **2020**, *34*, 1–9. [CrossRef] [PubMed]
50. Warden, B.A.; Duell, P.B. Inclisiran: A Novel Agent for Lowering Apolipoprotein B-containing Lipoproteins. *J. Cardiovasc. Pharm.* **2021**, *78*, e157–e174. [CrossRef] [PubMed]
51. Ray, K.K.; Landmesser, U.; Leiter, L.A.; Kallend, D.; Dufour, R.; Karakas, M.; Hall, T.; Troquay, R.P.; Turner, T.; Visseren, F.L.; et al. Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. *N. Engl. J. Med.* **2017**, *376*, 1430–1440. [CrossRef]
52. Ray, K.K.; Wright, R.S.; Kallend, D.; Koenig, W.; Leiter, L.A.; Raal, F.J.; Bisch, J.A.; Richardson, T.; Jaros, M.; Wijngaard, P.L.J.; et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N. Engl. J. Med.* **2020**, *382*, 1507–1519. [CrossRef] [PubMed]
53. Raal, F.J.; Kallend, D.; Ray, K.K.; Turner, T.; Koenig, W.; Wright, R.S.; Wijngaard, P.L.J.; Curcio, D.; Jaros, M.J.; Leiter, L.A.; et al. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. *N. Engl. J. Med.* **2020**, *382*, 1520–1530. [CrossRef]
54. Wang, Y.; Gusarova, V.; Banfi, S.; Gromada, J.; Cohen, J.C.; Hobbs, H.H. Inactivation of ANGPTL3 reduces hepatic VLDL-triglyceride secretion. *J. Lipid Res.* **2015**, *56*, 1296–1307. [CrossRef]
55. Dewey, F.E.; Gusarova, V.; Dunbar, R.L.; O'Dushlaine, C.; Schurmann, C.; Gottesman, O.; McCarthy, S.; Van Hout, C.V.; Bruse, S.; Dansky, H.M.; et al. Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease. *N. Engl. J. Med.* **2017**, *377*, 211–221. [CrossRef]
56. Gaudet, D.; Gipe, D.A.; Pordy, R.; Ahmad, Z.; Cuchel, M.; Shah, P.K.; Chyu, K.Y.; Sasiela, W.J.; Chan, K.C.; Brisson, D.; et al. ANGPTL3 Inhibition in Homozygous Familial Hypercholesterolemia. *N. Engl. J. Med.* **2017**, *377*, 296–297. [CrossRef]
57. Rosenson, R.S.; Burgess, L.J.; Ebenbichler, C.F.; Baum, S.J.; Stroes, E.S.G.; Ali, S.; Khilla, N.; Hamlin, R.; Pordy, R.; Dong, Y.; et al. Evinacumab in Patients with Refractory Hypercholesterolemia. *N. Engl. J. Med.* **2020**, *383*, 2307–2319. [CrossRef]
58. Regeneron Pharmaceuticals. Evaluate the Long-Term Safety and Efficacy of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia. Available online: https://www.clinicaltrials.gov/ct2/show/NCT03409744 (accessed on 16 June 2022).

59. Bergmark, B.A.; Marston, N.A.; Bramson, C.R.; Curto, M.; Ramos, V.; Jevne, A.; Kuder, J.F.; Park, J.G.; Murphy, S.A.; Verma, S.; et al. Effect of Vupanorsen on Non-High-Density Lipoprotein Cholesterol Levels in Statin-Treated Patients With Elevated Cholesterol: TRANSLATE-TIMI 70. *Circulation* **2022**, *145*, 1377–1386. [CrossRef] [PubMed]
60. Gaudet, D.; Karwatowska-Prokopczuk, E.; Baum, S.J.; Hurh, E.; Kingsbury, J.; Bartlett, V.J.; Figueroa, A.L.; Piscitelli, P.; Singleton, W.; Witztum, J.L.; et al. Vupanorsen, an N-acetyl galactosamine-conjugated antisense drug to ANGPTL3 mRNA, lowers triglycerides and atherogenic lipoproteins in patients with diabetes, hepatic steatosis, and hypertriglyceridaemia. *Eur. Heart J.* **2020**, *41*, 3936–3945. [CrossRef] [PubMed]
61. Pfizer. Pfizer and Ionis Announce Discontinuation of Vupanorsen Clinical Development Program. Available online: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-ionis-announce-discontinuation-vupanorsen (accessed on 14 June 2022).
62. Watts, G.F.; Schwabe, C.; Scott, R.; Gladding, P.; Sullivan, D.; Baker, J.; Clifton, P.; Hamilton, J.; Given, B.; Martin, J.S.; et al. Abstract 15751: Pharmacodynamic Effect of ARO-ANG3, an Investigational RNA Interference Targeting Hepatic Angiopoietin-like Protein 3, in Patients With Hypercholesterolemia. *Circulation* **2020**, *142*, A15751. [CrossRef]
63. Nurmohamed, N.S.; Ditmarsch, M.; Kastelein, J.J.P. CETP-inhibitors: From HDL-C to LDL-C lowering agents? *Cardiovasc. Res.* **2021**. [CrossRef]
64. Nicholls, S.J.; Bubb, K. The mystery of evacetrapib—Why are CETP inhibitors failing? *Expert Rev. Cardiovasc. Ther.* **2020**, *18*, 127–130. [CrossRef]
65. Colantonio, L.D.; Rosenson, R.S.; Deng, L.; Monda, K.L.; Dai, Y.; Farkouh, M.E.; Safford, M.M.; Philip, K.; Mues, K.E.; Muntner, P. Adherence to Statin Therapy Among US Adults Between 2007 and 2014. *J. Am. Heart Assoc.* **2019**, *8*, e010376. [CrossRef]
66. AstraZeneca. A Study of AZD8233 in Participants with Dyslipidemia. Available online: https://clinicaltrials.gov/ct2/show/NCT04641299 (accessed on 30 June 2022).

Journal of
Clinical Medicine

MDPI

Review

Current and Emerging Therapies for Atherosclerotic Cardiovascular Disease Risk Reduction in Hypertriglyceridemia

Reed Mszar [1], Sarah Bart [2], Alexander Sakers [3], Daniel Soffer [4] and Dean G. Karalis [5,*]

[1] Department of Physiology, Georgetown University, Washington, DC 20057, USA
[2] Frank H. Netter MD School of Medicine, Quinnipiac University, North Haven, CT 06473, USA
[3] Department of Medicine, Massachusetts General Hospital, Boston, MA 02114, USA
[4] Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[5] Department of Cardiology, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA
* Correspondence: dean.karalis@jefferson.edu

Abstract: Hypertriglyceridemia (HTG) is a prevalent medical condition in patients with cardiometabolic risk factors and is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), if left undiagnosed and undertreated. Current guidelines identify HTG as a risk-enhancing factor and, as a result, recommend clinical evaluation and lifestyle-based interventions to address potential secondary causes of elevated triglyceride (TG) levels. For individuals with mild to moderate HTG at risk of ASCVD, statin therapy alone or in combination with other lipid-lowering medications known to decrease ASCVD risk are guideline-endorsed. In addition to lifestyle modifications, patients with severe HTG at risk of acute pancreatitis may benefit from fibrates, mixed formulation omega-3 fatty acids, and niacin; however, evidence does not support their use for ASCVD risk reduction in the contemporary statin era. Novel therapeutics including those that target apoC-III and ANGPTL3 have shown to be safe, well-tolerated, and effective for lowering TG levels. Given the growing burden of cardiometabolic disease and risk factors, public health and health policy strategies are urgently needed to enhance access to effective pharmacotherapies, affordable and nutritious food options, and timely health care services.

Keywords: fibrates; lipids; lipoproteins; niacin; omega-3 fatty acids; statins; triglycerides

Citation: Mszar, R.; Bart, S.; Sakers, A.; Soffer, D.; Karalis, D.G. Current and Emerging Therapies for Atherosclerotic Cardiovascular Disease Risk Reduction in Hypertriglyceridemia. *J. Clin. Med.* **2023**, *12*, 1382. https://doi.org/10.3390/jcm12041382

Academic Editors: Alessandro Delitala and Nathan Wong

Received: 14 January 2023
Revised: 5 February 2023
Accepted: 7 February 2023
Published: 9 February 2023

1. Introduction

Normal fasting triglyceride (TG) levels are defined as <150 mg/dL, while mild to moderate hypertriglyceridemia (HTG) is defined as TG levels between 150 to 499 mg/dL and severe HTG as TG levels of ≥500 mg/dL [1]. Mild to moderate HTG is common, with roughly 25% of the U.S. population being affected, while severe HTG occurs in <1% of the population (Table 1) [2–4]. Almost all individuals with HTG have a combination of inherited and environmental causes, such as obesity, insulin resistance with or without diabetes mellitus (DM), and fatty liver disease, that collectively contribute to its presence and severity.

Observational and genetic studies have established HTG as an important contributor to atherosclerotic cardiovascular disease (ASCVD) and acute pancreatitis (AP). For this reason, there is a renewed focus on identifying and treating HTG both for primary and secondary prevention. In this review, we discuss the physiology, etiology, and landscape of current and emerging pharmacologic therapies for the treatment of HTG to reduce ASCVD risk.

Table 1. Classification of hypertriglyceridemia and risks associated with triglyceride ranges.

HTG Categories	TG Levels (mg/dL)	Lipoproteins	Prevalence *	Clinical Risks	Treatment Approaches
Mild-to-Moderate	150–499	↑ VLDL, TRLs	~1:4–10	ASCVD	• Lifestyle/behavioral • Statins
Severe	≥500	↑ VLDL, ↑ chylomicrons, or both	~1:10,000	ASCVD + Acute Pancreatitis	• Lifestyle/behavioral • Very low-fat diet • Statins • Omega-3 fatty acids • Fibrates • Niacin

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HTG, hypertriglyceridemia; TG, triglyceride; TRL, triglyceride-rich lipoproteins; VLDL-C, very low-density lipoprotein cholesterol. * Estimated prevalence based on all individuals with TG levels >150 mg/dL. Note: ↑ indicates increased levels of lipoproteins.

2. Overview of Triglyceride Metabolism

TG has important physiological roles, serving as a fuel source for energy production in skeletal and cardiac muscle and facilitating the storage of excess energy in adipose tissue [5]. TG is trafficked throughout the body in apolipoprotein B (apoB)-containing particles called triglyceride rich lipoproteins (TRL), which carry TG as their principal cargo. TRL have a three-stage lifecycle, consisting of: (1) the production by the liver or intestines, (2) metabolism in the circulation, and (3) clearance by the liver (Figure 1) [6].

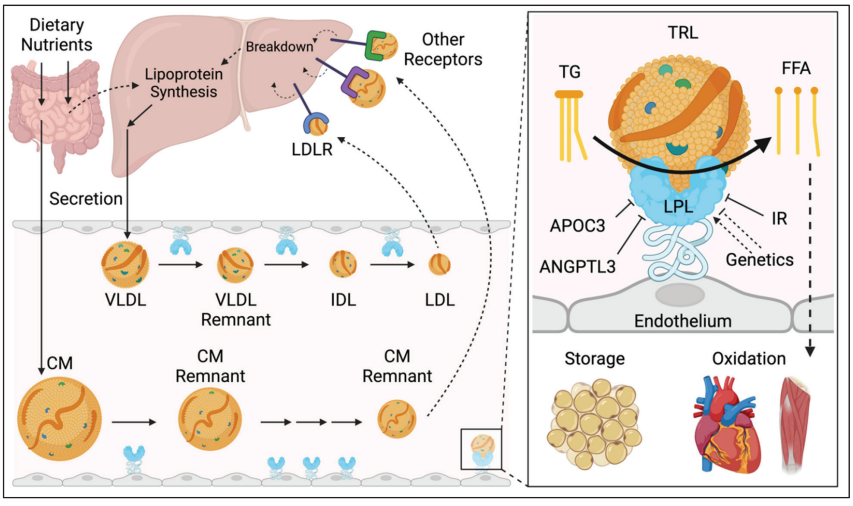

Figure 1. Transport and metabolism of triglyceride-rich lipoproteins. TRL synthesis occurs in both the intestine and the liver. In the intestine, dietary lipids are packaged into chylomicrons (apoB48), and in the liver cholesterol and triglycerides, they are packaged into VLDL (apoB100). Lipoprotein lipase (LPL) releases the TG from TRL by catalyzing the hydrolysis of TG to free fatty acids (FFA). FFA cross the endothelium for oxidation or storage in the underlying tissue. Successive rounds of this process yield denser, triglyceride depleted particles. These particles are taken up by specialized receptors on the surface on hepatocytes, allowing the recycling of their lipid and protein contents. Inset: Several factors inhibit LPL activity, including APOC3 and ANGPTL3, which are novel targets for TG-lowering therapy. Insulin resistance (IR) likewise reduces LPL activity through pleiotropic mechanisms. Genetic variants in LPL or other factors required for its synthesis and functioning also modulate LPL activity. Created with biorender.com (accessed on 26 December 2022). Abbreviations: CM, chylomicron; FFA, free fatty acids; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LDL, lipoprotein lipase; TG, triglyceride; TRL, triglyceride-rich lipoprotein; VLDL, very low-density lipoprotein.

In the intestine, dietary lipids are packaged into ApoB48-containing chylomicrons. In the liver, hepatic cholesterol and triglycerides are packaged into ApoB100-containing very low-density lipoproteins (VLDL). Several sources contribute to the hepatic lipid pool, including dietary nutrients (i.e., protein/carbohydrates which are converted to lipids by de novo lipogenesis), circulating free fatty acids, and lipoprotein breakdown.

In the circulation, the enzyme lipoprotein lipase (LPL) releases the TG from TRL by catalyzing the hydrolysis of TG to free fatty acids (FFA). FFA then cross the endothelium for oxidation in skeletal and cardiac muscle or for storage in adipose tissue. Successive rounds of metabolism by LPL yield increasingly dense, more cholesterol rich, and less triglyceride rich particles, termed remnant lipoproteins [7]. Specifically, chylomicrons are metabolized to chylomicron remnants and VLDL are metabolized to VLDL remnants, then intermediate-density lipoproteins (IDL), and eventually low-density lipoproteins (LDL). It is important to note that the term TRL applies to all the aforementioned particles with the exception of LDL. The term "remnant lipoprotein" applies to all partially metabolized TRL.

In the final stage of their lifecycle, particles are taken up by specialized receptors on the surface on hepatocytes, notably the LDL-receptor (LDL-R) and LDL-related receptor 1 (LRP1) among others, which facilitate the recycling of TRL lipid and protein contents. Steady-state TG levels and the abundance of TRL in the circulation are determined by the relative rates of TRL production, metabolism, and clearance. Accordingly, factors which increase production or reduce the clearance of TRL can lead to HTG [8].

3. Hypertriglyceridemia and ASCVD Risk

HTG promotes atherosclerosis through several mechanisms. First, HTG reflects elevated TRL concentrations in the circulation and TRL, as with other apoB-containing lipoproteins, are directly atherogenic. In fact, research indicates that nearly all apoB-containing lipoproteins (i.e., those that are small enough to cross the endothelium, with a ~70 nm diameter or less) are approximately equal in atherogenicity on a per particle basis [9]. Second, high plasma TG concentrations promote several characteristic alterations in the circulating lipoprotein profile that are associated with increased atherogenesis. HTG stimulates the activity of cholesteryl ester transfer protein (CETP), which remodels lipoproteins by exchanging TG for cholesterol esters (CE) between TG-rich and TG-poor lipoproteins. This process directly leads to the cholesterol depletion of LDL and high-density lipoprotein (HDL) particles, reducing their particle size and cholesterol content [10]. The resulting small-dense LDL particles are more atherogenic than may be expected from their cholesterol content alone, since there are many molecules of apoB for each unit of cholesterol [9]. Additionally, small cholesterol-depleted HDL particles are more rapidly cleared by the kidneys, further reducing HDL-C and resulting in fewer HDL particles. Overall, in individuals with HTG, although LDL-C cholesterol levels may be normal, non-HDL-C (atherogenic cholesterol) and apoB (number of atherogenic particles) levels tend to be higher, reflecting increased atherogenic risk [11].

Multiple lines of evidence indicate that elevated TRL levels (defined as elevated TG or elevated remnant cholesterol) are associated with ASCVD risk in both primary and secondary prevention, even among statin-treated patients [12,13]. In a recent retrospective study, both primary and secondary prevention participants receiving statin therapy with TG levels of $\geq$150 mg/dL had a lower adjusted risk of death, but a significantly higher risk of major adverse cardiovascular events (MACE) [14]. Fan and colleagues estimated the occurrence of nearly 3.5 million ASCVD events in the next 10 years among individuals with TG levels of $\geq$150 mg/dL [2] and Mendelian randomization studies have provided causal evidence for the role of TG-mediated pathways in coronary heart disease (CHD) incidence [15–17].

The atherosclerotic risk associated with TRL is related to the concentration of these atherogenic apoB-containing particles and enhanced by their TG content. Especially in cases of HTG, calculated LDL-C levels may underestimate an individual's ASCVD risk when there is significant discordance between LDL-C and apoB or non-HDL-C. Consistent with

this, non-HDL-C and apoB levels reflect the full risk due to atherogenic lipoproteins better than LDL-C in observational and interventional clinical trials [18]. Therefore, these authors favor using apoB (or non-HDL-C, if not available) levels to estimate the atherogenic risk due in individual patients. However, since national guidelines promote the use of LDL-C as the primary risk assessment and treatment metric, the best methods to calculate LDL-C should be favored. In conventional lipid panels, reported LDL-C levels are calculated from directly measured total cholesterol, HDL-C, and TG levels using the Friedewald formula, which is less accurate when TG levels are high. The Martin–Hopkins table and the Sampson-NIH formula both outperform the traditional Friedewald method and are now preferred up to TG levels of 400 mg/dL [19,20].

Current guidelines for patients with mild to moderate HTG focus on lifestyle modifications and a consideration of statin therapy based on an individual's cardiovascular risk [21]. For high-risk adult patients with established ASCVD or DM on a maximally tolerated statin whose TG remains elevated, icosapent ethyl omega-3 fatty acids dosed at 4 g a day has been shown to reduce cardiovascular events and should be considered [22].

4. Hypertriglyceridemia and Acute Pancreatitis

In addition to the increased ASCVD risk associated with mild to moderately elevated TG levels, HTG is also responsible for up to 15% of AP cases, with the risk and severity of AP increasing in a dose-dependent manner with elevations in TG levels [23,24]. Specifically, the risk of AP in individuals with serum TG levels of >1000 mg/dL is approximately 5%, compared to 10–20% among those with TG levels of >2000 mg/dL [25]. A recent cohort analysis showed that HTG was causative in 7.7% cases of AP, and that TG levels of >11.3 mmol/L (approximately 1000 mg/dL) were associated with a greater incidence of moderately severe AP and longer hospitalization stays [23]. A meta-analysis of 16 studies including nearly 12,000 patients showed that HTG was also associated with pancreatic necrosis and persistent organ/renal failure, and groups of patients with severe HTG had higher rates of complications and mortality for AP [26]. All prior and current guidelines recommend lifestyle modification, along with TG-lowering pharmacologic therapy, for patients with severe HTG to reduce their risk of AP [21].

5. Genetic and Environmental Causes of Hypertriglyceridemia

Mild to moderate HTG occurs because of inherited and environmental factors. Even in patients with pathologic genetic variants that affect TG metabolism, environmental and modifiable characteristics have an important impact on TG levels and health outcomes (Figure 2). Contemporary dietary patterns contribute directly to HTG, and indirectly by their impact on the development of visceral adiposity, fatty liver, and insulin resistance. Diets composed of calorie-rich, nutrient-poor, fatty, sweetened, and ultra-processed foods contribute to the growing incidence and prevalence of DM, obesity, and HTG.

Monogenic disorders that cause HTG are rare; however, they are more likely to be found in individuals with the most severe HTG (TG levels > 1000 mg/dL) [27]. Recent reports have indicated that severe HTG due to a monogenic disorder occurs with a prevalence of approximately 0.01% in the general population and between 1–2% among all adults with more severe HTG [28–30]. Genetic testing is generally not recommended for the identification or treatment of HTG given that the genes regulating TG levels are often recessive with heterogeneity in penetrance [7,31,32]. However, when a monogenic condition such as familial chylomicronemia syndrome, familial lipodystrophy, and familial dysbetalipoproteinemia is suspected, genetic testing may inform disease prognosis, management strategies, and expectations of lifestyle and pharmacologic response.

In addition to genetic and lifestyle factors associated with HTG, secondary causes leading to elevated TG levels may include certain classes of medications including beta blockers, corticosteroids, and antipsychotics, as well as medical and metabolic conditions such as chronic kidney disease, uncontrolled hypothyroidism, and psoriasis (Table 2).

Clinicians should assess and address potential secondary causes of HTG when determining appropriate strategies for TG lowering and cardiovascular risk reduction.

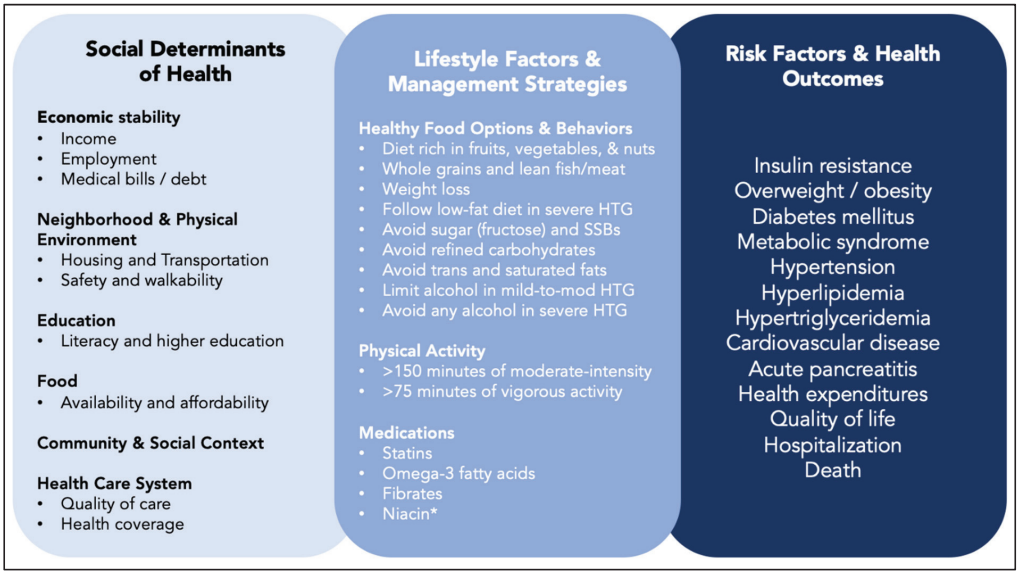

Figure 2. Schematic representation of the proximal and distal factors related to the association between environmental, lifestyle, and social factors contributing to disparities in clinical risk factors and outcomes. Abbreviations: HTG, hypertriglyceridemia; SSB, sugar-sweetened beverages. * Niacin is not recommended for the clinical management of atherosclerotic cardiovascular disease.

Table 2. Genetic disorders and secondary factors (conditions and medications) associated with elevated triglyceride levels and increased hypertriglyceridemia risk.

Genetic Disorders	Secondary Disorders	Medications
• Familial combined hyperlipidemia • Familial dysbetalipoproteinemia • Familial hypertriglyceridemia • Multifactorial chylomicronemia syndrome • Familial chylomicronemia syndrome • Transient infantile hypertriglyceridemia • Polygenic hypertriglyceridemia • Congenital lipodystrophy	• Obesity • Metabolic syndrome • Diabetes mellitus • Hypothyroidism • Chronic liver disease • Chronic kidney disease • Nephrotic syndrome • Lipodystrophy • Autoimmune disorders • Pregnancy (3rd trimester) • Weight gain after weight loss • Rheumatoid arthritis • Glycogen storage diseases • Psoriasis • Sepsis • Multiple myeloma • Systemic lupus • Cushing syndrome	• Beta blockers • Thiazides • L-asparaginase • Bile acid resins • Atypical antipsychotics • Rosiglitazone • Sirolimus • Cyclophosphamide • Isotretinoin • Oral estrogens • Tamoxifen • Glucocorticoids • Retinoids • Raloxifene • Cyclosporine • Interferon • Tacrolimus • Propofol

6. Current Treatments for Hypertriglyceridemia

6.1. Lifestyle and Behavioral Modifications

Given the strong association between lifestyle and behavioral factors with elevated TG levels, as well as significant associations between HTG and metabolic syndrome, many of the same treatment approaches for managing insulin resistance, DM, obesity, cardiovascular disease, and fatty liver can be integrated into the care for those with high TG levels. To address the risk of ASCVD associated with HTG, current guidelines recommend an approach to clinical management based on lifestyle strategies, as well as pharmacotherapies utilized for an LDL-C risk-based approach. For patients with severe HTG, lifestyle modifications and pharmacotherapies that specifically lower TG are recommended to reduce the risk of AP. Lifestyle modifications that may result in TG reductions include weight loss (as much as 70% reduction), dietary modifications (including alcohol restriction) (>70%), and physical activity ($\leq$30%) [33–35]. Referral to a registered dietitian is strongly recommended to personalize nutrition-based strategies for patients with HTG.

There are different management strategies for optimizing diet, but all should follow healthful approaches that are evidence-based and feasible. Counseling should begin by stressing the elimination or avoidance of caloric-sweetened beverages and ultra-processed foods, along with reviewing what constitutes a heart-healthy diet. Such a diet should be rich in vegetables, fruits, nuts, whole grains, while minimizing simple starches. There should also be a focus on small portions of lean cuts of meat, favoring seafood when possible, and the preference for polyunsaturated (PUFA) or monounsaturated fats as cooking oil in food preparation, as opposed to saturated and trans-fats. Individuals with severe HTG and hyperchylomicronemia (typically with TG levels of >1000 mg/dL), should also reduce total fat from their diet until they have TG levels of <500 mg/dL.

In line with the TG-lowering benefit of PUFA, it is recommended for all individuals to consume $\geq$2 servings of fish or seafood per week ($\geq$8 ounces), which among other benefits, will increase the intake of omega-3 PUFA and take the place of other less healthy food choices. While fatty fish are recommended for individuals with mild to moderate HTG, those with severe HTG may require leaner seafood options.

It is also important to note the effect of alcohol consumption on TG levels and related metabolic conditions. It has been shown that consuming one ounce of alcohol per day corresponds with a 5–10% higher concentration of TGs when compared with non-drinkers [36]. For individuals with pre-existing HTG, excess alcohol consumption can lead to a substantial increase in TG levels and an increased risk of AP [37]. In patients with severe HTG, it is recommended that they abstain from alcohol use entirely. In addition, a sedentary lifestyle is also associated with HTG, reduced oxidation of muscle fatty acids, and visceral adiposity [21]. Aerobic training has the capacity to decrease TG levels by ~11% and resistance training can lead to reductions of ~6%, though the effect of TG lowering depends on baseline TG levels, caloric expenditure, and intensity/duration of physical activity [38]. It is recommended for adults to engage in $\geq$150 min per week of moderate-intensity or $\geq$75 min per week of vigorous-intensity aerobic activity for ASCVD risk reduction [39]. Despite these recommendations, there is unlikely a lower limit on the amount of moderate-to-vigorous physical activity necessary before cardiovascular benefits begin to accrue, so some exercise is always better than none.

6.2. Statins

While statins are generally known for their role in decreasing LDL-C levels and reducing individuals' ASCVD risk, they also provide a 10–30% dose-dependent reduction in TGs in patients with HTG [40]. In patients with severe HTG, with TG levels as high as >800 mg/dL, the dose-dependent effect on the lowering of TG levels with statins has an efficacy of 40–44% [41]. More importantly, clinical trial evidence has shown that individuals with HTG can achieve a meaningful ASCVD risk reduction with statin therapy. The 2018 AHA/ACC/multi-society Guidelines on the Management of Blood Cholesterol consider

an elevated TG level of ≥175 mg/dL as a risk-enhancing factor and, when present, would favor statin therapy in individuals with a low or borderline 10-year ASCVD risk [1].

However, among statin-treated patients whose LDL-C levels are controlled, elevated TG levels may account for a significant proportion of their residual risk of a recurrent cardiovascular event. In a pooled analysis of 10 clinical trials (N = 5724) of statin-treated individuals with ASCVD, remnant cholesterol was significantly associated with coronary atheroma progression, which was independent of LDL-C, HDL-C, apoB, C-reactive protein, and other clinical risk factors. Higher concentrations of remnant cholesterol, the cholesterol content present in VLDL, is also associated with increased MACE risk [42]. In addition to data derived from clinical trials and meta-analyses, observational cohort studies in statin-treated individuals have also provided key insight into cardiovascular risks correlated with elevated TG levels.

A study using CANHEART (Cardiovascular Health in Ambulatory care Research Team) cohort data from nearly 2.5 million adults in the Ontario population found that nearly one in four statin-treated individuals with ASCVD had HTG and controlled LDL-C levels, and that the risk of ASCVD events increased in a stepwise manner with increasing TG levels [43]. In a post hoc analysis of the TNT (Treating to New Targets) trial, increased TRL levels were associated with a greater cardiovascular risk in patients with stable CHD who had mild to moderate HTG despite their statin therapy. However, more intensive statin therapy (atorvastatin 80 mg) led to greater cardiovascular disease risk reduction in patients with higher TRL levels, which was independent of changes in LDL-C levels [44].

Statins lower LDL-C, but also lower TRL, and higher intensity statins do so more than lower intensity statins. Although statins lower ASCVD risk in patients with HTG, elevated TG levels in statin-treated patients is a marker of residual cardiovascular risk even when the LDL-C is well controlled. Consequently, it is suggested that these individuals may be candidates for interventions such as more intensive lifestyle modifications, high-intensity statins, and high dose icosapent ethyl omega-3 fatty acids, as well as emerging therapies to further reduce their residual cardiovascular risk.

6.3. Fibrates

Fibric acid derivatives are the most potent TG-lowering pharmacotherapy along with high dose omega 3 fatty acids. They have shown a benefit for ASCVD risk reduction when used as monotherapy, but not when added to statins. Over the past 35 years, there have been a number of key fibrate trials conducted to determine their utility for cardiovascular risk reduction including HHS (Helsinki Heart Study), VA-HIT (VA HDL Intervention Trial), ACCORD (Action to Control Cardiovascular Risk in Diabetes), FIELD (Fenofibrate Intervention and Event Lowering in Diabetes), DAIS (Diabetes Atherosclerosis Intervention Study), BIP (Bezafibrate Infarction Prevention), and most recently the PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) trial (Figure 3 and Table 3). A recent systematic review and trial-level meta-regression of nine fibrate trials (N = 41,520), which did not include the results from PROMINENT, concluded that fibrates offer a clinical benefit that is proportional to the degree of non-HDL-C lowering; however, careful consideration should be given to the increased risk of myopathy when added to statin therapy and gemfibrozil should never be combined with statin because of the increased myotoxicity from this combination [45].

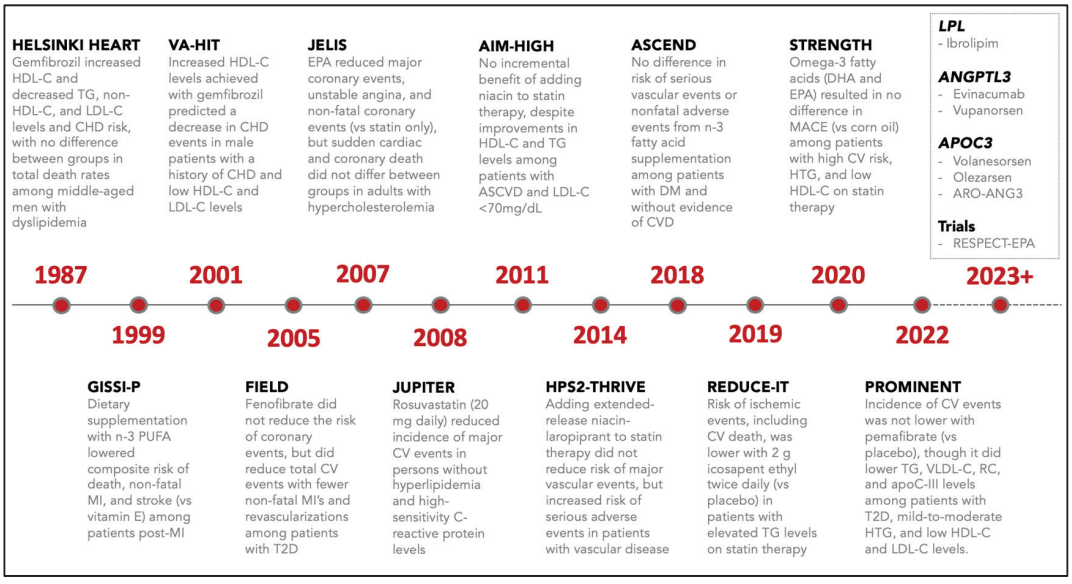

Figure 3. Brief timeline and summary of key clinical trials focused on triglyceride lowering with statins and non-statin therapies (e.g., niacin, fibrates, and omega-3 fatty acids). Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; PUFA, poly-unsaturated fatty acids; RC, remnant cholesterol; T2D, type 2 diabetes; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

Table 3. List of key clinical trials investigating non-statin therapies for cardiovascular risk reduction.

Therapeutic Medication Class	Clinical Trials
Fibrates	• HHS (1987) [46] • BIP (2000) [47] • VA-HIT (2001) [48] • DAIS (2003) [49] • FIELD (2005) [50] • ACCORD (2008) [51] • LEADER (2016) [52] • PROMINENT (2022) [53]
Omega-3 fatty acids	• GISSI-P (1999) [54] • JELIS (2007) [55] • GISSI-HF (2008) [56] • ORIGIN (2012) [57] • ASCEND (2018) [58] • REDUCE-IT (2019) [59] • VITAL (2019) [60] • STRENGTH (2020) [61] • EVAPORATE (2020) [62] • OMEMI (2021) [63]
Niacin	• AIM HIGH (2011) [64] • HPS2-Thrive (2014) [65]

Despite null findings from PROMINENT, there are several key takeaways that can inform clinical practice and future research trials. First, given that several post hoc and

secondary analyses of previous fibrate trials suggested the clinical benefits of fibrate therapy among individuals with HTG and low HDL-C levels, the subsequent findings that fibrates do not reduce ASCVD events in statin-treated patients with HTG strengthen the case for conducting rigorous studies assessing the validity of post hoc analyses before implementing them into clinical practice [66]. Second, while it confirmed that fibrates should not be used for ASCVD risk reduction in statin-treated individuals, they could still be used to reduce the risk of pancreatitis associated with severe HTG. Third, the PROMINENT trial provided further evidence that, in order for lipid-lowering therapies to show an effect, there needs to be a significant reduction in the levels of apoB-containing lipoproteins [67]. It is suspected that the apoB lowering associated with fibrate therapy is overshadowed by the effect of moderate-to-high intensity statins, thus mitigating the benefit unless used as monotherapy, or unless significant apoB lowering is achieved [68].

6.4. Omega-3 Fatty Acids

Omega-3 fatty acids including mixtures of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and purified EPA (icosapent ethyl) have been shown to decrease very high TG levels despite different effects on other physiologic parameters. There have been a number of key studies investigating the role of omega-3 fatty acids for ASCVD risk reduction, including GISSI-P (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione), JELIS (Japan EPA Lipid Intervention Study), ORIGIN (Outcome Reduction with an Initial Glargine Intervention), ASCEND (A Study of Cardiovascular Events iN Diabetes), REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial), VITAL (the Vitamin D and Omega-3 Trial), STRENGTH (A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia), and OMEMI (Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction). It is important to note that baseline TG levels were not included as part of the eligibility criteria for several of these large trials (Table 3). The recent meta-regression conducted by Marston and colleagues included 13 trials (N = 125,544) on marine-derived omega-3 fatty acids and found that each 1 g/d of EPA administered was associated with a 7% relative risk reduction in major vascular events [45].

The GISSI-P study was conducted in patients with a recent MI ($\leq$3 months) and found that low doses of EPA+DHA was beneficial; however, only a relatively small subset of participants were on statin therapy [54]. Since the GISSI-P study, several large studies including ASCEND, VITAL, and OMEMI have investigated the cardiovascular benefits of low doses of a mixture of EPA+DHA in the statin era, and all failed to show significant reductions in cardiovascular endpoints [58,60,63]. Conversely, JELIS and REDUCE-IT were conducted to examine the effects of moderate to high dose of EPA alone. JELIS was an open-label study of Japanese patients (N = 18,645) with elevated LDL-C on statin therapy, randomized to 2 g of EPA or usual care. Elevated TG levels were not an inclusion criterion in JELIS. Overall, patients randomized to EPA showed a 19% relative risk reduction in major coronary events at a mean follow-up of 4.6 years [55]; however, among participants in the EPA treatment group with HTG and low HDL-C levels, their risk of a major cardiac event fell by 53% [69].

The REDUCE-IT study sought to confirm the findings of the JELIS study and address its limitations in a double-blinded randomized placebo-controlled clinical trial with a higher dose form of purified EPA. The investigators found that icosapent ethyl significantly lowered the risk of ischemic events including cardiovascular death among statin-treated adults (N = 8179) with ASCVD or DM and other risk factors who had mild to moderate HTG and LDL-C levels of 41–100 mg/dL [59]. Analysis of REDUCE-IT found that icosapent ethyl reduced first and then total ischemic events, with well-controlled LDL-C across a range of baseline TG levels, indicating that its observed clinical benefits stem primarily from variation in baseline risk and non-TG-related effects [70].

In contrast to the findings in REDUCE-IT, the STRENGTH trial found that the addition of a carboxylic acid formulation of EPA and DHA (omega-3 CA) resulted in no significant differences in the composite MACE outcome, when compared with the corn oil placebo among statin-treated patients (N = 13,078) with high cardiovascular risk, HTG, and low HDL-C levels [61]. Potential explanations between the differential trial outcomes observed in REDUCE-IT vs. STRENGTH include the different EPA vs. EPA/DHA formulations studied, longer follow-up durations, different placebos utilized (mineral oil vs. corn oil), and different proportions of patients with established ASCVD [21]. To date, icosapent ethyl at high doses is the only omega-3 fatty acid preparation that has been shown to reduce cardiovascular events in high-risk patients with mild to moderate HTG.

7. Emerging Treatments for Hypertriglyceridemia

7.1. Apolipoprotein C-III Inhibitors

Given the substantial evidence on the association between apoC-III and ASCVD risk, it represents one of the major targets of emerging therapies for TG lowering and cardiovascular risk reduction. Several key genetic and observational studies have shown that *APOC3* loss-of-function mutations are associated with a 40% reduction in TG levels and CHD risk [71,72]. A recent meta-analysis showed that the low risk of ischemic vascular disease observed in *APOC3* loss-of-function heterozygotes is primarily driven by low remnant cholesterol, and not low LDL-C levels, strengthening the case for targeting apoC-III and remnant cholesterol to reduce cardiovascular risk [73]. Additionally, data from a contemporary prospective cohort study (EPIC-Norfolk) found that the top quintile of apoC-III levels predicted CAD risk after adjusting for traditional risk factors and lipid-lowering therapy, but lost statistical significance when adjusted for other lipoproteins. These results suggest that, rather than TG or apoC-III, apoB-containing TRL particles mediate ASCVD risk [74,75].

In 2014, results from the first study to inhibit *APOC3* mRNA (with volanesorsen [previously ISIS 304801]) in humans found that—among three patients with FCS and TG levels between 1406 and 2083 mg/dL—plasma apoC-III levels were reduced by 71% to 90% and TG levels decreased by 56% to 86% [76]. Several years later, in a phase 3, double-blinded RCT of patients with FCS (N = 66), volanesorsen lowered TG levels to <750 mg/dL in 77% of participants; however, a large proportion of patients in the volanesorsen group reported thrombocytopenia and injection-site reactions [77]. To address safety and tolerability concerns, the antisense oligonucleotide (ASO) sequence was combined with a GalNAc moiety to form AKCEA-APOCIII-LRx and inhibit apoC-III protein synthesis in the liver. In a dose-escalation phase 1/2a study in 114 healthy volunteers, AKCEA-APOCIII-LRx (olezarsen) was associated with substantial improvements in the atherogenic lipid profile with only one injection site reaction with erythema, no platelet count reductions, or liver–renal safety signals [78]. Compared to volanesorsen, olezarsen was better tolerated and also associated with favorable changes in lipoprotein concentration and particle size, results that were primarily mediated by decreased TRL levels in patients with mild to moderate HTG who were at high ASCVD risk [79]. It is of note that apoC-III treatment represents the first pharmacologic option to lower TG in FCS patients who are at very high risk for AP, for whom fibrates, omega-3 fatty acids, and statins are usually not effective in lowering TG levels.

7.2. ANGPTL3 Inhibitors

In addition to ApoC-III, emerging TG-lowering therapies are also targeting ANGPTL3, given that previous studies have shown loss-of-function variants to be associated with decreased plasma TG and LDL-C levels, as well as a reduction in CHD risk [80,81]. Several pharmacologic compounds that target ANGPTL3 have been developed including the ASO Vupanorsen (previously IONIS-ANGPTL3-LRx) and evinacumab, a monoclonal antibody (mAb) against ANGPTL3.

In terms of the former, recent data from the TRANSLATE-TIMI 70 trial (TaRgeting ANGPTL3 with an aNtiSense oLigonucleotide in AdulTs with dyslipidEmia) showed that Vupanorsen significantly reduced non-HDL-C and TG levels, with modest effects on LDL-C and apoB levels among statin-treated adults (N = 286) with non-HDL-C levels of ≥100 mg/dL and TG levels of ≥150–500 mg/dL [82]. Injection site reactions and elevations in liver enzymes were increased at higher doses of Vupanorsen.

So far, evinacumab investigation has been focused on LDL-C reduction in patients with homozygous familial hypercholesterolemia for whom the FDA has approved its use. Its potential role in the care of individuals with HTG at risk for ASCVD and/or AP is under investigation. However, it has been reported that evinacumab does not lower TG levels in individuals with FCS who lack LPL activity, but may still have an important role in managing moderate and severe HTG in non-FCS patients [83].

8. Conclusions

HTG is commonly encountered in the primary and secondary medical care of patients, especially in those with DM and other cardiometabolic conditions, and contributes to a higher risk for ASCVD and AP.

National practice guidelines recognize HTG as a risk-enhancing factor and favor an algorithmic stepwise approach to the care of at-risk patients. All individuals with HTG should be evaluated for and address secondary causes, as well as to undergo individualized lifestyle counseling. Individuals with severe HTG should receive TG-lowering pharmacotherapy, along with lifestyle modification, as primary treatment to reduce AP risk. Those at risk for ASCVD should receive statin-based care, with attention to LDL-C (as well as non-HDL-C and/or apoB), with pharmacotherapy known to reduce ASCVD risk including ezetimibe, proprotein convertase subtilisin-kexin 9 monoclonal antibodies (PCSK9 mAb), and/or a high dose icosapent ethyl esters according to the level of risk and lipid/lipoprotein response. Fibrates, over the counter and prescription mixed formulation omega-3 fatty acids, and niacin have no role in treating elevated TG to reduce ASCVD risk in statin-treated patients in contemporary care, though they may be of value in lowering TG levels in patients with severe HTG to reduce their risk of AP. Patients with HTG often have DM and pharmacologic therapies aimed at treating DM, such as glucagon-like peptide-1 receptor agonists (GLP1-RA), sodium glucose transporter-2 inhibitors (SGLT2i), and metformin, can enable weight loss, improve glycemic control, lower TG, and reduce ASCVD risk.

Novel therapeutics in development including those that target apoC-III and ANGPTL3 appear to be safe, well-tolerated, and effective for the lowering of TG. They may have differing roles in treating individuals with severe HTG and have the potential to offer additional ASCVD risk reduction for those with mild to moderate HTG as well, depending on the results from clinical trials specifically designed to explore this question.

Clinicians must be mindful of the additional burden of pharmacotherapy and the relative powerful impact of lifestyle modifications. The authors acknowledge the important role of personal responsibility for managing lifestyle factors, but stress to our patients and to the readers that we live in a toxic food environment. The current diet in the U.S. has resulted in ~70% of adults with overweight/obesity, ~50% with prediabetes/DM, and ~25% with HTG. Addressing this concern will require a sustained and concerted societal effort beyond what any individual clinician–patient interaction(s) can achieve. However, until that time, clinicians must address care for the patient with HTG with a holistic, empathetic, and individualized approach. In addition to personalized dietary/lifestyle counseling, optimally supported by a registered dietitian nutritionist, appropriate use of evidence-based pharmacotherapies is needed to reduce ASCVD risk.

Author Contributions: Conceptualization, R.M., S.B., A.S., D.S. and D.G.K.; writing–original draft preparation, R.M., S.B., A.S., D.S. and D.G.K.; writing–review and editing, R.M., S.B., A.S., D.S. and D.G.K.; visualization, R.M. and A.S.; supervision, D.S. and D.G.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: Soffer is a consultant for Akcea, Ionis, Novartis, and Regeneron, and is a clinical trial investigator for Akcea, Amgen, Amryt, Astra-Zeneca, Ionis, Novartis, Regeneron, RegenXBio, and Verve Therapeutics. Karalis has received consulting fees from Amarin, Novartis, and Esperion. He is on the speakers bureau for Amarin and Esperion, and has received research grants from Amgen, Sanofi-Regeneron, and Novartis. Other authors declare no conflicts of interest.

References

1. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **2019**, *139*, e1082–e1143. [CrossRef] [PubMed]
2. Fan, W.; Philip, S.; Granowitz, C.; Toth, P.P.; Wong, N.D. Hypertriglyceridemia in statin-treated US adults: The National Health and Nutrition Examination Survey. *J. Clin. Lipidol.* **2018**, *13*, 100–108. [CrossRef] [PubMed]
3. Carroll, M.D.; Kit, B.K.; Lacher, D.A. *Trends in Elevated Triglyceride in Adults: United States, 2001–2012*; NCHS data brief, no 198; National Center for Health Statistics: Hyattsville, MD, USA, 2015.
4. Rosinger, A.; Carroll, M.D.; Lacher, D.; Ogden, C. Trends in Total Cholesterol, Triglycerides, and Low-Density Lipoprotein in US Adults, 1999–2014. *JAMA Cardiol.* **2017**, *2*, 339–341. [CrossRef] [PubMed]
5. Ginsberg, H.N.; Packard, C.J.; Chapman, M.J.; Borén, J.; Aguilar-Salinas, C.A.; Averna, M.; Ference, B.A.; Gaudet, D.; Hegele, R.A.; Kersten, S.; et al. Triglyceride-rich lipoproteins and their remnants: Metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—A consensus statement from the European Atherosclerosis Society. *Eur. Heart J.* **2021**, *42*, 4791–4806. [CrossRef]
6. Ference, B.A.; Kastelein, J.J.P.; Catapano, A.L. Lipids and Lipoproteins in 2020. *JAMA* **2020**, *324*, 595–596. [PubMed]
7. Mszar, R.; Webb, G.B.; Kulkarni, V.T.; Ahmad, Z.; Soffer, D. Genetic Lipid Disorders Associated with Atherosclerotic Cardiovascular Disease. *Med. Clin. N. Am.* **2022**, *106*, 325–348. [CrossRef]
8. Lewis, G.F.; Xiao, C.; Hegele, R.A. Hypertriglyceridemia in the Genomic Era: A New Paradigm. *Endocr. Rev.* **2015**, *36*, 131–147. [CrossRef]
9. Glavinovic, T.; Thanassoulis, G.; de Graaf, J.; Couture, P.; Hegele, R.A.; Sniderman, A.D. Physiological Bases for the Superiority of Apolipoprotein B Over Low-Density Lipoprotein Cholesterol and Non–High-Density Lipoprotein Cholesterol as a Marker of Cardiovascular Risk. *J. Am. Heart Assoc.* **2022**, *11*, e025858. [CrossRef]
10. Sniderman, A.D.; Thanassoulis, G.; Glavinovic, T.; Navar, A.M.; Pencina, M.; Catapano, A.; Ference, B.A. Apolipoprotein B Particles and Cardiovascular Disease: A Narrative Review. *JAMA Cardiol.* **2019**, *4*, 1287–1295. [CrossRef]
11. Varbo, A.; Benn, M.; Tybjærg-Hansen, A.; Jørgensen, A.B.; Frikke-Schmidt, R.; Nordestgaard, B.G. Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease. *J. Am. Coll. Cardiol.* **2012**, *61*, 427–436. [CrossRef]
12. Nichols, G.A.; Philip, R.S.; Reynolds, K.; Granowitz, C.B.; Fazio, S. Increased Cardiovascular Risk in Hypertriglyceridemic Patients With Statin-Controlled LDL Cholesterol. *J. Clin. Endocrinol. Metab.* **2018**, *103*, 3019–3027. [CrossRef] [PubMed]
13. Rosenson, R.S.; Davidson, M.H.; Hirsh, B.J.; Kathiresan, S.; Gaudet, D. Genetics and Causality of Triglyceride-Rich Lipoproteins in Atherosclerotic Cardiovascular Disease. *J. Am. Coll. Cardiol.* **2014**, *64*, 2525–2540. [CrossRef] [PubMed]
14. Ambrosy, A.P.; Yang, J.; Sung, S.H.; Allen, A.R.; Fitzpatrick, J.K.; Rana, J.S.; Wagner, J.; Philip, S.; Abrahamson, D.; Granowitz, C.; et al. Triglyceride Levels and Residual Risk of Atherosclerotic Cardiovascular Disease Events and Death in Adults Receiving Statin Therapy for Primary or Secondary Prevention: Insights From the KP REACH Study. *J. Am. Heart Assoc.* **2021**, *10*, e020377. [CrossRef]
15. Triglyceride Coronary Disease Genetics Consortium Emerging Risk Factors Collaboration; Sarwar, N.; Sandhu, M.S.; Ricketts, S.L.; Butterworth, A.S.; Di Angelantonio, E.; Boekholdt, S.M.; Ouwehand, W.; Watkins, H.; Samani, N.J.; et al. Triglyceride-mediated pathways and coronary disease: Collaborative analysis of 101 studies. *Lancet* **2010**, *375*, 1634–1639. [PubMed]
16. Holmes, M.V.; Asselbergs, F.W.; Palmer, T.M.; Drenos, F.; Lanktree, M.B.; Nelson, C.P.; Dale, C.E.; Padmanabhan, S.; Finan, C.; Swerdlow, D.I.; et al. Mendelian randomization of blood lipids for coronary heart disease. *Eur. Heart J.* **2015**, *36*, 539–550. [CrossRef] [PubMed]
17. Allara, E.; Morani, G.; Carter, P.; Gkatzionis, A.; Zuber, V.; Foley, C.N.; Rees, J.M.; Mason, A.M.; Bell, S.; Gill, D.; et al. Genetic Determinants of Lipids and Cardiovascular Disease Outcomes. *Circ. Genom. Precis. Med.* **2019**, *12*, e002711. [CrossRef]

18. Johannesen, C.D.L.; Mortensen, M.B.; Langsted, A.; Nordestgaard, B.G. Apolipoprotein B and Non-HDL Cholesterol Better Reflect Residual Risk Than LDL Cholesterol in Statin-Treated Patients. *J. Am. Coll. Cardiol.* **2021**, *77*, 1439–1450.
19. Sampson, M.; Ling, C.; Sun, Q.; Harb, R.; Ashmaig, M.; Warnick, R.; Sethi, A.; Fleming, J.K.; Otvos, J.D.; Meeusen, J.W.; et al. A New Equation for Calculation of Low-Density Lipoprotein Cholesterol in Patients With Normolipidemia and/or Hypertriglyceridemia. *JAMA Cardiol.* **2020**, *5*, 540. [CrossRef]
20. Martin, S.S.; Giugliano, R.; Murphy, S.A.; Wasserman, S.M.; Stein, E.A.; Ceška, R.; Lopez-Miranda, J.; Georgiev, B.; Lorenzatti, A.J.; Tikkanen, M.J.; et al. Comparison of Low-Density Lipoprotein Cholesterol Assessment by Martin/Hopkins Estimation, Friedewald Estimation, and Preparative Ultracentrifugation. *JAMA Cardiol.* **2018**, *3*, 749–753. [CrossRef]
21. Virani, S.S.; Morris, P.B.; Agarwala, A.; Ballantyne, C.M.; Birtcher, K.K.; Kris-Etherton, P.M.; Ladden-Stirling, A.B.; Miller, M.; Orringer, C.E.; Stone, N.J. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia. *J. Am. Coll. Cardiol.* **2021**, *78*, 960–993. [CrossRef]
22. Skulas-Ray, A.C.; Wilson, P.W.F.; Harris, W.S.; Brinton, E.A.; Kris-Etherton, P.M.; Richter, C.K.; Jacobson, T.A.; Engler, M.B.; Miller, M.; Robinson, J.G.; et al. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. *Circulation* **2019**, *140*, e673–e691. [PubMed]
23. Mosztbacher, D.; Hanák, L.; Farkas, N.; Szentesi, A.; Mikó, A.; Bajor, J.; Sarlós, P.; Czimmer, J.; Vincze, Á.; Hegyi, P.J.; et al. Hypertriglyceridemia-induced acute pancreatitis: A prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases. *Pancreatology* **2020**, *20*, 608–616. [CrossRef] [PubMed]
24. Roberts, S.E.; Akbari, A.; Thorne, K.; Atkinson, M.; Evans, P.A. The incidence of acute pancreatitis: Impact of social deprivation, alcohol consumption, seasonal and demographic factors. *Aliment. Pharmacol. Ther.* **2013**, *38*, 539–548. [CrossRef]
25. Scherer, J.; Singh, V.P.; Pitchumoni, C.S.; Yadav, D. Issues in hypertriglyceridemic pancreatitis: An update. *J. Clin. Gastroenterol.* **2014**, *48*, 195–203. [CrossRef] [PubMed]
26. Kiss, L.; Fűr, G.; Mátrai, P.; Hegyi, P.; Iványi, E.; Cazacu, I.M.; Szabó, I.; Habon, T.; Alizadeh, H.; Gyöngyi, Z.; et al. The effect of serum triglyceride concentration on the outcome of acute pancreatitis: Systematic review and meta-analysis. *Sci. Rep.* **2018**, *8*, 14096. [CrossRef]
27. Carrasquilla, G.D.; Christiansen, M.R.; Kilpeläinen, T.O. The Genetic Basis of Hypertriglyceridemia. *Curr. Atheroscler. Rep.* **2021**, *23*, 39. [CrossRef]
28. Chyzhyk, V.; Kozmic, S.; Brown, A.S.; Hudgins, L.C.; Starc, T.J.; Davila, A.D.; Blevins, T.C.; Diffenderfer, M.R.; He, L.; Geller, A.S.; et al. Extreme hypertriglyceridemia: Genetic diversity, pancreatitis, pregnancy, and prevalence. *J. Clin. Lipidol.* **2018**, *13*, 89–99. [CrossRef]
29. Laufs, U.; Parhofer, K.G.; Ginsberg, H.N.; Hegele, R.A. Clinical review on triglycerides. *Eur. Heart J.* **2019**, *41*, 99–109c. [CrossRef]
30. Simha, V. Management of hypertriglyceridemia. *BMJ* **2020**, *371*, m3109. [CrossRef]
31. Nawawi, H.; Chua, Y.-A.; Watts, G.F. The brave new world of genetic testing in the management of the dyslipidaemias. *Curr. Opin. Cardiol.* **2020**, *35*, 226–233. [CrossRef]
32. Brown, E.E.; Sturm, A.C.; Cuchel, M.; Braun, L.T.; Duell, P.B.; Underberg, J.; Jacobson, T.A.; Hegele, R.A. Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. *J. Clin. Lipidol.* **2020**, *14*, 398–413. [CrossRef] [PubMed]
33. Johnston, S.C.; Fung, L.H.; Gillum, L.A.; Smith, W.S.; Brass, L.M.; Lichtman, J.H.; Brown, A.N. Utilization of intravenous tissue-type plasminogen activator for ischemic stroke at academic medical centers: The influence of ethnicity. *Stroke* **2001**, *32*, 1061–1068. [CrossRef] [PubMed]
34. Rhodes, K.S.; Weintraub, M.; Marchlewicz, E.H.; Rubenfire, M.; Brook, R.D. Medical nutrition therapy is the essential cornerstone for effective treatment of "refractory" severe hypertriglyceridemia regardless of pharmaceutical treatment: Evidence from a Lipid Management Program. *J. Clin. Lipidol.* **2015**, *9*, 559–567. [CrossRef] [PubMed]
35. Gordon, B.; Chen, S.; Durstine, J.L. The Effects of Exercise Training on the Traditional Lipid Profile and Beyond. *Curr. Sports Med. Rep.* **2014**, *13*, 253–259. [CrossRef] [PubMed]
36. Foerster, M.; Marques-Vidal, P.; Gmel, G.; Daeppen, J.-B.; Cornuz, J.; Hayoz, D.; Pécoud, A.; Mooser, V.; Waeber, G.; Vollenweider, P.; et al. Alcohol Drinking and Cardiovascular Risk in a Population With High Mean Alcohol Consumption. *Am. J. Cardiol.* **2009**, *103*, 361–368. [CrossRef]
37. Ewald, N.; Hardt, P.D.; Kloer, H.U. Severe hypertriglyceridemia and pancreatitis: Presentation and management. *Curr. Opin. Lipidol.* **2009**, *20*, 497–504.
38. Kraus, W.E.; Houmard, J.A.; Duscha, B.D.; Knetzger, K.J.; Wharton, M.B.; McCartney, J.S.; Bales, C.W.; Henes, S.; Samsa, G.P.; Otvos, J.D.; et al. Effects of the Amount and Intensity of Exercise on Plasma Lipoproteins. *N. Engl. J. Med.* **2002**, *347*, 1483–1492. [CrossRef]
39. Arnett, D.K.; Blumenthal, R.S.; Albert, M.A.; Buroker, A.B.; Goldberger, Z.D.; Hahn, E.J.; Himmelfarb, C.D.; Khera, A.; Lloyd-Jones, D.; McEvoy, J.W.; et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2019**, *74*, 1376–1414.
40. Miller, M.; Stone, N.J.; Ballantyne, C.; Bittner, V.; Criqui, M.H.; Ginsberg, H.N.; Goldberg, A.C.; Howard, W.J.; Jacobson, M.S.; Kris-Etherton, P.M.; et al. Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association. *Circulation* **2011**, *123*, 2292–2333.

41. Rosenson, R.S.; Shaik, A.; Song, W. New Therapies for Lowering Triglyceride-Rich Lipoproteins: JACC Focus Seminar 3/4. *J. Am. Coll. Cardiol.* **2021**, *78*, 1817–1830. [CrossRef]
42. Elshazly, M.B.; Mani, P.; Nissen, S.; Brennan, D.M.; Clark, D.; Martin, S.; Jones, S.R.; Quispe, R.; Donnellan, E.; Nicholls, S.J.; et al. Remnant cholesterol, coronary atheroma progression and clinical events in statin-treated patients with coronary artery disease. *Eur. J. Prev. Cardiol.* **2020**, *27*, 1091–1100. [PubMed]
43. Lawler, P.R.; Kotrri, G.; Koh, M.; Goodman, S.G.; Farkouh, M.E.; Lee, D.S.; Austin, P.C.; Udell, J.A.; Ko, D.T. Real-world risk of cardiovascular outcomes associated with hypertriglyceridaemia among individuals with atherosclerotic cardiovascular disease and potential eligibility for emerging therapies. *Eur. Heart J.* **2019**, *41*, 86–94. [CrossRef] [PubMed]
44. Vallejo-Vaz, A.J.; Fayyad, R.; Boekholdt, M.; Hovingh, G.K.; Kastelein, J.J.; Melamed, S.; Barter, P.; Waters, D.D.; Ray, K.K. Triglyceride-Rich Lipoprotein Cholesterol and Risk of Cardiovascular Events Among Patients Receiving Statin Therapy in the TNT Trial. *Circulation* **2018**, *138*, 770–781. [CrossRef] [PubMed]
45. Marston, N.A.; Giugliano, R.P.; Im, K.; Silverman, M.G.; O'Donoghue, M.L.; Wiviott, S.D.; Ference, B.A.; Sabatine, M.S. Association Between Triglyceride Lowering and Reduction of Cardiovascular Risk Across Multiple Lipid-Lowering Therapeutic Classes: A Systematic Review and Meta-Regression Analysis of Randomized Controlled Trials. *Circulation* **2019**, *140*, 1308–1317. [CrossRef] [PubMed]
46. Frick, M.H.; Elo, O.; Haapa, K.; Heinonen, O.P.; Heinsalmi, P.; Helo, P.; Huttunen, J.K.; Kaitaniemi, P.; Koskinen, P.; Manninen, V.; et al. Helsinki Heart Study: Primary-Prevention Trial with Gemfibrozil in Middle-Aged Men with Dyslipidemia. *N. Engl. J. Med.* **1987**, *317*, 1237–1245. [CrossRef]
47. Bezafibrate Infarction Prevention (BIP) study. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. *Circulation* **2000**, *102*, 21–27.
48. Robins, S.J.; Collins, D.; Wittes, J.T.; Papademetriou, V.; Deedwania, P.C.; Schaefer, E.J.; McNamara, J.R.; Kashyap, M.L.; Hershman, J.M.; Wexler, L.F.; et al. Veterans Affairs High-Density Lipoprotein Intervention Trial. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: A randomized controlled trial. *JAMA* **2001**, *285*, 1585–1591.
49. Vakkilainen, J.; Steiner, G.; Ansquer, J.C.; Aubin, F.; Rattier, S.; Foucher, C.; Hamsten, A.; Taskinen, M.R.; DAIS Group. Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: The Diabetes Atherosclerosis Intervention Study (DAIS). *Circulation* **2003**, *107*, 1733–1737.
50. Keech, A.; Simes, R.J.; Barter, P.; Best, J.; Scott, R.; Taskinen, M.R.; Forder, P.; Pillai, A.; Davis, T.; Glasziou, P.; et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. *Lancet* **2005**, *366*, 1849–1861.
51. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein, H.C.; Miller, M.E.; Byington, R.P.; Goff, D.C., Jr.; Bigger, J.T.; Buse, J.B.; Cushman, W.C.; Genuth, S.; Ismail-Beigi, F.; et al. Effects of intensive glucose lowering in type 2 diabetes. *N. Engl. J. Med.* **2008**, *358*, 2545–2559.
52. Marso, S.P.; Daniels, G.H.; Brown-Frandsen, K.; Kristensen, P.; Mann, J.F.E.; Nauck, M.A.; Nissen, S.E.; Pocock, S.; Poulter, N.R.; Ravn, L.S.; et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N. Engl. J. Med.* **2016**, *375*, 311–322. [CrossRef] [PubMed]
53. Das Pradhan, A.; Glynn, R.J.; Fruchart, J.C.; MacFadyen, J.G.; Zaharris, E.S.; Everett, B.M.; Campbell, S.E.; Oshima, R.; Amarenco, P.; Blom, D.J.; et al. Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. *N. Engl. J. Med.* **2022**, *387*, 1923–1934. [CrossRef] [PubMed]
54. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* **1999**, *354*, 447–455.
55. Yokoyama, M.; Origasa, H.; Matsuzaki, M.; Matsuzawa, Y.; Saito, Y.; Ishikawa, Y.; Oikawa, S.; Sasaki, J.; Hishida, H.; Itakura, H.; et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis. *Lancet* **2007**, *369*, 1090–1098. [CrossRef]
56. Tavazzi, L.; Maggioni, A.P.; Marchioli, R.; Barlera, S.; Franzosi, M.G.; Latini, R.; Lucci, D.; Nicolosi, G.L.; Porcu, M.; Tognoni, G.; et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): A randomised, double-blind, placebo-controlled trial. *Lancet* **2008**, *372*, 1223–1230.
57. ORIGIN Trial Investigators; Bosch, J.; Gerstein, H.C.; Dagenais, G.R.; Díaz, R.; Dyal, L.; Jung, H.; Maggiono, A.P.; Probstfield, J.; Ramachandran, A.; et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N. Engl. J. Med.* **2012**, *367*, 309–318. [PubMed]
58. ASCEND Study Collaborative Group; Bowman, L.; Mafham, M.; Wallendszus, K.; Stevens, W.; Buck, G.; Barton, J.; Murphy, K.; Aung, T.; Haynes, R.; et al. Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus. *N. Engl. J. Med.* **2018**, *379*, 1540–1550.
59. Bhatt, D.L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Ketchum, S.B.; Doyle, R.T., Jr.; Juliano, R.A.; Jiao, L.; Granowitz, C.; et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N. Engl. J. Med.* **2019**, *380*, 11–22. [CrossRef]
60. Manson, J.E.; Cook, N.R.; Lee, I.-M.; Christen, W.; Bassuk, S.S.; Mora, S.; Gibson, H.; Albert, C.M.; Gordon, D.; Copeland, T.; et al. Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N. Engl. J. Med.* **2019**, *380*, 23–32. [CrossRef]
61. Nicholls, S.J.; Lincoff, A.M.; Garcia, M.; Bash, D.; Ballantyne, C.M.; Barter, P.J.; Davidson, M.H.; Kastelein, J.J.P.; Koenig, W.; McGuire, D.K.; et al. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. *JAMA* **2020**, *324*, 2268–2280.

62. Budoff, M.J.; Bhatt, D.L.; Kinninger, A.; Lakshmanan, S.; Muhlestein, J.B.; Le, V.T.; May, H.T.; Shaikh, K.; Shekar, C.; Roy, S.K.; et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: Final results of the EVAPORATE trial. *Eur. Heart. J.* **2020**, *41*, 3925–3932. [CrossRef] [PubMed]
63. Kalstad, A.A.; Myhre, P.L.; Laake, K.; Tveit, S.H.; Schmidt, E.B.; Smith, P.; Nilsen, D.W.T.; Tveit, A.; Fagerland, M.W.; Solheim, S.; et al. Effects of n-3 Fatty Acid Supplements in Elderly Patients After Myocardial Infarction: A Randomized, Controlled Trial. *Circulation* **2021**, *143*, 528–539. [CrossRef] [PubMed]
64. AIM-HIGH Investigators; Boden, W.E.; Probstfield, J.L.; Anderson, T.; Chaitman, B.R.; Desvignes-Nickens, P.; Koprowicz, K.; McBride, R.; Teo, K.; Weintraub, W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N. Engl. J. Med.* **2011**, *365*, 2255–2267. [PubMed]
65. HPS2-THRIVE Collaborative Group; Landray, M.J.; Haynes, R.; Hopewell, J.C.; Parish, S.; Aung, T.; Tomson, J.; Wallendszus, K.; Craig, M.; Jiang, L.; et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N. Engl. J. Med.* **2014**, *371*, 203–212.
66. Virani, S.S. The Fibrates Story—A Tepid End to a PROMINENT Drug. *N. Engl. J. Med.* **2022**, *387*, 1991–1992. [CrossRef]
67. Ference, B.; Kastelein, J.J.; Ray, K.K.; Ginsberg, H.N.; Chapman, M.J.; Packard, C.J.; Laufs, U.; Oliver-Williams, C.; Wood, A.; Butterworth, A.; et al. Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease. *JAMA* **2019**, *321*, 364–373. [CrossRef]
68. Ishibashi, S.; Arai, H.; Yokote, K.; Araki, E.; Suganami, H.; Yamashita, S.; K-877 Study Group. Efficacy and safety of pemafibrate (K-877), a selective peroxisome proliferator-activated receptor α modulator, in patients with dyslipidemia: Results from a 24-week, randomized, double blind, active-controlled, phase 3 trial. *J. Clin. Lipidol.* **2018**, *12*, 173–184. [CrossRef]
69. Saito, Y.; Yokoyama, M.; Origasa, H.; Matsuzaki, M.; Matsuzawa, Y.; Ishikawa, Y.; Oikawa, S.; Sasaki, J.; Hishida, H.; Itakura, H.; et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* **2008**, *200*, 135–140. [CrossRef]
70. Bhatt, D.L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Jiao, L.; Tardif, J.-C.; Gregson, J.; Pocock, S.J.; Ballantyne, C.M. Reduction in First and Total Ischemic Events With Icosapent Ethyl Across Baseline Triglyceride Tertiles. *J. Am. Coll. Cardiol.* **2019**, *74*, 1159–1161. [CrossRef]
71. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute; Crosby, J.; Peloso, G.M.; Auer, P.L.; Crosslin, D.R.; Stitziel, N.O.; Lange, L.A.; Lu, Y.; Tang, Z.Z.; Zhang, H.; et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N. Engl. J. Med.* **2014**, *371*, 22–31.
72. Jørgensen, A.B.; Frikke-Schmidt, R.; Nordestgaard, B.G.; Tybjærg-Hansen, A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N. Engl. J. Med.* **2014**, *371*, 32–41. [PubMed]
73. Wulff, A.B.; Nordestgaard, B.G.; Tybjærg-Hansen, A. APOC3 Loss-of-Function Mutations, Remnant Cholesterol, Low-Density Lipoprotein Cholesterol, and Cardiovascular Risk: Mediation- and Meta-Analyses of 137 895 Individuals. *Arterioscler. Thromb. Vasc. Biol.* **2018**, *38*, 660–668. [PubMed]
74. van Capelleveen, J.C.; Lee, S.R.; Verbeek, R.; Kastelein, J.J.P.; Wareham, N.J.; Stroes, E.S.G.; Hovingh, G.K.; Khaw, K.T.; Boekholdt, S.M.; Witztum, J.L.; et al. Relationship of lipoprotein-associated apolipoprotein C-III with lipid variables and coronary artery disease risk: The EPIC-Norfolk prospective population study. *J. Clin. Lipidol.* **2018**, *12*, 1493–1501.e11.
75. Reeskamp, L.F.; Tromp, T.R.; Stroes, E.S.G. The next generation of triglyceride-lowering drugs: Will reducing apolipoprotein C-III or angiopoietin like protein 3 reduce cardiovascular disease? *Curr. Opin. Lipidol.* **2020**, *31*, 140–146. [CrossRef] [PubMed]
76. Gaudet, D.; Brisson, D.; Tremblay, K.; Alexander, V.J.; Singleton, W.; Hughes, S.G.; Geary, R.S.; Baker, B.F.; Graham, M.J.; Crooke, R.M.; et al. Targeting APOC3 in the Familial Chylomicronemia Syndrome. *N. Engl. J. Med.* **2014**, *371*, 2200–2206. [CrossRef] [PubMed]
77. Witztum, J.L.; Gaudet, D.; Freedman, S.D.; Alexander, V.J.; Digenio, A.; Williams, K.R.; Yang, Q.; Hughes, S.G.; Geary, R.S.; Arca, M.; et al. Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome. *N. Engl. J. Med.* **2019**, *381*, 531–542. [CrossRef]
78. Alexander, V.J.; Xia, S.; Hurh, E.; Hughes, S.G.; O'Dea, L.; Geary, R.S.; Witztum, J.L.; Tsimikas, S. N-acetyl galactosamine-conjugated antisense drug to APOC3 mRNA, triglycerides and atherogenic lipoprotein levels. *Eur. Heart J.* **2019**, *40*, 2785–2796.
79. Karwatowska-Prokopczuk, E.; Tardif, J.-C.; Gaudet, D.; Ballantyne, C.M.; Shapiro, M.D.; Moriarty, P.M.; Baum, S.J.; Amour, E.S.; Alexander, V.J.; Xia, S.; et al. Effect of olezarsen targeting APOC-III on lipoprotein size and particle number measured by NMR in patients with hypertriglyceridemia. *J. Clin. Lipidol.* **2022**, *16*, 617–625. [CrossRef]
80. Dewey, F.E.; Gusarova, V.; Dunbar, R.L.; O'Dushlaine, C.; Schurmann, C.; Gottesman, O.; McCarthy, S.; Van Hout, C.V.; Bruse, S.; Dansky, H.M.; et al. Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease. *N. Engl. J. Med.* **2017**, *377*, 211–221. [CrossRef]
81. Stitziel, N.O.; Khera, A.V.; Wang, X.; Bierhals, A.J.; Vourakis, A.C.; Sperry, A.E.; Natarajan, P.; Klarin, D.; Emdin, C.A.; Zekavat, S.M.; et al. ANGPTL3 Deficiency and Protection Against Coronary Artery Disease. *J. Am. Coll. Cardiol.* **2017**, *69*, 2054–2063. [CrossRef]

82. Bergmark, B.A.; Marston, N.A.; Bramson, C.R.; Curto, M.; Ramos, V.; Jevne, A.; Kuder, J.F.; Park, J.-G.; Murphy, S.A.; Verma, S.; et al. Effect of Vupanorsen on Non–High-Density Lipoprotein Cholesterol Levels in Statin-Treated Patients With Elevated Cholesterol: TRANSLATE-TIMI 70. *Circulation* **2022**, *145*, 1377–1386. [CrossRef] [PubMed]
83. Rosenson, R.; Gaudet, D.; Ballantyne, C.; Baum, S.; Bergeron, J.; Kershaw, E.; Moriarty, P.; Rubba, P.; Banerjee, P.; Ponda, M.; et al. A phase 2 trial of the efficacy and safety of evinacumab in patients with severe hypertriglyceridemia. *Atherosclerosis* **2021**, *331*, e293. [CrossRef]

Journal of
Clinical Medicine

MDPI

Review

Evinacumab, an ANGPTL3 Inhibitor, in the Treatment of Dyslipidemia

Bożena Sosnowska [1,†], Weronika Adach [1,†], Stanisław Surma [2], Robert S. Rosenson [3] and Maciej Banach [1,4,5,*]

[1] Department of Preventive Cardiology and Lipidology, Medical University of Lodz, 93-338 Lodz, Poland
[2] Faculty of Medical Sciences in Katowice, Medical University of Silesia, 40-752 Katowice, Poland
[3] Metabolism and Lipids Unit, Mount Sinai Hospital and Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
[4] Cardiovascular Research Centre, University of Zielona Gora, 65-417 Zielona Gora, Poland
[5] Department of Cardiology and Adult Congenital Heart Diseases, Polish Mother's Memorial Hospital Research Institute (PMMHRI), 93-338 Lodz, Poland
* Correspondence: maciej.banach@icloud.com
† These authors contributed equally to this work.

Abstract: Familial hypercholesterolemia (FH) is an inherited disorder. The level of low-density lipoprotein cholesterol (LDL-C) in patients with homozygous FH can be twice as high as that in patients with heterozygous FH. The inhibition of ANGPTL3 shows an important therapeutic approach in reducing LDL-C and triglycerides (TG) levels and, thus, is a potentially effective strategy in the treatment of FH. Evinacumab is a monoclonal antibody inhibiting circulating ANGPTL3, available under the trade name Evkeeza® for the treatment of homozygous FH. It was reported that evinacumab is effective and safe in patients with homozygous and heterozygous FH, as well as resistant hypercholesterolemia and hypertriglyceridemia. This paper summarizes existing knowledge on the role of ANGPTL3, 4, and 8 proteins in lipoprotein metabolism, the findings from clinical trials with evinacumab, a fully human ANGPTL3 mAb, and the place for this new agent in lipid-lowering therapy.

Keywords: ANGPTL3 inhibitors; evinacumab; familial hypercholesterolemia; LDL cholesterol

Citation: Sosnowska, B.; Adach, W.; Surma, S.; Rosenson, R.S.; Banach, M. Evinacumab, an ANGPTL3 Inhibitor, in the Treatment of Dyslipidemia. *J. Clin. Med.* **2023**, *12*, 168. https://doi.org/10.3390/jcm12010168

Academic Editor: Nathan Wong

Received: 28 November 2022
Revised: 19 December 2022
Accepted: 21 December 2022
Published: 25 December 2022

1. Homozygous Familial Hypercholesterolemia

Homozygous familial hypercholesterolemia (HoFH) affects an average of 1 in 300,000 subjects. It is a very rare genetic disorder of lipoprotein metabolism. It is caused by mutations in both alleles of the LDL receptor (LDLR) gene and less often by mutations in APOB, the ligand for LDLR and proprotein convertase subtilisin kexin type 9 (PCSK9), a protein that degrades LDLR [1]. Higher levels of low-density lipoprotein cholesterol (LDL-C) are characterized by genetic changes that show no expression of the LDL receptor (null homozygotes), compared to changes with two non-zero alleles or one zero and one non-null homozygotes, which only partially reduce the LDL receptor activity [2,3]. These mutations impair the function of the liver to remove LDL-C from the bloodstream, resulting in high total cholesterol and LDL-C [4]. In comparison, LDL particles that bind PCSK9 are targeted for lysosomal degradation and destruction. Loss-of-function mutations of the PCSK9 gene decrease the level of LDL-C and lower the risk of myocardial infarctions in white and black persons and reduce the risk of stroke in black persons. It can be concluded that PCSK9 inhibitors prevent an atherosclerotic cardiovascular event [1].

Patients with HoFH have very high levels of LDL-C from birth, which result in high risks of premature atherosclerosis and other cardiovascular diseases. Clinically, HoFH is characterized by an LDL-C level > 500 mg/dL (>13 mmol/L). Statins and lipid-lowering drugs are largely dependent on the activity of the LDL receptor; therefore, in patients

with two null alleles, they may show diminished efficacy. Therefore, most patients with HoFH do not achieve guideline-recommended levels of LDL-C despite treatment with multiple agents [3]. Unfortunately, mutations in patients with familial hypercholesterolemia are associated with an increased probability (up to 3.8 times) of myocardial infarctions under the age of 55 years [5]. Early diagnosis of FH and follow-up, with comprehensive longitudinal care and particular emphasis on aortic valve obstruction and stenosis, are of key importance in the prevention of premature atherosclerotic cardiovascular disease (ASCVD) [2].

According to the 2019 guidelines of the European Society of Cardiology (ESC) and the European Society of Atherosclerosis (EAS), LDL-C levels should be below 1.42 mmol/L (55 mg/dL) in patients at very high risk of ASCVD, below 1.81 mmol/L (70 mg/dL) in patients at high risk, and below 2.59 mmol/L (100 mg/dL) in moderate-risk patients [5].

2. ANGPTL3, 4, and 8 Protein System-Characteristics and Role in Lipid Metabolism

The angiopoietin-like proteins (ANGPTLs) are a family of proteins consisting of members 1–8 of the angiopoietins, which differ in terms of tissue expression and regulation. They each consist of a common domain at the amino terminus (N-terminal), a coiled-coil domain (CCD), a fibrinogen-like domain (FLD) at the C-terminus of the carboxyl, and a linker region. Angiopoietin-8 differs from the other ANGPTLs in that it does not contain a fibrinogen-like domain at the C-terminus [6]. ANGPTL proteins belong to the vascular endothelial growth factor (VEGF) family and play various roles in biological and pathological processes, including hormone regulation, glucose metabolism, and insulin resistance [7].

ANGPTL3, ANGPTL4, and ANGPTL8 are most important in lipoprotein metabolism because they are responsible for the metabolism of triglycerides (TGs)—rich lipoproteins (chylomicrons, VLDL)—by inhibiting the activities of lipoprotein lipase (LPL), VLDL, and LDL mediated by the inhibition of endothelial lipase (EL) [6,8]. LPL activity is reduced by changing the conformation from homodimeric, which is biologically active, to biologically inactive, or monomeric. LPL is an enzyme produced in fat and muscle cells that limits the rate of hydrolysis of TG-rich lipoproteins to free fatty acids (FFA). When this process is disturbed, severe hypertriglyceridemia occurs in plasma [9]. The best-known ANGPTL is ANGPTL3, which was discovered in 1999. ANGPTL3 is produced in the liver. In the following year, 2000, ANGPTL4 was discovered, and it is produced in the liver, skeletal muscle, adipose tissue, gut, brain, and heart. Additionally, ANGPTL8 was discovered in 2012, and its main source is adipose tissue and the liver [10].

ANGPTL3, 4, and 8 control the availability of triglyceride-rich lipoproteins, LDL, and high-density lipoprotein cholesterol (HDL-C), depending on the nutritional status of the body, temperature, and physical activity, by regulating LPL secretion. LPL activity is increased after a meal, and triglycerides are stored in the white adipose tissue of WAT. In contrast, after a meal, LPL activity is reduced in the heart, brown adipose tissue, and skeletal muscle by ANGPTL3 and 8 (ANGPTL8 expression is especially increased). The opposite occurs during fasting, where LPL activity increases in the heart, brown adipose tissue, and skeletal muscle. In white adipose tissue, the activity of LPL during fasting is reduced by ANGPTL4 [11–15] (Figure 1).

ANGPTL3, apart from its effect on LPL, also reduces the activity of EL, which leads to a slowdown in the metabolism of triglyceride-rich lipoproteins [16].

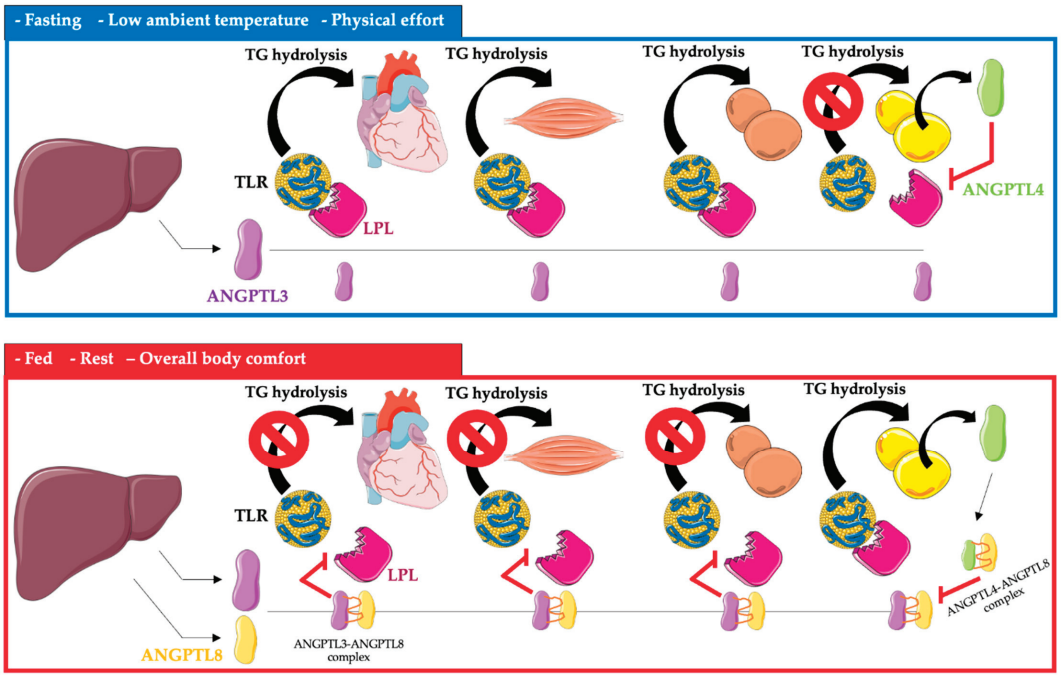

Figure 1. Regulation of triglyceride metabolism in heart, muscle, brown adipose tissue, and white adipose tissue by ANGPTL3, ANGPTL4, and ANGPTL8. Abbreviations: TG—triglyceride; TLR—triglyceride-rich lipoprotein; LPL—lipoprotein lipase; ANGPTL3—angiopoietin-like protein 3; ANGPTL4—angiopoietin-like protein 4; ANGPTL8—angiopoietin-like protein 8. The following was used in the preparation of the figure: https://smart.servier.com (free-access; 20 October 2022).

3. ANGPTL3, 4, and 8 as Biomarkers of Cardiovascular Risk

Several publications have reported that ANGPTL3 deficiency protects against coronary artery disease (CAD). According to the research of Stitziel et al., in subjects with complete ANGPTL3 deficiency, the coronary arteries lacked atherosclerotic plaque [12]. Moreover, healthy patients showed lower concentrations of ANGPTL3 compared to patients who experienced myocardial infarctions (MIs) [12]. In patients with ANGPTL33 concentrations of 18–271 ng/mL, the risk of a heart attack was reduced by up to 29%. Researchers also demonstrated an association of the loss-of-function (LOF) mutation in *ANGPTL3* with the risk of CAD. The levels of low-density lipoprotein LDL-C, high-density HDL-C, and TGs are dependent on the LOF in *ANGPTL3*. Patients carrying the LOF mutation showed a 34% reduction in the risk of CAD compared to patients who did not carry the LOF mutation. In addition, patients with the LOF mutation showed 11% lower total cholesterol, 12% lower LDL, and 17% lower TG levels compared to those without the mutation. In addition to the fact that the loss of ANGPTL3 increases LPL activity, leading to a reduction in TGs and LDL-rich lipoproteins, it may affect insulin sensitivity and play an important role in glucose hemostasis [12].

In another study on the effects of ANGPTL3 and 4 on CAD, the team of Sun et al. presented the results of a study involving 305 patients. A high level of ANGPTL3 was closely related to the severity of atherosclerotic lesions in the coronary vessels, while the level of ANGPTL4 was reduced. The levels of these glycoproteins may have significant impacts on the development of CAD [17]. Another study showed the relationship between mutations inactivating the ANGPTL4 gene on the risk of ischemic heart disease. This study included over 42,000 subjects. Dewey et al. in 2017 proved that the reductions in the levels

of TGs, total cholesterol, and LDL-C were caused by the inactivation of ANGPTL4 through the heterozygous mutation E40k. Patients with this ANGPTL4 mutation showed a 19% lower risk of coronary heart disease [18]. In a similar study led by Stitziel et al., patients with the E40K ANGPTL4 mutation showed about 35% lower TG concentration. Additionally, the risk of coronary heart disease was 53% lower. However, no significant effect of ANGPTL4 p.E40K on LDL-C was observed [19]. The research team of Gusarova et al. showed the effect of the E40K ANGPTL4 mutation on the reduction of the risk of type-2 diabetes by 12%. This study was conducted on 58,000 participants in the DiscovEHR Study [20]. Similar results were presented by the team of Klarin et al. in a study of 310,000 subjects. The effect of the loss-of-function (LOF) ANGPTL4 mutation on the risk of ischemic heart disease and type-2 diabetes was assessed. It was shown that the risk of ischemic heart disease was reduced by 16% and the risk of type 2 diabetes was reduced by 12% [21].

4. Evinacumab-Structure and the Mechanism of Action

Evinacumab (Evkeeza®; formerly RENG1500) is a fully human monoclonal antibody, inhibiting circulating ANGPTL3, which was invented by Regeneron Pharmaceuticals Inc. [3] and manufactured with the use of the cell culture method with genetically engineered recombinant Chinese hamster ovary cells [22]. Evinacumab is an IgG4 monoclonal antibody consisting of two disulfide-linked human heavy chains (453 amino acids each) and human kappa light chains (214 amino acids). Heavy chains are covalently linked by disulfide bonds to light chains [22].

Evinacumab was approved by the US Food and Drug Administration on February 2021 and the European Medicines Agency (EMA) in June 2021 and is now available on the market under the trade name Evkeeza to treat adult and adolescent patients ($\geq$12 years) with homozygous familial hypercholesterolemia [23]. The recommended dose of this new drug is 15 mg/kg, administered by intravenous infusion (IV) over one hour once monthly [23].

After administration, evinacumab binds its target, ANGPTL3, and inhibits its function, leading to increased LPL and EL activities and lower TG, LDL-C, and HDL-C plasma levels [24]. The mechanism associated with the reduction of LDL-C by evinacumab is not fully known; however, this effect is independent of the LDL receptor and, thus, probably due to the promotion of very-low-density lipoprotein (VLDL) processing and the upstream clearance of LDL formation [12–15,24]. The mechanism of the action of evinacumab is presented in Figure 2.

Clinical Trials and Scientific Research

In the first phase, phase 1, a randomized, placebo-controlled, double-blind clinical trial with evinacumab (NCT01749878) was performed with subjects with hypertriglyceridemia (HTG) to evaluate its safety, tolerability, and bioeffect. A total of 83 healthy volunteers with fasting triglyceride levels of 150–450 mg/dL (1.7 $\leq$ 5.1 mmol/L) or LDL-C levels of $\geq$100 mg/dL (2.6 mmol/L) were enrolled in cohort A, and each received a single dose of evinacumab administrated subcutaneously (SC) (75, 150, and 250 mg) or intravenously (IV) (5 mg/kg, 10 mg/kg, and 20 mg/kg) versus placebo [18]. Participants (n = 7) allocated to cohort B (moderate HTG) had TG levels of >150 and $\leq$450 mg/dL, and each received evinacumab IV at a dose of 10 mg/kg or placebo [19]. Cohort C (severe HTG) participants (n = 9) had LPL pathway sequence variations and TG levels of >1000 mg/dL and received evinacumab at a dose of 250 mg SC or 20 mg/kg IV versus placebo [18]. Evinacumab caused a dose-dependent reduction in lipids levels. The greatest reductions of TG, LDL-C, and HDL-C were 76.0% (day 4) (95% CI: −97.29, −62.02; $p < 0.0001$); 23.2% (day 15) (95% CI: −7.59, −38.80; $p = 0.0047$); and 18.4% (day 15) (95% CI: −5.96, −30.77; $p = 0.0049$), respectively, and these reductions were noted in cohort A participants who received a dose of 20 mg/kg IV [18].

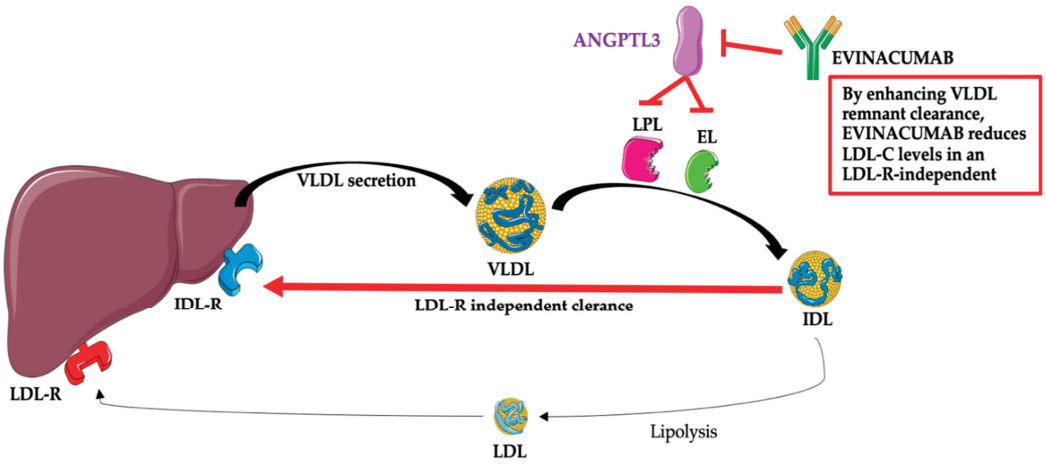

Figure 2. Evinacumab—mechanism of action. Abbreviations: ANGPTL3—angiopoietin-like protein 3; EL—endothelial lipase; IDL—intermediate-density lipoprotein (VLDL remnants); IDL-R—intermediate-density lipoprotein receptor (VLDL remnant receptor); LDL—low-density lipoprotein; LDL-C—low-density lipoprotein; LDL-R—low-density lipoprotein receptor; LPL—lipoprotein lipase; VLDL—very-low-density lipoprotein. The following was used in the preparation of the figure: https://smart.servier.com (free-access; 20 October 2022).

There were no treatment discontinuations due to adverse safety events in all cohorts (A–C) [18,25]. Treatment-emergent adverse events occurred in 51.6% of cohort A (vs. 42.9% placebo) and 100% of cohorts B–C (vs. 81.8% placebo) [18,25]. The most frequent adverse events (AEs) observed in evinacumab-treated patients (cohort A) were headache (11% vs. 0% placebo), upper respiratory tract infection (6.5% vs. 4.0% placebo), increased alanine aminotransferase (11.3% vs. 0% placebo), and increased aspartate aminotransferase (4.8% vs. 0% placebo).

In cohort B, evinacumab caused a maximal reduction of TGs by 81.8% (vs. 20.6% placebo) and VLDL-C by 82.2% (vs. 0.8% placebo) on day 4. Treatment with evinacumab-induced wide-ranging responses in subjects with severe hypertriglyceridemia (cohort C) showed a TG reduction of 0.9 to 93.2% on day 3 [25].

In cohort C, evinacumab IV at a dose of 20 mg/kg caused a maximum mean reduction in VLDL-C of 64.9% (vs. 42.0% placebo) on day 22, while evinacumab SC at a dose of 250 mg resulted in a maximum reduction of 37.8% (vs. increase of 18.4% placebo) on day 8. The levels of LDL-C after treatment with evinacumab increased in participants with moderate and severe HTG (cohorts B and C), which was explained by the authors as a reason for the enhanced conversion of VLDL and IDL to LDL [25].

Another phase 1 clinical trial (NCT02107872) with subjects with triglycerides >150 and $\leq$500 mg/dL and LDL-C $\geq$ 100 mg/dL was conducted to assess the effect of multi-doses of evinacumab [26]. A total of 56 participants were enrolled, and each was assigned to one of the six cohorts as follows: evinacumab SC at doses of 150, 300, or 450 mg QW, 300 or 450 mg Q2W, or IV doses of 20 mg/kg Q4W up to day 56 versus placebo with 183 days of follow-up [26]. Treatment-emergent adverse events occurred in 67.7% of patients with evinacumab SC (vs. 75% placebo) and 85.7% of the subjects with evinacumab IV (vs. 50% placebo). No serious treatment-emergent adverse events, events related to death, or treatment discontinuation were reported. The most commonly reported adverse events were headache (42.9% vs. 0% placebo) in the group with evinacumab IV and nausea (13% vs. 0% placebo) in the group with evinacumab SC [26].

Dose-dependent reductions in triglycerides were observed, with a maximum reduction at a dose of 20 mg/kg Q4W IV by 88.2% at day 2 (p = 0.0003). Other lipids such as non-HDL,

apoB, LDL-C, and total cholesterol were maximally reduced at dose 20 mg/kg Q4W IV by 45.8% (day 36) ($p < 0.0001$), 30.7% (day 57) ($p < 0.0001$), 25.1% (day 57) ($p = 0.0074$), and 33.8% (day 57) ($p < 0.0001$), respectively [26].

The pharmacokinetics, tolerability, safety, and lipid-lowering effect of evinacumab were evaluated in phase 1 with a randomized, double-blind, placebo-controlled clinical trial (NCT03146416) with healthy Caucasian and Japanese volunteers with LDL-C concentrations between 100 and 160 mg/dL (2.6–4.1 mmol/L). A total of 96 enrolled participants was divided into four cohorts: a single dose of 300 mg of evinacumab SC; 300 mg (SC) once weekly for eight doses; 5 mg/kg IV once every 4 weeks for two doses; and 15 mg/kg IV once every 4 weeks for two doses. Each cohort comprised 12 Japanese and 12 Caucasians, who each received an investigational drug or placebo with a 24-week follow-up [3]. The results of the study indicated that the safety of evinacumab treatment at all doses and routes of administration in both ethnic groups was comparable with that of the placebo. Observed adverse events related to the treatment were nausea, fatigue, nasopharyngitis, upper respiratory infection, rhinitis, back pain, headache, and tension headache. In cohorts with IV evinacumab administration, adverse events occurred in 15 subjects (41.7%) with the drug versus 6 subjects (50%) in the placebo group. In cohorts with evinacumab SC, adverse events were noted in 19 subjects (52.8%) with the drug versus 3 subjects (25.0%) with a placebo. No severe or serious adverse event was observed. Moreover, the pharmacokinetic and pharmacodynamic profiles of evinacumab were similar in both ethnicities in all treatment groups [4]. Evinacumab caused dose-dependent reductions in LDL-C, TG, and apoB levels. The administration of evinacumab IV at a dose of 15 mg/kg every 4 weeks in two doses caused the greatest lipid-lowering power. In addition, the reductions of LDL-C, triglycerides, non-HDL cholesterol, HDL cholesterol, total cholesterol, apoB, apoA-I, apoC-III, and Lp(a) in plasma after 8 weeks were 40.2%, 63.1%, 44.2%, 23.8%, 40.2%, 37.4%, 33.5%, 77.1%, and 22.2%, respectively [4].

The safety and efficacy of evinacumab in patients with refractory hypercholesterolemia were assessed in the phase 2 clinical trial (NCT03175367) [5]. A total of 272 subjects with HeFH or without HeFH with refractory hypercholesterolemia and who had LDL-C $\geq$ 70 mg/dL with ASCVD or LDL-C $\geq$ 100 mg/dL without ASCVD were enrolled. Participants received evinacumab SC in different doses of 450 mg QW, 300 mg QW, or 300 mg Q2W vs. placebo or evinacumab IV in a dose of 15 mg/kg Q4W or 5 mg/kg Q4W versus placebo [5].

The most common side effects reported by the participants during the trial in the group treated with SC evinacumab were urinary tract infections (11% vs. 8%), injection-site erythema (6% vs. 3%), myalgia (5% vs. 0%), and arthralgia (5% vs. 3%), whereas the group receiving IV evinacumab had nasopharyngitis (12% vs. 6%), dizziness (7% vs. 0%), nausea (7% vs. 0%), abdominal pain (6% vs. 0%), back pain (7% vs. 6%), fatigue (7% vs. 6%), and arm or leg pain (7% vs. 6%). Serious adverse events were noted in 5–8% (8% placebo) in the group with SC evinacumab and in 6–16% (versus 3% placebo) in the group with IV evinacumab [5]. Treatment with evinacumab caused a reduction in the level of LDL-C. In the group with SC administration, the reductions were between 38.5% (95% CI: –56.5, –20.6; $p < 0.001$) and 56.0% (95% CI: –73.7, –38.3; $p < 0.001$), while the group with IV administration had reductions from 24.2% (95% CI: –42.6, –5.7) to 50.5% (95% CI: –68.4, –32.6; $p < 0.001$) depending on the dose used. The greatest decrease in LDL-C was observed with a dose of 450 mg QW of evinacumab SC (56.0%) (95% CI: −73.7, −38.3; $p < 0.001$) [5].

Several clinical trials evaluating the efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia have been completed. A phase 2, open-label, proof-of-concept clinical trial (NCT02265952) included nine HoFH participants receiving maximum-tolerated lipid-lowering treatment. All subjects were administered evinacumab at doses of 250 mg SC and 15 mg/kg IV after 2 weeks [27]. All participants reported at least one adverse event, but no event led to treatment discontinuation. Injection-site reactions, myalgia, hot flush, and epistaxis were reported as treatment-emergent AEs, and each of these AE was observed by only one patient [27]. Evinacumab caused reductions in LDL-C,

non-HDL cholesterol, triglycerides, apolipoprotein B, and HDL cholesterol by mean values of 49 ± 23%, 49 ± 22%, 47 ± 17%, 46 ± 18%, and 36 ± 16%, respectively [27].

Banerjee et al. analyzed the effects of evinacumab on LDLR activity in lymphocytes drawn from participants in the above-mentioned study (NCT02265952). Obtained results suggested that the inhibition of ANGPTL3 by evinacumab in humans lowers LDL-C through a mechanism independent of the LDLR [28].

A small kinetic study (NCT04722068) with four subjects already participating in the study (NCT02265952) was conducted to investigate the apolipoprotein B (apoB) containing lipoprotein kinetic parameters before and after treatment with evinacumab [29]. A stable isotope of Leucine was measured in VLDL (very-low-density lipoprotein), IDL (intermediate-density lipoprotein; VLDL remnants), and LDL before and after IV administration of evinacumab at a dose of 15 mg/kg. Evinacumab decreased LDL-C by 59 ± 2% and increased IDL-apoB and LDL-apoB fractional catabolic rates in all four HoFH participants by 616 ± 504% and 113 ± 14%, respectively. The VLDL-apoB production rate was reduced in two of the four subjects. These results suggest that the mechanism of lowering LDL-C by evinacumab is associated with the increased clearance of apoB-containing lipoprotein [29].

A phase 3, double-blind, placebo-controlled clinical trial (ELIPSE HoFH, NCT03399786) enrolled 65 subjects with HoFH on stable lipid-lowering therapy. Ninety-three percent of the subjects were on statin therapy, and the majority of the patients were receiving high-intensity statin (77%). Moreover, trial patients' background therapy also included PCSK9 inhibitor (77%), ezetimibe (75%), lomitapide (25%), and apheresis (34%). Of the patients, 63% used at least three different lipid-lowering drugs. Participants received evinacumab IV 15 mg/kg every 4 weeks for 24 weeks or a placebo. Treatment with evinacumab caused significant decreases in plasma levels of LDL-C, total cholesterol, non-HDL, HDL, triglycerides, apoB, apoC-III, and Lp(a) by 47.1% (95% CI: −65.0, −33.1; $p < 0.001$), 47.4% (95% CI: −58.7 to −38.1; $p < 0.001$), 49.7% (95% CI: −64.8 to −38.5; $p < 0.001$), 29.6%, 55.0% (95% CI: −65.6, −35.2), 41.4% (95% CI: −48.6, −25.2; $p < 0.001$), 84.1% (95% CI: −103.5 to −76.5), and 5.5% (95% CI: −15.7, 12.0), respectively [3]. A 50% reduction in plasma LDL-C concentration was achieved in 56% ($p = 0.003$) of patients; moreover, 28% of patients had plasma LDL-C levels below 70 mg/dL. The efficacy of the LDL-C reduction with evinacumab was independent of the type of LDL receptor gene mutations (non/null or null/null). Adverse events were comparable in the group with evinacumab and the placebo group. An influenza-like illness occurred in 5 of 44 patients (11%) vs. 0 in the placebo group. No events related to death or treatment discontinuation were reported [3].

Additionally, the study of Reeskamp et al. analyzed whether intensive lipid-lowering therapy with evinacumab might result in plaque regression. Using computed tomography (CT) coronary angiography, soft plaque regression occurred in the coronary arteries of two participants, ages 12 and 16, of a clinical trial (NCT03399786) with HoFH and null/null LDLR variants. Total plaque volumes were reduced by 76% and 85%, respectively, after 6 months of evinacumab treatment [30].

Most of the completed clinical trials with evinacumab had small sample sizes. Jin et al. conducted a meta-analysis of five randomized controlled trials with 568 participants and revealed that treatment with evinacumab was safe and caused a reduction of LDL-C, TG, and HDL cholesterol by 33.12% (95%: 248.639%, 217.606%, $p < 0.0001$), 50.96% (95% CI: 256.555%, 245.362%; $p < 0.0001$), and 12.77% (95% CI: 216.359, 29.186%, $p < 0.0001$), respectively [31]. The results of this meta-analysis found evinacumab as a possible valuable therapeutic in the management of hypercholesterolemia.

The efficacy of evinacumab is under clinical trial phase 2 (NCT04863014) [32] and two phase 3 studies (NCT03409744; NCT04233918) [33,34] (Table 1).

Table 1. Summary of the results of clinical trials with evinacumab.

Clinical Phase/Status	NCT Identification Number	Population/*N*	Duration	Dose/Treatment Arms	Key Results	Safety	Ref.
Phase 1 Completed	NCT01749878	HTG Cohort A: 150 < TG ≤ 450 mg/dL or LDL-C ≥ 100 mg/dL *N* = 83 Cohort B: 450 ≤ TG < 1500 mg/dL *N* = 7 Cohort C: LPL pathway sequence variations, TG > 1000 mg/dL *N* = 9	126 days	Single dose: Cohort A: 75, 150, 250 mg SC or 5, 10, 20 mg/kg IV vs. placebo Cohort B: 10 mg/kg IV vs. placebo Cohort C: 250 mg SC or 20 mg/kg IV vs. placebo	Max reduction: Cohort A: At a dose of 20 mg/kg IV TG: 76.0% LDL-C: 23.2% HDL: 18.4% Cohort B TG: 81.8% VLDL-C: 82.2% Cohort C TG: 0.9 to 93.2%, VLDL-C: 64.9% (IV 20 mg/kg), 37.8% (SC 250 mg)	TEAEs Cohort A 51.6% vs. 42.9% placebo Cohorts B and C 100% vs. 81.8% placebo Frequent AE (cohort A): headache (11% vs. 0% placebo), upper respiratory tract infection (6.5% vs. 4.0% placebo), increased alanine aminotransferase (11.3% vs. 0% placebo), increased aspartate aminotransferase (4.8% vs. 0% placebo)	[18,25, 26]
Phase 1 Completed	NCT02107872	HTG: 150< TG ≤500 mg/dL and LDL-C ≥ 100 mg/dL *N* = 56	183 days	Multiple doses: **SC**: 150, 300, 450 mg QW or 300, 450 mg Q2W **IV**: 20 mg/kg Q4W up to day 56 vs. placebo	Max reduction at IV 20 mg/kg Q4W TG: 88.2% (day 2) non-HDL: 45.8% (day 36) apoB: 30.7% (day 57) LDL-C: 25.1% (day 57) total cholesterol: 33.8% (day 57)	TEAEs **SC**: 51.6% vs. 42.9% placebo **IV**: 85.7% vs. 50% placebo Common AE: **SC**: nausea (13% vs. 0% placebo) **IV**: headache (42.9% vs. 0% placebo); No SAE	[26]
Phase 2 Completed	NCT02265952	HoFH *N* = 9	26 weeks	Two doses: 250 mg SC on day 1 and 15 mg/kg IV on week 2	Max reduction (week 4): LDL-C: 49 ± 23% non-HDL-C: 49 ± 22% TG: 47 ± 17% apo B: 46 ± 18% HDL-C: 36 ± 16%	TEAEs: Injection-site reactions (11%), myalgia (11%), hot flush (11%), epistaxis (11%); No SAE	[27, 28]
Phase 1 Completed	NCT03146416	Healthy Japanese and Caucasian *N* = 96	24 weeks	Cohorts: I: single dose of 300 mg (SC) II: 300 mg (SC) QW for eight doses III: 5 mg/kg (IV) IV: 15 mg/kg (IV) Q4W for two doses vs. placebo	Max reduction, 15 mg/kg (IV) Q4W for two doses (week 8): LDL: 40.2% TG: 63.1% non-HDL: 44.2% HDL: 23.8% total cholesterol: 40.2% apoB: 37.4% apoA-I: 33.5% apoC-III: 77.1% Lp(a): 22.2%	TEAEs SC: 52.8% vs. 25.0% placebo IV: 41.7% vs. 50% placebo Common TEAEs: nausea, fatigue, nasopharyngitis, upper respiratory infection, rhinitis, back pain, headache, tension headache; No SAE	[4]

Table 1. *Cont.*

Clinical Phase/Status	NCT Identification Number	Population/*N*	Duration	Dose/Treatment Arms	Key Results	Safety	Ref.
Phase 2 Completed	NCT03175367	Hypercholesterolemia: HeFH or non-HeFH with ASCVD ASCVD: LDL-C ≥ 70 mg/dL or non-ASCVD: LDL-C ≥ 100 mg/dL *N* = 272	16 weeks	SC: 450 mg QW, 300 mg QW, or 300 mg Q2W vs. placebo; IV: 15 mg/kg Q4W or 5 mg/kg Q4W vs. placebo	LDL-C reduction: SC: 38.5% to 56.0%, IV: 24.2% to 50.5%	SC AE: 68–82% vs. 54% placebo; urinary tract infection (11% vs. 8%), injection-site erythema (6% vs. 3%), arthralgia (5% vs. 3%), myalgia (5% vs. 0%) SAE: 5–8% vs. 8% IV AE: 75–84% vs. 70% placebo; abdominal pain (6% vs. 0%), back pain (7% vs. 6%), dizziness (7% vs. 0%), fatigue (7% vs. 6%), pain in an arm or leg (7% vs. 6%), nausea (7% vs. 0%), and nasopharyngitis (12% vs. 6%); SAE: 6–16% vs. 3%	[5]
Phase 2 Completed	NCT03452228	sHTG, TG values ≥ 500 mg/dL (5.6 mmol/L) *N* = 52	24 weeks	Evinacumab IV vs. placebo	NA	NA	
Phase 3 Completed	NCT03399786	HoFH LDL-C ≥ 70 mg/dL (1.8 mmol/L) *N* = 65	24 weeks	Evinacumab IV 15 mg/kg Q4W vs. placebo	Reduction: LDL-C: 47.1%, total cholesterol: 47.4%, non-HDL: 49.7%, HDL: 29.6%, TG: 55.0%, apoB: 41.4%, apoC-III: 84.1% Lp(a): 5.5%	AE: 66% vs. 81% placebo, SAE: 5% vs. 0 placebo	[3]
Kinetics test	NCT04722068	HoFH *N* = 4	8 weeks	Evinacumab IV 15 mg/kg	Decrease: LDL-C: 59 ± 2%, Increase: IDL-ApoB: 616 ± 504%, LDL-ApoB: 113 ± 14%,	NA	[29]
Phase 3 Ongoing	NCT03409744	HoFH, adolescent subjects (≥12 years) *N* = 116	192 weeks	Evinacumab IV	Study completion date: January 2023		[23]
Phase 3 Ongoing	NCT04233918	HoFH, pediatric subjects (5–11 years), LDL-C > 130 mg/dL *N* = 20	24 weeks	Part A: single IV dose; Part B: IV dose Q4W until week 20; Part C: IV dose Q4W	Study completion date: May 2023		[23]
Phase 2 Ongoing	NCT04863014	sHTG, adult subjects (18–80 years) TG > 880 mg/dL (10 mmol/L) or >500 mg/dL (5.6 mmol/L); *N* = 21	52 weeks	IV Q4W vs. placebo	Study completion date: February 2023		[23]

ASCVD, atherosclerotic cardiovascular; AE, adverse event; CVD, cardiovascular disease; HoFH, homozygous familial hypercholesterolemia; HTG, Hypertriglyceridemia; IV, intravenous; LPL, lipoprotein lipase; NA, no data are available; SAE, serious adverse event; SC, subcutaneous; sHTG, severe hypertriglyceridemia disease; QXW, once every X weeks; TEAEs, treatment-emergent adverse events.

A phase 2, double-blind clinical trial NCT04863014 started on July 2021, and the estimated study completion date is February 2023. The study enrolled 21 adult participants with severe hypertriglyceridemia and will assess the efficacy and safety of evinacumab for the prevention of recurrent acute pancreatitis [32].

A phase 3, open-label clinical trial (NCT04233918) with 20 pediatric participants (5–11 years) with HoFH aims to evaluate the efficacy and safety of evinacumab. The estimated completion date is May 2023 [34]. A phase 3, open-label clinical trial (NCT03409744) enrolled 116 adolescent participants (≥12 years) with HoFH. The aim of the study is to evaluate the long-term safety and efficacy of evinacumab. Initial results are expected in January 2023 [30]. Completed and ongoing clinical trials with evinacumab are summarized in Table 1.

5. Perspectives of Evinacumab in Clinical Lipidology

Guidelines of the Polish Lipid Association (PoLA) from 2021 regarding lipid-lowering treatment place evinacumab in the group of drugs supporting the therapy of familial hypercholesterolaemia [35]. In the guidelines of the European Society of Cardiology (ESC) and the European Atherosclerotic Society (EAS) from 2019 regarding the management of dyslipidemias, evinacumab is characterized in the context of new approaches to reduce triglyceride-rich lipoproteins and their remnants [36]. There are currently no official recommendations regarding evinacumab and its place in the treatment of lipid disorders.

Evinacumab may be of great help in lowering LDL-C levels in patients with HoFH in whom the available treatment (statins, ezetimibe, PCSK9 inhibitors) did not achieve the therapeutic goal [37]. Experts have also indicated that evinacumab may be an important drug in the context of the reduction of triglycerides associated with ASCVD residual risk, especially in patients with diabetes [38].

The future of evinacumab seems to be slightly different from that of other drugs intended for severe hypercholesterolemia, such as PCSK9 inhibitors (alirocumab, evolocumab) and inclisiran. These examples do not relate to hypertriglyceridemia. However, new clinical trials are needed to expand our experience of combining evinacumab with ezetimibe, bempedoic acid, or even PCSK9 modulators in patients currently treated with LDL apheresis. The authors of this article pose some open questions about the future of evinacumab: (1) Will evinacumab be a better choice in the future than the concept of PCSK9 blockade? (2) Will this change the way we currently treat hypertriglyceridemia? (3) What will be the optimal algorithm for introducing this drug to the family of old and new hypolipemic therapies?

The approval and availability of evinacumab in the lipid-lowering armamentarium will undoubtedly constitute significant progress, providing a drug with high efficacy in not only hypercholesterolaemia but also hypertriglyceridemia. The authors believe that, in addition to the expected breakthrough therapies in the field of lowering lipoprotein (a) concentrations, i.e., the intensively studied pelacarsen and olpasiran or SLN360, the entry into the pharmaceutical armamentarium of evinacumab may become the most important event of lipoprotein pharmacotherapy in the current decade. An antisense oligonucleotide (ASO) that reduces ANGPTL3 synthesis in the liver-vupanorsen is also in clinical trials [39]. During the Congress of the European Atherosclerosis Society (EAS) in 2022, a liver-specific treatment of the target protein ANGPTL4 was also presented [40]. Thus, the system of proteins ANGPTL3, ANGPTL4, and ANGPTL8 is currently a widely studied point of the pharmacological action of lipid-lowering drugs.

6. Conclusions

The above-mentioned findings from clinical trials (Table 1) and scientific research proved that evinacumab is effective and safe as an add-on treatment in the management of HoFH. Evinacumab decreases the level of LDL cholesterol by approximately 50% in individuals with maximally tolerated lipid-lowering therapy, and its mechanism is independent of residual LDLR activity [3,27]. Moreover, it was indicated that evinacumab might also

cause plaque regression; [30] however; this finding should be validated in randomized, placebo-controlled trials in large groups of patients.

Traditional lipid-lowering therapies, such as statins and PCSK9 inhibitors [8,41–43], which upregulate the LDLR pathway, are ineffective or less effective in individuals with two null alleles present in HoFH [44]. In contrast, evinacumab lowers LDL-C levels independent of LDLR activity, so it can be considered a major tool in the armamentarium of patients with HoFH who failed to achieve their minimal guideline-recommended LDL-C goals, despite receiving multiple classes of lipid-lowering therapies and LDL apheresis, or as an alternative for patients who do not tolerate or have no access to apheresis or lomitapide [45,46].

Unfortunately, access to evinacumab, similar to other newly approved potent lipid-lowering therapeutics (PCSK9 inhibitors, lomitapide), is commonly restricted by regulatory approval and high cost [47,48].

Although evinacumab is approved for use by the FDA and EMA, the long-term effect of its action still needs to be studied. Currently, the long-term effect of evinacumab is being studied in an ongoing clinical trial, and the first results are expected in 2023.

Author Contributions: Conceptualization, M.B.; writing—original draft preparation, B.S., W.A. and S.S.; writing—review and editing, M.B. and R.S.R.; visualization, S.S.; supervision, M.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: B.S., W.A., S.S.—no conflict of interest; R.S.R.—receives research grants to his institution from Amgen, Arrowhead, Eli Lilly, Novartis, and Regeneron; consulting fees from Amgen, Arrowhead, CRISPR Therapeutics, Eli Lilly, Precision BioSciences, Regeneron, and Ultragenyx; and royalties from Wolters Kluwer (UpToDate) and has stock holdings in MediMergent, LLC; M.B.—speakers bureau: Amgen, Herbapol, Kogen, KRKA, Polpharma, Mylan/Viatris, Novartis, Novo-Nordisk, Sanofi-Aventis, Teva, and Zentiva; consultant to Abbott Vascular, Amgen, Daichii Sankyo, Esperion, Freia Pharmaceuticals, NewAmsterdam, Novartis, Polfarmex, and Sanofi-Aventis; grants from Amgen, Mylan/Viatris, Sanofi, and Valeant; and CMO at the Nomi Biotech Corporation.

References

1. Rosenson, R.S. Existing and emerging therapies for the treatment of familial hypercholesterolemia. *J. Lipid Res.* **2021**, *62*, 100060. [CrossRef] [PubMed]
2. Cuchel, M.; Bruckert, E.; Ginsberg, H.N.; Raal, F.J.; Santos, R.D.; Hegele, R.A.; Kuivenhoven, J.A.; Nordestgaard, B.G.; Descamps, O.S.; Steinhagen-Thiessen, E.; et al. Homozygous familial hypercholesterolaemia: New insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur. Heart J.* **2014**, *35*, 2146–2157. [CrossRef] [PubMed]
3. Raal, F.J.; Rosenson, R.S.; Reeskamp, L.F.; Hovingh, G.K.; Kastelein, J.J.P.; Rubba, P.; Ali, S.; Banerjee, P.; Chan, K.C.; Gipe, D.A.; et al. Evinacumab for Homozygous Familial Hypercholesterolemia. *N. Engl. J. Med.* **2020**, *383*, 711–720. [CrossRef] [PubMed]
4. Harada-Shiba, M.; Ali, S.; Gipe, D.A.; Gasparino, E.; Son, V.; Zhang, Y.; Pordy, R.; Catapano, A.L. A randomized study investigating the safety, tolerability, and pharmacokinetics of evinacumab, an ANGPTL3 inhibitor, in healthy Japanese and Caucasian subjects. *Atherosclerosis* **2020**, *314*, 33–40. [CrossRef] [PubMed]
5. Rosenson, R.S.; Burgess, L.J.; Ebenbichler, C.F.; Baum, S.J.; Stroes, E.S.G.; Ali, S.; Khilla, N.; Hamlin, R.; Pordy, R.; Dong, Y.; et al. Evinacumab in Patients with Refractory Hypercholesterolemia. *N. Engl. J. Med.* **2020**, *383*, 2307–2319. [CrossRef] [PubMed]
6. Dijk, W.; Kersten, S. Regulation of lipid metabolism by angiopoietin-like proteins. *Curr. Opin. Lipidol.* **2016**, *27*, 249–256. [CrossRef]
7. Abu-Farha, M.; Ghosh, A.; Al-Khairi, I.; Madiraju, S.R.M.; Abubaker, J.; Prentki, M. The multi-faces of Angptl8 in health and disease: Novel functions beyond lipoprotein lipase modulation. *Prog. Lipid Res.* **2020**, *80*, 101067. [CrossRef]
8. Solnica, B.; Sygitowicz, G.; Sitkiewicz, D.; Cybulska, B.; Jóźwiak, J.; Odrowąż-Sypniewska, G.; Banach, M. 2020 Guidelines of the Polish Society of Laboratory Diagnostics (PSLD) and the Polish Lipid Association (PoLA) on laboratory diagnostics of lipid metabolism disorders. *Arch. Med. Sci.* **2020**, *16*, 237–252. [CrossRef]

9. Li, J.; Li, L.; Guo, D.; Li, S.; Zeng, Y.; Liu, C.; Fu, R.; Huang, M.; Xie, W. Triglyceride metabolism and angiopoietin-like proteins in lipoprotein lipase regulation. *Clin. Chim. Acta* **2020**, *503*, 19–34. [CrossRef]
10. Morelli, M.B.; Chavez, C.; Santulli, G. Angiopoietin-like proteins as therapeutic targets for cardiovascular disease: Focus on lipid disorders. *Expert Opin. Ther. Targets* **2020**, *24*, 79–88. [CrossRef]
11. Zhang, R. The ANGPTL3-4-8 model, a molecular mechanism for triglyceride trafficking. *Open Biol.* **2016**, *6*, 150272. [CrossRef] [PubMed]
12. Stitziel, N.O.; Khera, A.V.; Wang, X.; Bierhals, A.J.; Vourakis, A.C.; Sperry, A.E.; Natarajan, P.; Klarin, D.; Emdin, C.A.; Zekavat, S.M.; et al. ANGPTL3 Deficiency and Protection Against Coronary Artery Disease. *J. Am. Coll. Cardiol.* **2017**, *69*, 2054–2063. [CrossRef] [PubMed]
13. Surma, S.; Romańczyk, M.; Filipiak, K.J. Angiopoietin-like proteins inhibitors: New horizons in the treatment of atherogenic dyslipidemia and familial hypercholesterolemia. *Cardiol. J.* **2021**. [CrossRef] [PubMed]
14. Surma, S.; Romańczyk, M.; Filipiak, K.J. Evinacumab—The new kid on the block. Is it important for cardiovascular prevention? *Int. J. Cardiol. Cardiovasc. Risk Prev.* **2021**, *11*, 200107. [CrossRef] [PubMed]
15. Surma, S.; Romańczyk, M.; Filipiak, K.J. Evinacumab—An ANGPTL3 inhibitor; a new drug in the treatment of lipid disorders. Review on the literature and clinical studies. *Folia Cardiol.* **2021**, *16*, 30–39. [CrossRef]
16. Khetarpal, S.A.; Vitali, C.; Levin, M.G.; Klarin, D.; Park, J.; Pampana, A.; Millar, J.S.; Kuwano, T.; Sugasini, D.; Subbaiah, P.V.; et al. Endothelial lipase mediates efficient lipolysis of triglyceride-rich lipoproteins. *PLoS Genet.* **2021**, *17*, e1009802. [CrossRef] [PubMed]
17. Sun, T.; Zhan, W.; Wei, L.; Xu, Z.; Fan, L.; Zhuo, Y.; Wang, C.; Zhang, J. Circulating ANGPTL3 and ANGPTL4 levels predict coronary artery atherosclerosis severity. *Lipids Health Dis.* **2021**, *20*, 154. [CrossRef]
18. Dewey, F.E.; Gusarova, V.; Dunbar, R.L.; O'Dushlaine, C.; Schurmann, C.; Gottesman, O.; McCarthy, S.; Van Hout, C.V.; Bruse, S.; Dansky, H.M.; et al. Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease. *N. Engl. J. Med.* **2017**, *377*, 211–221. [CrossRef]
19. Stitziel, N.O.; Stirrups, K.E.; Masca, N.G.; Erdmann, J.; Ferrario, P.G.; König, I.R.; Weeke, P.E.; Webb, T.R.; Auer, P.L.; Schick, U.M.; et al. Coding Variation in ANGPTL4, LPL, and SVEP1 and the Risk of Coronary Disease. *N. Engl. J. Med.* **2016**, *374*, 1134–1144.
20. Gusarova, V.; O'Dushlaine, C.; Teslovich, T.M.; Benotti, P.N.; Mirshahi, T.; Gottesman, O.; Van Hout, C.V.; Murray, M.F.; Mahajan, A.; Nielsen, J.B.; et al. Genetic inactivation of ANGPTL4 improves glucose homeostasis and is associated with reduced risk of diabetes. *Nat. Commun.* **2018**, *9*, 2252. [CrossRef]
21. Klarin, D.; Damrauer, S.M.; Cho, K.; Sun, Y.V.; Teslovich, T.M.; Honerlaw, J.; Gagnon, D.R.; DuVall, S.L.; Li, J.; Peloso, G.M.; et al. Genetics of blood lipids among ~300,000 multi-ethnic participants of the Million Veteran Program. *Nat. Genet.* **2018**, *50*, 1514–1523. [CrossRef] [PubMed]
22. Evkeeza. EMA/250315/2021, 22 April 2021, Assesment Report. Procedure No. EMEA/H/C/005449/000. Available online: https://www.ema.europa.eu/en/documents/assessment-report/evkeeza-h-c-5449-0000-epar-assessment-report_en.pdf. (accessed on 20 October 2022).
23. Evkeeza. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/evkeeza (accessed on 31 October 2022).
24. Gusarova, V.; Banfi, S.; Alexa-Braun, C.A.; Shihanian, L.M.; Mintah, I.J.; Lee, J.S.; Xin, Y.; Su, Q.; Kamat, V.; Cohen, J.C.; et al. ANGPTL8 Blockade With a Monoclonal Antibody Promotes Triglyceride Clearance, Energy Expenditure, and Weight Loss in Mice. *Endocrinology* **2017**, *158*, 1252–1259. [CrossRef] [PubMed]
25. Ahmad, Z.; Pordy, R.; Rader, D.J.; Gaudet, D.; Ali, S.; Gonzaga-Jauregui, C.; Ponda, M.P.; Shumel, B.; Banerjee, P.; Dunbar, R.L. Inhibition of Angiopoietin-Like Protein 3 With Evinacumab in Subjects With High and Severe Hypertriglyceridemia. *J. Am. Coll. Cardiol.* **2021**, *78*, 193–195. [CrossRef] [PubMed]
26. Ahmad, Z.; Banerjee, P.; Hamon, S.; Chan, K.C.; Bouzelmat, A.; Sasiela, W.J.; Pordy, R.; Mellis, S.; Dansky, H.; Gipe, D.A.; et al. Inhibition of Angiopoietin-Like Protein 3 With a Monoclonal Antibody Reduces Triglycerides in Hypertriglyceridemia. *Circulation* **2021**, *140*, 470–486, Erratum in *Circulation* **2021**, *143*, e799. [CrossRef]
27. Gaudet, D.; Gipe, D.A.; Pordy, R.; Ahmad, Z.; Cuchel, M.; Shah, P.K.; Chyu, K.Y.; Sasiela, W.J.; Chan, K.C.; Brisson, D.; et al. ANGPTL3 Inhibition in Homozygous Familial Hypercholesterolemia. *N. Engl. J. Med.* **2017**, *377*, 296–297. [CrossRef]
28. Banerjee, P.; Chan, K.C.; Tarabocchia, M.; Benito-Vicente, A.; Alves, A.C.; Uribe, K.B.; Bourbon, M.; Skiba, P.J.; Pordy, R.; Gipe, D.A.; et al. Functional Analysis of LDLR (Low-Density Lipoprotein Receptor) Variants in Patient Lymphocytes to Assess the Effect of Evinacumab in Homozygous Familial Hypercholesterolemia Patients With a Spectrum of LDLR Activity. *Arterioscler. Thromb. Vasc. Biol.* **2019**, *39*, 2248–2260. [CrossRef]
29. Reeskamp, L.F.; Millar, J.S.; Wu, L.; Jansen, H.; van Harskamp, D.; Schierbeek, H.; Gipe, D.A.; Rader, D.J.; Dallinga-Thie, G.M.; Hovingh, G.K.; et al. ANGPTL3 Inhibition With Evinacumab Results in Faster Clearance of IDL and LDL apoB in Patients With Homozygous Familial Hypercholesterolemia-Brief Report. *Arterioscler. Thromb. Vasc. Biol.* **2021**, *41*, 1753–1759. [CrossRef]
30. Reeskamp, L.F.; Nurmohamed, N.S.; Bom, M.J.; Planken, R.N.; Driessen, R.S.; van Diemen, P.A.; Luirink, I.K.; Groothoff, J.W.; Kuipers, I.M.; Knaapen, P.; et al. Marked plaque regression in homozygous familial hypercholesterolemia. *Atherosclerosis* **2021**, *327*, 13–17. [CrossRef]
31. Jin, M.; Meng, F.; Yang, W.; Liang, L.; Wang, H.; Fu, Z. Efficacy and Safety of Evinacumab for the Treatment of Hypercholesterolemia: A Meta-Analysis. *J. Cardiovasc. Pharmacol.* **2021**, *78*, 394–402. [CrossRef]

32. NCT04863014. Available online: https://www.clinicaltrials.gov/ct2/show/NCT04863014 (accessed on 24 October 2022).
33. NCT03409744. Available online: https://www.clinicaltrials.gov/ct2/show/NCT03409744 (accessed on 24 October 2022).
34. NCT04233918. Available online: https://www.clinicaltrials.gov/ct2/show/NCT04233918 (accessed on 24 October 2022).
35. Banach, M.; Burchardt, P.; Chlebus, K.; Dobrowolski, P.; Dudek, D.; Dyrbuś, K.; Gąsior, M.; Jankowski, P.; Jóźwiak, J.; Kłosiewicz-Latoszek, L.; et al. PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. *Arch. Med. Sci.* **2021**, *17*, 1447–1547. [CrossRef]
36. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis* **2019**, *290*, 140–205. [CrossRef] [PubMed]
37. Pirillo, A.; Catapano, A.L. Evinacumab: A new option in the treatment of homozygous familial hypercholesterolemia. *Expert Opin. Biol. Ther.* **2022**, *22*, 813–820. [CrossRef]
38. Banach, M.; Surma, S.; Reiner, Z.; Katsiki, N.; Penson, P.E.; Fras, Z.; Sahebkar, A.; Paneni, F.; Rizzo, M.; Kastelein, J. Personalized Management of Dyslipidemias in Patients with Diabetes—It Is Time for a New Approach (2022). *Cardiovasc. Diabetol.* **2022**, *21*, 263. [CrossRef] [PubMed]
39. Surma, S.; Romańczyk, M.; Filipiak, K.J. Evinacumab—A new drug in the treatment of severe lipid disorders. Up-to-date review of the literature and clinical studies. *Kardiol. Inwaz.* **2022**, *17*, 8–18.
40. Deng, M.; Kutrolli, E.; Sadewasser, A.; Michel, S.; Joibari, M.M.; Jaschinski, F.; Olivecrona, G.; Nilsson, S.K.; Kersten, S. ANGPTL4 silencing via antisense oligonucleotides reduces plasma triglycerides and glucose in mice without causing lymphadenopathy. *J. Lipid Res.* **2022**, *63*, 100237. [CrossRef] [PubMed]
41. Banach, M.; López-Sendon, J.L.; Averna, M.; Cariou, B.; Loy, M.; Manvelian, G.; Batsu, I.; Poulouin, Y.; Gaudet, D. Treatment adherence and effect of concurrent statin intensity on the efficacy and safety of alirocumab in a real-life setting: Results from ODYSSEY APPRISE. *Arch. Med. Sci.* **2021**, *18*, 285–292. [CrossRef]
42. Momtazi-Borojeni, A.A.; Jaafari, M.R.; Afshar, M.; Banach, M.; Sahebkar, A. PCSK9 immunization using nanoliposomes: Preventive efficacy against hypercholesterolemia and atherosclerosis. *Arch. Med. Sci.* **2021**, *17*, 1365–1377. [CrossRef]
43. Banach, M.; Kaźmierczak, J.; Mitkowski, P.; Wita, K.; Broncel, M.; Gąsior, M.; Gierlotka, M.; Gil, R.; Jankowski, P.; Niewada, M.; et al. Which patients at risk of cardiovascular disease might benefit the most from inclisiran? Polish experts' opinion. The compromise between EBM and possibilities in healthcare. *Arch. Med. Sci.* **2022**, *18*, 569–576. [CrossRef]
44. Gupta, S. LDL cholesterol, statins and PCSK 9 inhibitors. *Indian Heart J.* **2015**, *67*, 419–424. [CrossRef]
45. D'Erasmo, L.; Gallo, A.; Cefalù, A.B.; Di Costanzo, A.; Saheb, S.; Giammanco, A.; Averna, M.; Buonaiuto, A.; Iannuzzo, G.; Fortunato, G.; et al. Long-term efficacy of lipoprotein apheresis and lomitapide in the treatment of homozygous familial hypercholesterolemia (HoFH): A cross-national retrospective survey. *Orphanet J. Rare Dis.* **2021**, *16*, 381. [CrossRef]
46. D'Erasmo, L.; Steward, K.; Cefalù, A.B.; Di Costanzo, A.; Boersma, E.; Bini, S.; Arca, M.; van Lennep, J.R. Italian and European Working Group on Lomitapide in HoFH. Efficacy and safety of lomitapide in homozygous familial hypercholesterolaemia: The pan-European retrospective observational study. *Eur. J. Prev. Cardiol.* **2022**, *29*, 832–841, Erratum in *Eur. J. Prev. Cardiol.* **2022**, *29*, 1812. [CrossRef] [PubMed]
47. Kuehn, B.M. Evinacumab Approval Adds a New Option for Homozygous Familial Hypercholesterolemia with a Hefty Price Tag. *Circulation* **2021**, *143*, 2494–2496. [CrossRef] [PubMed]
48. Kosmas, C.E.; Bousvarou, M.D.; Sourlas, A.; Papakonstantinou, E.J.; Peña Genao, E.; Echavarria Uceta, R.; Guzman, E. Angiopoietin-Like Protein 3 (ANGPTL3) Inhibitors in the Management of Refractory Hypercholesterolemia. *Clin. Pharmacol.* **2022**, *14*, 49–59. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Review

Role of Lipid-Lowering Therapy in Peripheral Artery Disease

Agastya D. Belur [1], Aangi J. Shah [2], Salim S. Virani [3], Mounica Vorla [1] and Dinesh K. Kalra [1,*]

[1] Division of Cardiology, University of Louisville, Louisville, KY 40202, USA
[2] Department of Internal Medicine, University of Louisville, Louisville, KY 40292, USA
[3] Section of Cardiovascular Research, Baylor College of Medicine and Section of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX 77030, USA
* Correspondence: dinesh.kalra@louisville.edu; Tel.: +1-502-852-1358; Fax: +1-502-852-6233

Abstract: Atherosclerosis is a multifactorial, lipoprotein-driven condition that leads to plaque formation within the arterial tree, leading to subsequent arterial stenosis and thrombosis that accounts for a large burden of cardiovascular morbidity and mortality globally. Atherosclerosis of the lower extremities is called peripheral artery disease and is a major cause of loss in mobility, amputation, and critical limb ischemia. Peripheral artery disease is a common condition with a gamut of clinical manifestations that affects an estimated 10 million people in the United States of America and 200 million people worldwide. The role of apolipoprotein B-containing lipoproteins, such as LDL and remnant lipoproteins in the development and progression of atherosclerosis, is well-established. The focus of this paper is to review existing data on lipid-lowering therapies in lower extremity atherosclerotic peripheral artery disease.

Keywords: atherosclerosis; peripheral artery disease; intermittent claudication; amputation; critical limb ischemia; lipoprotein; statin; PCSK9 inhibitors; icosapent ethyl; inclisiran

Citation: Belur, A.D.; Shah, A.J.; Virani, S.S.; Vorla, M.; Kalra, D.K. Role of Lipid-Lowering Therapy in Peripheral Artery Disease. *J. Clin. Med.* **2022**, *11*, 4872. https://doi.org/10.3390/jcm11164872

Academic Editors: Nathan D. Wong and Patrick De Boever

Received: 25 June 2022
Accepted: 16 August 2022
Published: 19 August 2022

1. Introduction

Acute and chronic arterial atherothrombosis accounts for a high burden of cardiovascular (CV) morbidity and mortality globally [1,2]. Atherosclerosis affects arteries of all sizes and is the consequence of oxidized lipids that become entrapped in the extracellular matrix of the subendothelial space [3]. Arterial branch points and sites along the inner curvature of arteries that have low or oscillatory endothelial shear stress often serve as a nidus for atheroma formation. Atherosclerosis of the lower extremities is called peripheral artery disease (PAD). Although other arterial diseases can also cause ischemia of the legs (such as thromboangiitis obliterans, embolism, fibromuscular dysplasia, and vasculitides), atherosclerotic occlusion is the commonest cause of PAD in the US.

PAD has a gamut of clinical manifestations, ranging from asymptomatic disease to acute or chronic symptoms due to a combination of ischemia, thrombosis, and/or embolism. Chronic PAD can have a few different subtypes, such as (i) symptomatic disease with classic symptoms of intermittent claudication (IC), often diagnosed by an abnormal ankle brachial index (ABI) value of <0.9; (ii) asymptomatic PAD with either a normal or abnormal ABI; or (iii) having had a prior lower extremity (LE) arterial revascularization procedure. The leading cause of morbidity in PAD is loss in mobility and ambulation due to IC, which is ischemia-induced discomfort, cramping, heaviness, or frank pain in the affected limb precipitated by physical activity and relieved by rest. Patients are usually able to reliably relate what distance they can walk before IC appears, and this is called the claudication distance. As the disease advances, the claudication distance diminishes. In severe disease, chronic limb-threatening ischemia (CLTI) is the most feared complication and is associated with limb loss and mortality [4]. Other complications of PAD that add to morbidity and mortality include the development of arterial ulcers, gangrene, poor wound healing, and deep soft tissue and bone infections. Regardless of symptoms, PAD is a strong harbinger

of associated current or future CV disease and major adverse CV events (MACE). As an example, stroke and myocardial infarction (MI) are three and four times more likely, respectively, in patients suffering from PAD [5–7]. A reduced ABI has a two-fold higher risk of MI, angina, congestive heart failure, and cerebrovascular disease [8]; overall mortality in PAD correlates strongly with a decline in the ABI [9].

2. Role of Lipids in Atherosclerosis

Atherosclerosis is a multifactorial, lipoprotein-mediated condition that leads to plaque formation at vulnerable sites of arteries through inflammation, necrosis, fibrosis, and calcification over decades. Endothelial injury with subsequent accumulation of apolipoprotein B-containing lipoproteins, such as LDL and remnant lipoproteins, is the first step in the formation of atherosclerotic plaque in arteries (Figure 1) [10]. Hyperlipidemia can directly impair endothelial cell function by increasing free radical production, which accelerates the oxidation of cholesterol deposits in the endothelium. Oxidized lipoproteins are ingested by macrophages through scavenger receptors and accumulate in phagocytes that then transform into foam cells. Oxidized lipoproteins also stimulate the release of growth factors, cytokines, and chemokines that increase the recruitment of inflammatory cells into atherosclerotic lesions. Oxidized LDL exerts cytotoxic effects on endothelial cells and smooth muscle cells, which further potentiates endothelial cell dysfunction (Figure 2). Recent studies have explored the role of inflammation in the initiation and progression of plaque, such as neutrophils, normal-density granulocytes, and low-density granulocytes, especially in patients with chronic inflammatory disease states [11]. Atherosclerotic plaques may progress via fibrosis or calcification over decades, and eventually, a vulnerable plaque may undergo rupture, ulceration, or erosion, which then leads to acute thrombosis in the affected artery with catastrophic outcomes, such as MI, stroke, or CLTI.

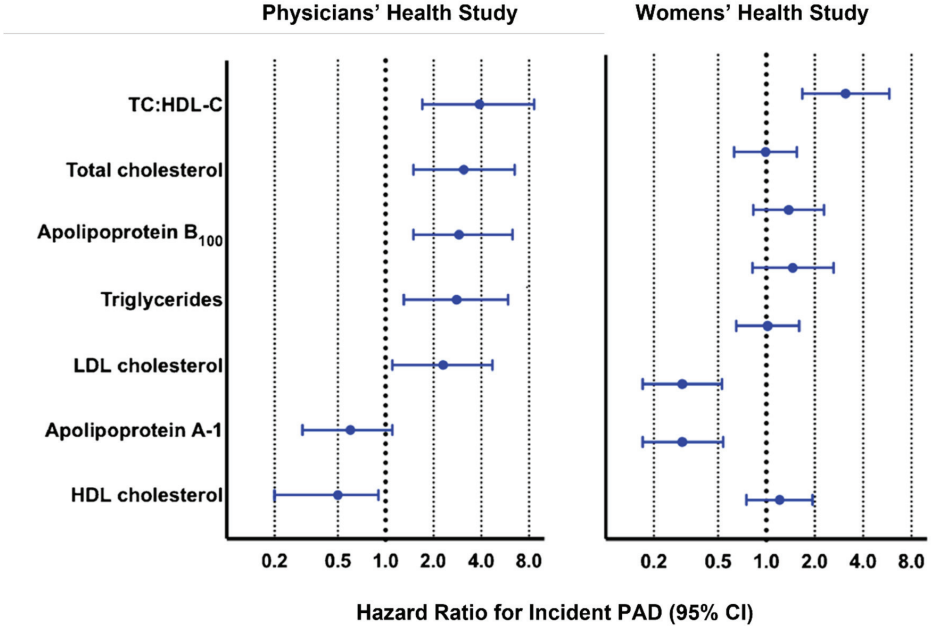

Figure 1. Left panel: Adjusted hazard ratio of lipids and apolipoproteins and PAD in the Physicians'

Health Study. Left panel: Adjusted hazard ratio of lipids and apolipoproteins and PAD in the Physicians' Health Study. Note relative risk and 95% confidence intervals for the top and bottom quartile of various lipid and lipoprotein levels after adjustment for smoking status, age, body mass index, frequency of exercise, presence of diabetes and hypertension, and family history of premature atherosclerotic disease. **Right panel**: Women's Health Study with hazard ratios and 95% confidence intervals for the top versus bottom tertile of various lipid and lipoprotein levels after adjustment for number of packs smoked over the years, age, body mass index, high-sensitivity C-reactive protein, and presence of hypertension, metabolic syndrome, prior lipid-lowering therapy, and hormonal therapy [12].

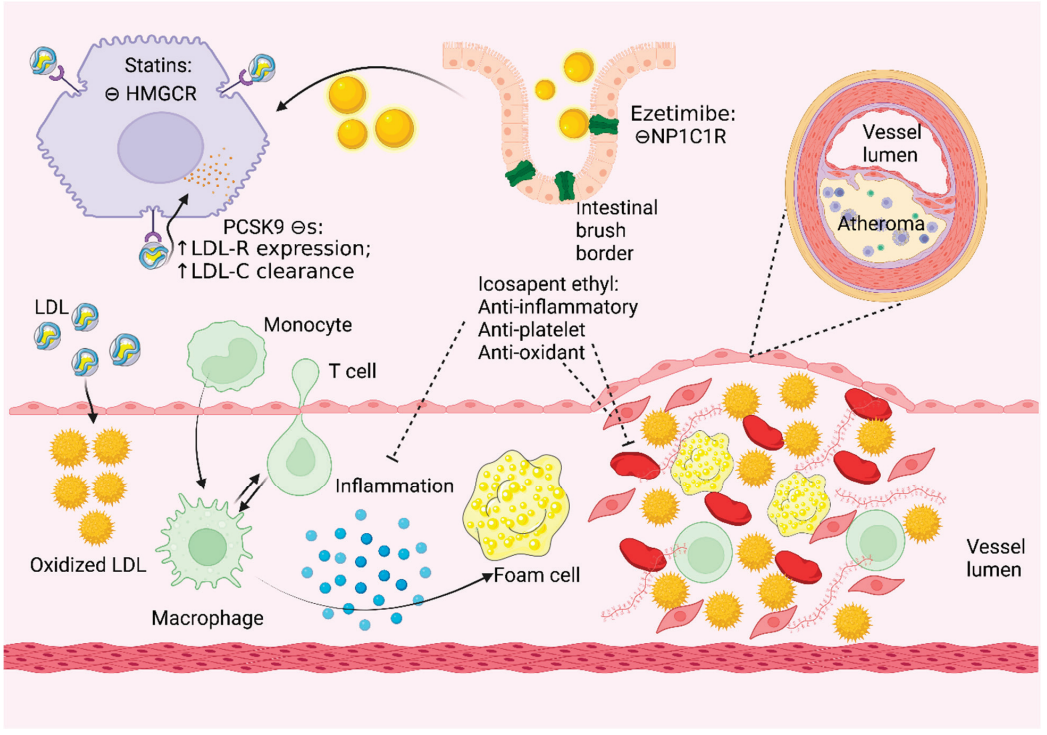

Figure 2. Role of oxidized lipoproteins in the development of atherosclerosis, with specific targets and mechanism of action of statins, ezetimibe, and PCSK9 inhibitors. HMGCR: 3-β-Hydroxy β-methylglutaryl-CoA reductase, LDL: Low-density lipoprotein, LDL-C: Low-density lipoprotein cholesterol, LDL-R: Low-density lipoprotein receptor, NP1C1R: Niemann–Pick C1-like 1 receptor, PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9.

3. Epidemiology and Clinical Burden of PAD

PAD is estimated to affect 10–25% people aged ≥55 years, and the prevalence increases with age to approximately 40% among people >80 years [13]. An estimated 8 to 10 million people in the USA and 200 million people worldwide suffer from PAD [14,15]. Males have a higher incidence of PAD compared to females, and black individuals are more likely to develop PAD than non-Hispanic white individuals [16]. However, despite efforts to increase screening for asymptomatic PAD with ABI and questionnaires to detect IC, the prevalence of this disease varies according to the population studied with underdiagnosis among Hispanic individuals and other racial and ethnic minorities [14,16]. The overall estimated prevalence of IC ranges from 1–4.5% in a population older than 40 years [6,17]. Approximately 10–30% of patients with PAD have some degree of IC. The prevalence and incidence of CLTI increase with age and are greater in men [16], with an incidence of 22 per

100,000 per year and affecting 1–2% of all patients with PAD. There is less data available on the incidence and prevalence of acute limb ischemia (ALI), with estimates of approximately 1–2% among patients with {Singh, 2021, Prescribing of Statins After Lower Extremity Revascularization Procedures in the US} symptomatic PAD [18]. CLTI has a mortality rate of ~25% in the first year after initial presentation and an estimated three-year limb loss rate as high as 40%, with five-year survival rate of <30%. Diabetic patients have a higher incidence of adverse outcomes and amputations [4,19]. Approximately one quarter of all patients with CLTI are not considered candidates for vascular surgery or endovascular procedures, and amputation is often the only option available. This corresponds to 120,000 amputations annually in the United States [20,21], with the overall incidence of amputation ranging from 112 to 250 per million per year. There is an association between recurrent CLTI due to the failure of LE revascularization and worse patient outcomes [22], and the bypass versus angioplasty in severe ischemia of the leg (BASIL) trial [23] demonstrated a re-intervention rate among 216 patients with CLTI treated by percutaneous transluminal angioplasty as high as 26% at one year. The increasing number of patients with CLTI and its overall poor prognosis has led to a higher need for novel therapies to induce angiogenesis, with the most emphasis being placed on gene and cell therapy.

PAD is often treated using a multifaceted approach, and treatment options depend on lipid levels, limb function, severity of symptoms, and presence of comorbidities, such as diabetes, smoking, and hypertension. Conservative medical management involves an exercise regimen and use of antiplatelet agents, antithrombotic drugs, and phosphodiesterase-3 inhibitors, such as cilostazol, when appropriate. Regardless of symptoms, all patients must receive lipid lowering therapy to reach goal lipid levels discussed below and should be counseled on a heart-healthy, low-fat diet. Complications of PAD and CLTI are often treated with invasive and expensive therapies that are associated with high morbidity and mortality directly and indirectly through limb loss, need for revascularization, and failure of conservative treatment leading to amputation. Early diagnosis and treatment of PAD is imperative in preventing complications that are frequently life- and limb-threatening.

4. Role of Statins in PAD

4.1. Mechanism of Action of Statins

Statins are recommended as first-line therapy in the treatment of patients with PAD to decrease the lipid plaque burden and reduce the risk of adverse CV events [6,7]. Statins competitively inhibit 3-β-Hydroxy β-methylglutaryl-CoA reductase, which is an enzyme responsible for the synthesis of mevalonic acid. This is a rate-limiting step in cholesterol synthesis. Inhibition of cholesterol synthesis causes an upregulation of LDL receptors on the surface of hepatocytes, thereby promoting greater hepatic uptake of LDL and reducing the circulating atherogenic low-density lipoprotein cholesterol (LDL-C) burden. In addition to promoting plaque stability, statins have also been associated with anti-inflammatory effects by inhibiting neointimal hyperplasia and vascular smooth muscle cell proliferation and increasing the release of nitric oxide, which allows for vasodilation and decreased platelet aggregation [24,25]. These pleiotropic effects of statins likely play a part in reducing downstream events by promoting plaque stability and some degree of plaque regression [26].

4.2. Clinical Outcomes Associated with Statin Use in Patients with PAD

One of the earliest studies involving statins was the Scandinavian Simvastatin Survival Study (4S) [27], a large clinical trial in which 4444 adults aged 35 to 70 years with prior MI or angina pectoris and with total serum cholesterol between 212.7 and 309.4 mg/dL were randomized to receive either a placebo or simvastatin 20–40 mg/day. Of the enrolled subjects, approximately 81% were males and 6% had symptomatic PAD with IC, 4% had diabetes, and 8% had coronary artery disease with previous bypass surgery or angioplasty at the time of enrollment. The mean baseline LDL-C level was 188.3 ± 25.9 mg/dL. Subjects were followed prospectively for a median of 5.4 years. The 4S study reported a 38% risk

reduction in new or worsening IC in the treatment arm [relative risk (RR) 0.62 (0.44–0.88), $p = 0.008$]. There was a 28% reduction in cerebrovascular event rate indicating that statins likely have a generalized plaque-stabilizing effect that is not confined to the coronary arterial bed.

The next study to show a similar benefit of statins was the Heart Protection Study (HPS) Collaborative [28], which enrolled 6748 patients with PAD and randomly assigned them to receive either simvastatin 40 mg or placebo. The mean follow-up period for this study was 5 years. Investigators found an overall 16% relative reduction in the rate of a first peripheral vascular event following randomization ($p = 0.006$). Furthermore, there was a 22% relative risk reduction in the rate of first vascular events ($p \leq 0.0001$) and a 20% relative risk reduction in non-coronary revascularization in PAD patients ($p = 0.002$). These benefits were independent of the pre-treatment lipid levels and the extent of PAD. The absolute reduction in major vascular events at baseline was found to be greater in patients with PAD (63 [SE 11] per 1000) than in those without (50 [SE 7] per 1000), reflecting a greater absolute reduction in revascularization among participants with PAD (42 [SE 9] per 1000) compared to those without (19 [SE 5] per 1000).

In a large analysis of benefits of statins in PAD, Kumbhani et al., analyzed 5861 patients with PAD enrolled in the REACH study (REduction of Atherothrombosis for Continued Health) [29] and reported on the rates of major adverse limb events (MALE) (defined as worsening claudication or a new episode of CLTI, any percutaneous or surgical revascularization, or amputation). They found an 18% relative risk reduction in MALE [hazard ratio (HR) 0.82, $p = 0.0013$] and 17% lower risk in the combined endpoint of CV death, non-fatal MI, or non-fatal stroke [hazard ratio (HR) 0.83, $p = 0.01$].

The first line treatment in patients with critical limb ischemia (CRITISCH) was an observational registry [30] that analyzed PAD outcomes and benefits of statin treatment. Their prospective observational cohort included 445 patients with CLTI who were on statin therapy and 371 patients who were not on statin therapy. Over a median follow-up period of 2 years, authors observed lower rates of amputation-free survival (HR 0.45, $p = 0.001$) and lower odds of major adverse CV and cerebral events [odds ratio (OR) 0.41, $p = 0.001$] in the group who were on statin therapy.

Similarly, the EUCLID trial (Examining the Use of Ticagrelor in Peripheral Artery Disease) [31] noted that the patients with a major amputation had a lower prevalence of statin use as compared to those who did not have an amputation (53% vs. 73.6%, $p \leq 0.001$). They reported a lower rate of major amputation associated with statin use in both the overall PAD patient cohort (HR = 0.52, $p < 0.001$) and patients stratified by baseline CLTI status (HR = 0.47 $p < 0.001$).

In another large analysis of statin benefit, Arya et al., studied 155,647 veterans with PAD over a median follow-up period of 5.9 years and evaluated lower extremity (LE) amputations and mortality. Statin intensity exposure (high-intensity statin versus low-to-moderate–intensity statin versus antiplatelet therapy but no statin use) was determined within 1 year of diagnosis of PAD. Authors reported a significant reduction in mortality and amputation risk, respectively, in the low-to-moderate–intensity statin group (HR, 0.83; 95% CI, 0.81–0.85 and HR, 0.76; 95% CI, 0.72–0.80) when compared to antiplatelets only. High-intensity statins had a more significant benefit for both outcomes with a 30% risk reduction in mortality (HR, 0.70; 95% CI, 0.67–0.73) and a 39% risk reduction in amputation risk (HR, 0.61; 95% CI, 0.56–0.66) when compared to the antiplatelet-only group. In a 3-level propensity score-matched analysis comparison, 30,780 patients were matched in a 1:1:1 high-intensity statin, low-to-moderate–intensity statin, and active comparator group (antiplatelet drugs only). There was a statistically significant reduction in amputation risk (crude HR, 0.69; 0.61–0.76 and adjusted HR, 0.60; 0.52–0.69) and all-cause mortality (crude HR, 0.72; 0.68–0.76 and adjusted HR, 0.70; 0.66–0.75) for high-intensity statin users when compared to those taking only antiplatelet medications. There was a modest but statistically significant reduction in amputations (crude HR, 0.84; 0.75–0.93 and adjusted HR, 0.80; 0.70–0.91) and mortality (crude HR, 0.83; 0.79–0.88 and adjusted HR, 0.80; 0.75–0.85)

for low-to-moderate–intensity statin users when compared to those taking only antiplatelet medications [32]. The risk reduction in amputation and mortality outcomes with high-intensity statins continued to be significant after propensity score matching and sensitivity and subgroup analyses.

Another observational study of 69,332 patients in Taiwan with diabetes and PAD assessed risk reduction in lower extremity amputations with statin use. Authors found a significantly lower risk of lower extremity amputation (HR 0.75, CI 0.62–0.90) and total amputations (HR 0.58, CI 0.36–0.93) among patients on statins as compared to those not on statins [33].

A Cochrane meta-analysis of 18 trials consisting of 10,049 patients with PAD was reported in 2009—the overall results surprisingly revealed no significant association of lipid-lowering treatment with either mortality or CV outcomes. However, after excluding an outlier study, the modified results showed a significant reduction in CV events (OR 0.74, CI 0.55–0.98) [34]. The study that was excluded in the modified analysis was the PQRST trial, which showed not only a reduction in total cholesterol and LDL-C but also high-density lipoprotein cholesterol (HDL-C) with probucol, the lipid-lowering agent studied in that trial [35]. Probucol may have had detrimental effects on outcomes via other mechanisms.

In a recent meta-analysis by Pastori et al., regarding statins and MALE in patients with PAD, the authors analyzed 51 studies that included 138,060 patients with PAD. Patients on statins had a 30% reduction in MALE (HR 0.70, CI 0.61–0.81) and a 35% reduction in amputations (HR 0.65, CI 0.52–0.82). The statin group also had a lower risk of all-cause mortality (HR 0.61, CI 0.54–0.68), CV death (HR 0.59, CI 0.46–0.78), composite CV endpoints (HR 0.66, CI 0.59–0.74), and ischemic stroke (HR 0.72, CI 0.62–0.83) [36]. Kokkinidis et al., conducted a systematic review and meta-analysis of 19 studies, including 26,985 patients with CLTI, and evaluated the effect of statin therapy on CV and limb events. Patients on statin therapy had a reduction in risk of major adverse CV and cerebral events (HR 0.5, CI 0.39–0.66, $I^2 = 0$) and fatal events (HR 0.62, CI 0.52–0.75, $I^2 = 41.2$) with a 25% decreased risk of amputation (HR 0.75, CI 0.59–0.95) [37].

Statins have also been shown to improve walking distance. Mondillo et al., reported a 90-m increase in pain-free walking distance in PAD patients after 6 months of simvastatin therapy ($p < 0.005$) [38]. In addition to increasing pain-free walking distance [39], statins have been shown to increase total walking distance [40–44], reduce severity of IC [45] and improve overall quality of life [43,46,47], especially when combined with an exercise regimen [48].

Multiple studies have described the benefits of statins in patients with established PAD or at moderate to high risk of vascular events as described above. However, until the last decade, the role of statin therapy in patients at lower risk of vascular events was not known. The Cholesterol Treatment Trialists published a meta-analysis of 27 randomized trials in 2012. Based on their baseline risk of 5-year major vascular events ranging from <5% to ≥30% on control therapy (no statin or low-intensity statin), participants were sorted into five categories. Major vascular events included major coronary events (nonfatal MI or coronary death), strokes, or coronary revascularization. Authors found a proportional reduction in major vascular events that was at least as high in the two lowest risk categories as in the higher risk categories (RR per 1 mmol/L reduction from lowest to highest risk: 0.62 [99% CI 0.47–0.81] for the <5% risk group, 0.69 [99% CI 0.60–0.79] for the ≥5% to <10% risk group, 0.79 [99% CI 0.74–0.85] for the ≥10% to <20% risk group, 0.81 [99% CI 0.77–0.86] for the ≥20% to <30% risk group, and 0.79 [99% CI 0.74–0.84] for the ≥30% risk group; trend $p = 0.04$). Furthermore, the study found that there were significant reductions in major coronary events (RR 0.57, 99% CI 0.36–0.89, $p = 0.0012$ and 0.61, 99% CI 0.50–0.74, $p < 0.0001$) and in coronary revascularizations (RR 0.52, 99% CI 0.35–0.75 and 0.63, 99% CI 0.51–0.79; both $p < 0.0001$) in the two lowest risk category groups, respectively. Among participants with 5-year risk of major vascular events <10%, risk reduction in stroke (RR per 1.0 mmol/L LDL-C reduction 0.76, 99% CI 0.61–0.95, $p = 0.0012$) was similar to that seen in higher risk categories (trend $p = 0.30$). Even among participants without a history of vascular disease,

statins reduced the risks of vascular (RR per 1.0 mmol/L LDL-C reduction 0.85, 95% CI 0.77–0.95) and all-cause mortality (RR 0.91, 95% CI 0.85–0.97). Authors found no evidence that reduction in LDL-C with a statin increased cancer incidence (RR per 1.0 mmol/L LDL-C reduction 1.00, 95% CI 0.96–1.04), cancer mortality (RR 0.99, 95% CI 0.93–1.06), or other non-vascular mortality. The study concluded that, among individuals with a 5-year risk of major vascular events lower than 10%, each 1 mmol/L (~38 mg/dL) reduction in LDL-C produced an absolute reduction in major vascular events of about 11 per 1000 over 5 years. Further, the proportional reduction in events in patients with established vascular disease (which included patients with PAD) was similar to those without established vascular disease; however, absolute event rates are higher in those with established vascular disease, suggesting a larger absolute benefit with statin therapy in this patient population. This large analysis thus firmly established that the benefit of statins exceeded the risk of therapy [49].

4.3. Current Guidelines

Current European guidelines recommend achieving a $\geq$50% reduction in blood LDL-C levels to <55 mg/dL in patients with atherosclerotic cardiovascular disease (ASCVD), which includes those with PAD. A high-intensity statin, at the highest tolerated dose, should be prescribed as first-line therapy given the evidence showing reductions in MALE and MACE. Addition of ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is recommended if the LDL-C remains above goal (based on the degree of risk, ESC guidelines give a goal of either <55 or <40 mg/dL in those with recurrent ASCVD events) [7]. The multi-society guidelines for management of patients in 2018 classified PAD as an ASCVD equivalent alongside MI, stroke, and CAD [50]. The 2016 AHA/ACC guidelines on PAD management also give statins a Class IA recommendation in patients with PAD; although PAD itself will not make a patient eligible for LDL-C lowering to <70 mg/dL per the ACC/AHA guidelines, it is one of the major ASCVD events that define the "very high-risk ASCVD" category [6]. Based on these guidelines, we propose a flowchart to approach lipid management in patients with PAD (Figure 3).

4.4. Underuse of Statins in PAD

Unfortunately, despite the substantial database for benefit of statins and other lipid-lowering therapies in PAD, there remains suboptimal usage of these drugs in PAD patients [51] The PREVENT III trial noted that 54% of patients with CLTI were not on any lipid-lowering therapy [52]. The observational study by Arya et al., discussed above also reported similar underuse of statins—the use of high-intensity statins was the lowest (6%) in PAD patients, as compared to patients with either coronary or carotid artery disease (18.4%). This highlights clinician and patient underappreciation of PAD as a systemic atherosclerotic disease. In the observational study of Hess et al., that included 250,103 patients with PAD, ~40% were not on any lipid-lowering therapy despite the observed increased risk of MALE and MACE. Similar to the prior observation, lipid-lowering therapies were used less often and at lower doses for PAD patients in contrast to coronary artery disease (CAD) patients who were more frequently prescribed high-intensity statins [53]. Colantonio et al., also noted similar findings in their database—although the risk of CV events in patients with PAD was comparable to those with CAD (HR 0.91, CI 0.86–0.95), the former was significantly less likely to have been prescribed statins. In addition, having coexisting CAD or cerebrovascular disease increased the rate of statin prescription in the PAD population (statins were prescribed to 33.9% of patients with PAD only; CAD only: 51.7%, PAD + cerebrovascular disease: 46.5%; PAD + CAD: 50.2%; PAD + CAD + cerebrovascular disease: 56.2%) [54].

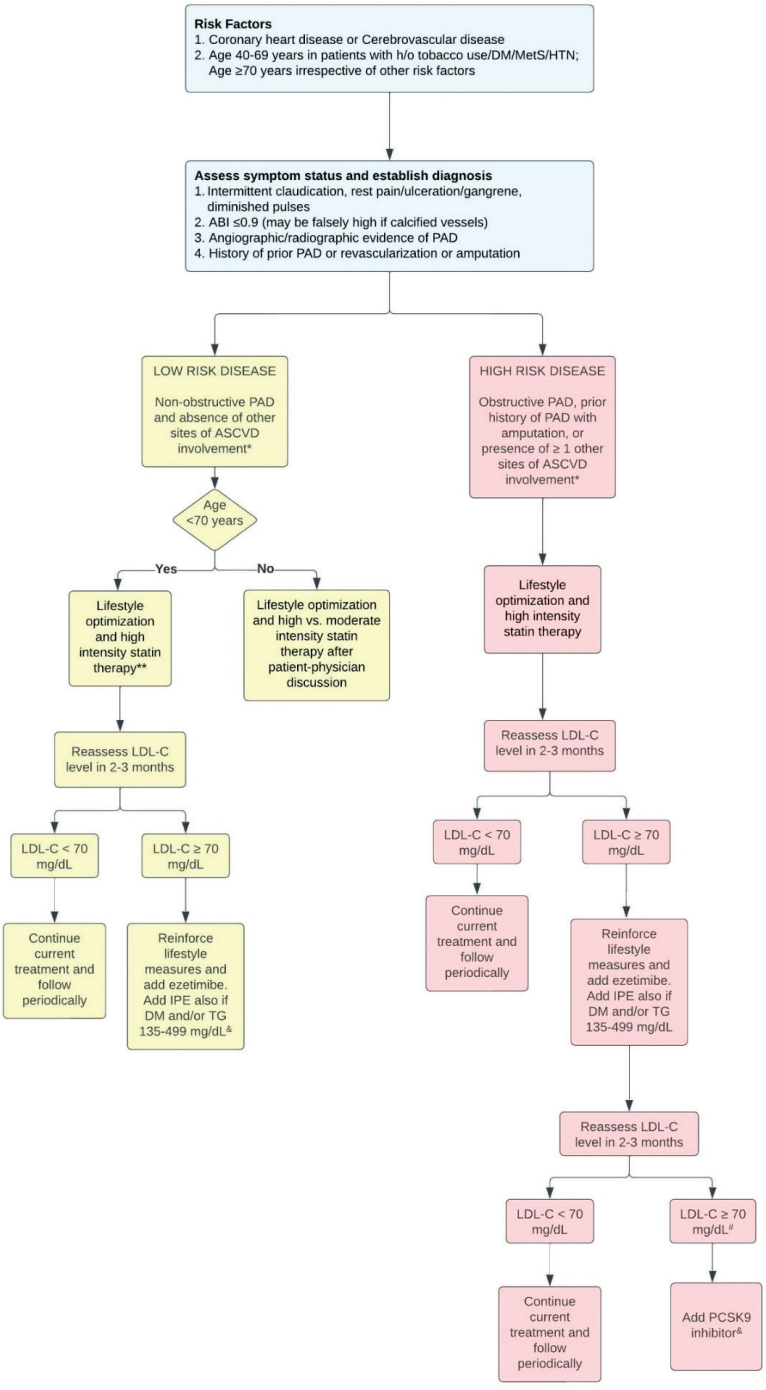

Figure 3. University of Louisville approach to PAD treatment based on current guidelines. * ASCVD disease includes CAD, PAD, TIA, stroke, history of myocardial infarction, aortic aneurysm, carotid atherosclerotic disease, history of coronary artery bypass grafting, or percutaneous coronary intervention. Risk factors include HTN, HLD, DM, age ≥70 years, LDL-C >100 mg/dL, high-sensitivity

CRP > 2 mg/dL, chronic kidney disease, and Lp(a) > 125 nmol/L. ** High-intensity statins include atorvastatin 40–80 mg and rosuvastatin 20–40 mg. Moderate-intensity statins include atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, and pravastatin 40–80 mg. & Bempedoic acid may also be considered, but it is pending data from an ongoing cardiovascular outcomes trial. # LDL-C > 55 mg/dL if in a very-high risk group as defined in the 2019 ESC guidelines [7]. CAD: Coronary artery disease, PAD: Peripheral artery disease, HTN: Hypertension, HLD: Hyperlipidemia, DM: Diabetes Mellitus, MetS: Metabolic syndrome, TIA: Transient ischemic attack, LDL-C: Low-density lipoprotein cholesterol, ASCVD: Atherosclerotic cardiovascular disease, TG: Triglycerides, IPE: icosapent ethyl, PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9.

5. Role of PCSK9 Inhibitors in Patients with PAD

5.1. Mechanism of Action of PCSK9 Inhibitors

PSCK9 is a serine protease involved in the degradation of LDL receptors on hepatocytes, which leads to higher plasma LDL-C levels. PSCK9 inhibitors, such as alirocumab and evolocumab, are humanized monoclonal antibodies that bind the PSCK9 protein, inhibiting its attachment to the LDL receptor and, therefore, decrease plasma LDL-C concentrations [55]. Statins upregulate PCSK9 levels—thus, combined statin and PCSK9 inhibitor therapy is especially beneficial in patients who are unable to reach therapeutic LDL-C lowering with statin therapy alone [56].

5.2. Clinical Outcomes of PCSK9 Inhibitors in Patients with PAD

The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial was a double-blinded randomized control trial that included 27,564 patients with stable atherosclerotic CV disease on statin therapy. Subjects were randomized to receive evolocumab (140 mg every 2 weeks or 420 mg monthly) vs. placebo. The FOURIER trial was continued till at least 1630 patients reached the composite endpoint of CV death, MI, or stroke, thus providing a 90% power to detect a relative reduction of $\geq$15% for the secondary endpoint [57]. Compared to placebo, patients receiving evolocumab were noted to have a 19% reduction in first acute arterial events (HR 0.84, CI 0.74–0.88) and a 24% reduction in total event rate (HR 0.76, CI 0.69–0.85) in the first year. Individual event rates of acute coronary events, peripheral vascular events, and cerebrovascular events also showed a decline, with a HR of 0.83 (CI 0.75–0.91), 0.58 (CI 0.38–0.88) and 0.77 (CI 0.65–0.92), respectively [58].

Bonaca et. al., conducted a subgroup analysis of 3647 patients with PAD in this trial with the primary endpoint being a composite of CV death, MI, stroke, hospital admission for unstable angina, or coronary revascularization. They evaluated MALE, ALI, major amputation, or urgent peripheral revascularization for ischemia. The evolocumab group had a 21% reduction in the primary endpoint (HR 0.79, CI 0.66–0.94, $p = 0.0098$) and a 42% reduction (HR 0.58, CI 0.38–0.88, $p = 0.0093$) in MALE [59]. Additionally, the absolute risk reduction in the primary endpoint was higher in the PAD subgroup than in those without PAD (3.5% vs. 1.6%) [59,60].

The ODYSSEY outcomes (evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab) trial was a multicenter double-blinded placebo-controlled trial with a median duration of 2.8 years follow-up involving 18,924 patients with a history of an acute coronary syndrome in the last 12 months, LDL-C at least 70 mg/dL, or non-HDL-C at least 100 mg/dL/or apoB level of at least 80 mg/dL on high-intensity or maximally tolerated dose of statin. The primary endpoint of the study was a composite of death from coronary artery disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. The primary endpoint rate was reduced in the alirocumab group by 15% (HR 0.85, CI 0.78–0.93, $p < 0.001$) [61]. A subgroup analysis of the ODYSSEY outcomes trial investigated PAD events after ACS. Alirocumab was found to reduce the risk of PAD events (HR 0.69, 95% CI 0.54–0.89, $p = 0.004$) [61,62].

Based on the above data, current guidelines recommend consideration of PCSK9 monoclonal antibodies in patients who do not meet LDL-C treatment goals with dietary modification and other lipid-lowering therapies, such as maximally tolerated statin plus ezetimibe [50].

6. Role of Icosapent Ethyl (IPE) in PAD

IPE is an ethyl ester of eicosapentaenoic acid and reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion, thereby enhancing TG clearance from circulating VLDL particles. Patients with elevated TG levels are at increased risk for ischemic events due to an increase in remnant lipoproteins. The REDUCE-IT trial enrolled 8179 patients who were randomized to receive IPE vs. placebo. The primary endpoint of this study was a composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. Among patients with TG levels 135–400 mg/dL despite the use of statins, a primary end-point event occurred in 17.2% of the patients in the IPE group, as compared with 22.0% of the patients in the placebo group (HR, 0.75; 95%, CI 0.68 to 0.83; $p < 0.001$) [63]. Furthermore, the EVAPORATE substudy of coronary CT imaging of plaque features also demonstrated a significant regression of low-attenuation coronary plaque volume on multidetector CT in patients who were randomized to IPE compared to placebo, over 18 months [64].

Current guidelines recommend that if the TG levels remain high after diet and exercise, IPE may be added to statin for reduction in CV risk [65]; however, their specific benefit in PAD patients remains to be explored.

7. Role of Fibrates, Ezetimibe and Niacin in PAD

The role of fibrates, ezetimibe, and niacin in PAD has mostly been studied with these drugs being used as an adjunct to statin therapy. Sohn et al., compared outcomes for patients with diabetes taking statins to those taking non-statin lipid-lowering agents, such as fibrates, bile acid sequestrants, nicotinic acid, and cholesterol absorption inhibitors (including ezetimibe) and found that those patients taking non-statin lipid therapy did not show a reduction in LE amputation rates [66]. A study by West et al., showed that statin initiation with or without ezetimibe in statin-naïve patients halted the progression of PAD. When ezetimibe was added to patients previously on statins, PAD paradoxically progressed—the authors concluded that ezetimibe's effect on PAD seemed to depend upon the relative timing of ezetimibe initiation with respect to statin therapy. However, this study had a few shortcomings, such as it was underpowered and small, 23% (20/87) of the patients initially enrolled in the study were not included in the final analysis, there was no placebo arm, and the endpoint was superficial femoral artery vessel wall plaque volume change over 2 years (as measured by MRI) rather than CV events or MALE [67].

8. Novel Drugs: Inclisiran

Inclisiran is a small interfering RNA that inhibits hepatic PCSK9 and upregulates the number of LDL-receptors on the hepatocytes. Inclisiran was approved in the European Union in 2020 for use in adults with primary hypercholesterolemia or mixed dyslipidemia based on the results of the ORION trials [68]. Inclisiran was shown to be effective in reducing LDL-C in patients with elevated LDL-C who were on maximally tolerated statin therapy. In a study conducted by Ray et al., 501 patients with high LDL-C levels (LDL-C > 70 mg/dL for patients with ASCVD or >100 mg/dL for those without) were randomly assigned to receive inclisiran or placebo. The primary endpoint was the change from baseline in LDL-C levels at 180 days. Safety data were available through day 210 and data on LDL-C and PCSK9 levels were available through day 240. At 180 days, the least-squares mean reductions in LDL-C levels ranged from 27.9 to 41.9% after a single dose of inclisiran and 35.5 to 52.6% after two doses ($p < 0.001$ for all comparisons with placebo). Greatest reduction in LDL-C levels was seen with the two-dose 300-mg inclisiran regimen; 48% of the patients who received this regimen had an LDL-C level below 50 mg/dL at 180 days. The reduction

in LDL-C and PCSK9 levels from baseline brought about by inclisiran persisted even at day 240 irrespective of the initial regimen [69]. The ongoing ORION-4/TIMI 65 trial is studying CV outcomes in patients with ASCVD or at high risk. The effects of inclisiran in PAD remain to be explored.

9. Role of Apheresis in PAD

The LIPAD study enrolled 213 patients with symptomatic PAD and matched them to controls for sex, age, and presence of diabetes. Lipoprotein (a) [Lp(a)] concentrations above the 75th percentile of the entire cohort were significantly associated with PAD with an odds ratio of 3.73 even after adjustment for potential confounding factors, highlighting the role of elevated Lp(a) in PAD [70]. The role of lipoproteins in PAD was confirmed in the MESA trial [16]. Among the 4618 participants enrolled in this study, the mean age was 62 ± 10 years. Mean Lp(a) was 30 ± 32 mg/dL and median (interquartile range) was 18 (8–40 mg/dL), and 11% of all participants had established PAD at the time of enrollment. After adjustment for traditional CV disease risk factors and interleukin-6, fibrinogen, D-dimer, and homocysteine levels, authors found an association between logarithmic increase in Lp(a) levels and higher odds for PAD (OR, 1.12; 95% CI, 1.01–1.25). The EPIC-Norfolk study showed that Lp(a) levels in the highest quartile were more predictive of incident PAD (adjusted HR 2.06) compared to CAD (adjusted HR 1.33) [71].

Apheresis for high Lp(a) has been used in selective patients with ASCVD especially in Germany [72,73]; however, its effects of reducing Lp(a) levels have been studied more for MACE rather than MALE [74–77]. Prospective cohort studies strongly suggest a causal relationship between elevated Lp(a) levels and PAD. However, data on the efficacy of lipoprotein apheresis in patients with PAD and elevated Lp(a) are scarce [78]. The HORIZON trial is an ongoing clinical trial to assess the impact of LP(a) lowering with Pelacarsen (TQJ230) on MACE in patients with CV disease [79].

A summary of landmark studies on the role of lipid-lowering therapy in PAD is described below (Table 1).

Table 1. Summary of landmark studies on the role of lipid-lowering therapy in PAD.

Study (Year)	Study Design	Sample Size	Patient Population	Intervention	Median Follow Up Time	Outcome	Interpretation
Pedersen (4S Study), 1994 [27]	Randomized controlled trial (RCT)	4444	MI or angina pectoris, serum cholesterol between 213–309 mg/dL	Simvastatin 20–40 mg daily vs. placebo	5.4 years	Intermittent claudication	Statin therapy may help in plaque stabilization and may also have a general anti-atherosclerotic effect.
Heart Protection Study Collaborative Group, 2002 [28]	RCT	6748	History of PAD, CAD, stroke, diabetes, treated hypertension	Simvastatin 40 vs. placebo	5 years	First major vascular event	Statin treatment showed improvement in MACE, overall revascularizations in all patients with PAD irrespective of their pre-treatment lipid levels.
Kumbhani (REACH registry), 2014 [29]	Retrospective review	5861	Symptomatic PAD	Statin vs. no statin	4 years	Primary adverse limb events, primary endpoints of CV death, non-fatal MI, or non-fatal stroke	Patients taking statins had significantly lower risk of MACE and MALE at 4 years.
Stavroulakis (CRITISCH registry), 2017 [30]	Retrospective analysis of prospectively collected data	816	Presence of new onset CLTI	Statin vs. no statin	2 years	MACE and cerebral events, amputation free survival	Statin treatment showed improvement in amputation-free survival and overall cardio/cerebrovascular events in patients with new onset CLTI
Arya, 2018 [32]	Retrospective observational cohort study	155,647	Incident PAD	High-intensity statin therapy vs. low-to-moderate–intensity statin vs. other or no therapies for PAD	5.9 years	High-intensity statin vs. antiplatelet therapy: Amputation rates, low-to-moderate–intensity statins vs. antiplatelet therapy only: Amputation rates	Statin therapy showed reduced risk of amputation and overall morality as compared to antiplatelet therapy and high-,intensity statin therapy noted more pronounced improvement in comparison to low–moderate-intensity statins.
Hsu, 2017 [33]	Retrospective observational cohort study	69,332	≥20 years old with diabetes and PAD	Statin vs. non-statin lipid treatments vs. non-user group	5.7 years	Statin vs. non statin user, incident LE amputation risk, in-hospital CV death, and all-cause mortality	Statin therapy noted decreased risk of incident and total amputations in patients with diabetes and PAD. It also showed improvement in CV and mortality outcomes.
Aung, 2007 [34]	Cochrane meta-analysis	10,049	PAD	Lipid lowering treatment vs. none	NA	Total CV events, total coronary events	Lipid lowering therapy improves CV outcomes in patients with PAD.
Pastori, 2020 [36]	Meta-analysis	138,060	PAD	Statins vs. no statins	NA	MALE, amputations, all-cause mortality, CV deaths, and ischemic stroke	Statin therapy in PAD patients reduces adverse limb outcomes and cardio and cerebrovascular events, as well as overall mortality.

Table 1. *Cont.*

Study (Year)	Study Design	Sample Size	Patient Population	Intervention	Median Follow Up Time	Outcome	Interpretation
Kokkinidis, 2020 [37]	Meta-analysis	26,985	Existing CLTI	Statins vs. no statins	NA	Major adverse CV and cerebral events, amputations	Statin use can decrease overall CV and cerebral outcomes in addition to overall mortality. It also might decrease amputation rates, but the data was noted to have significant heterogeneity.
Mondillo, 2003 [38]	RCT	86	PAD (Fontaine stage II), intermittent claudication and cholesterol levels >220 mg/dL	Simvastatin 40 mg daily vs. placebo	0, 3 and 6 months	Pain-free walking distance at 6 months, total walking distance	Simvastatin therapy in patients with pre-existing PAD, IC and hypercholesterolemia showed improvement in 6-month pain-free walking distance and total walking distance.
Mihaylova (Cholesterol Treatment Trialists group), 2012 [49]	Meta-analysis	134,537	NA	Statin vs. no statin	NA	Major vascular event in patients at low 5-year risk of major vascular event	Even in patients with low 5-year major vascular event risk, low-dose statins showed absolute reduction in major vascular events.
Oyama (FOURIER), 2018 [58] Bonaca (FOURIER Insights), 2021 [59]	RCT	27,564	Prior MI, non-hemorrhagic stroke, or symptomatic PAD, with LDL ≥70 mg/dL or non-HDL-C ≥100 mg/dL while on high- or moderate-intensity statin +/− ezetimibe	Evolucumab vs. placebo	2.2 years	First acute arterial event, total event rate, ACS, peripheral vascular events, cerebrovascular events	Addition of evolocumab over statin therapy with or without ezetimibe improves vascular outcomes in all territories.
Schwartz (ODYSSEY OUTCOMES), 2018, 2020 [61,62]	RCT	18,924	History of ACS in last 12 months, LDL-C ≥70 mg/dL, HDL-C at least 100 mg/dL, apoB at least 80 mg/dL on high-intensity or maximally tolerated dose of statin	Alirocumab vs. placebo	2.8 years	Composite death from CAD, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization	Alirocumab also shows improvement in overall CV outcomes when prescribed in addition to maximally tolerated or high-dose statin therapy. It also showed improvement in PAD and venous thromboembolism outcomes in these patients.

10. Conclusions

The impact of traditional risk factors, such as age, diabetes, elevated blood pressure, smoking, and high levels of LDL-C and Lp(a) on the risk of developing atherosclerosis and PAD has been well established [80]. Based on the above studies, there is a clear benefit of lipid-lowering therapy in patients with PAD. However, this clinical entity, unfortunately, continues to be underdiagnosed and undertreated when compared to coronary and cerebrovascular atherosclerosis, and there is a significant racial and socioeconomic disparity in the diagnosis and management of PAD.

Advances in basic science over the last three decades have established a fundamental role for inflammation in mediating all stages of atherosclerosis from initiation through progression and, ultimately, the thrombotic complications of this disease [81,82]. Decreased levels of LDL-C, better blood pressure control, and lower incidence of smoking have brought about an evolution in the risk factor profile for development of atherosclerosis. There is a focus on triglyceride-rich lipoproteins in addition to LDL as culprits in atherosclerosis. Non-traditional risk factors for atherosclerosis, such as disturbed sleep, the gut microbiome, physical inactivity, air pollution, and environmental stress, have also gained consideration. Both traditional and emerging risk factors for atherosclerosis are tied together by inflammatory pathways and leukocytes that have been incriminated in altering the behavior of arterial wall cells [83]. The role of these novel, non-traditional risk factors in the development and progression of PAD remains to be explored.

Atherosclerosis and PAD bear significant morbidity and mortality and form an important part of contemporary clinical practice. Preventive strategies, such as diet and lifestyle modification and lipid-lowering pharmacotherapy, form the cornerstone of prevention and treatment of PAD and its complications.

Author Contributions: A.D.B.: Draft manuscript preparation, figure preparation. A.J.S.: Draft manuscript preparation, figure preparation. S.S.V.: Draft manuscript preparation. M.V.: Figure preparation. D.K.K.: Study conception and design, draft manuscript preparation, figure preparation. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This paper is a review of the existing literature and involved no patient contact. Thus, the study did not require ethical approval from institutional review boards.

Informed Consent Statement: Not applicable as there was no patient contact or patient enrollment.

Data Availability Statement: Not applicable.

Conflicts of Interest: Belur A.D.—None. Shah A.J.–None. Virani S.S.—Research support: Department of Veterans Affairs, NIH, Tahir and Jooma Family. Honorarium—American College of Cardiology (Associate Editor for Innovations, acc.org). Vorla M.—None. Kalra D.K.—None.

References

1. Wendelboe, A.M.; Raskob, G.E. Global Burden of Thrombosis: Epidemiologic Aspects. *Circ. Res.* **2016**, *118*, 1340–1347. [CrossRef] [PubMed]
2. Palasubramaniam, J.; Wang, X.; Peter, K. Myocardial Infarction-From Atherosclerosis to Thrombosis. *Arter. Thromb. Vasc. Biol.* **2019**, *39*, e176–e185. [CrossRef] [PubMed]
3. Berliner, J.A.; Navab, M.; Fogelman, A.M.; Frank, J.S.; Demer, L.L.; Edwards, P.A.; Watson, A.D.; Lusis, A.J. Atherosclerosis: Basic Mechanisms. Oxidation, Inflammation, and Genetics. *Circulation* **1995**, *91*, 2488–2496. [CrossRef] [PubMed]
4. Krishna, S.M.; Moxon, J.V.; Golledge, J. A Review of the Pathophysiology and Potential Biomarkers for Peripheral Artery Disease. *Int. J. Mol. Sci.* **2015**, *16*, 11294–11322. [CrossRef]
5. Knowles, J.W.; Assimes, T.L.; Li, J.; Quertermous, T.; Cooke, J.P. Genetic Susceptibility to Peripheral Arterial Disease: A Dark Corner in Vascular Biology. *Arter. Thromb. Vasc. Biol.* **2007**, *27*, 2068–2078. [CrossRef] [PubMed]
6. Gerhard-Herman, M.D.; Gornik, H.L.; Barrett, C.; Barshes, N.R.; Corriere, M.A.; Drachman, D.E.; Fleisher, L.A.; Fowkes, F.G.R.; Hamburg, N.M.; Kinlay, S.; et al. 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **2017**, *135*, e726–e779. [CrossRef] [PubMed]

7. Belch, J.J.F.; Brodmann, M.; Baumgartner, I.; Binder, C.J.; Casula, M.; Heiss, C.; Kahan, T.; Parini, P.; Poredos, P.; Catapano, A.L.; et al. Lipid-Lowering and Anti-Thrombotic Therapy in Patients with Peripheral Arterial Disease: European Atherosclerosis Society/European Society of Vascular Medicine Joint Statement. *Atherosclerosis* **2021**, *338*, 55–63. [CrossRef]
8. Fowkes, F.G.R.; Murray, G.D.; Butcher, I.; Folsom, A.R.; Hirsch, A.T.; Couper, D.J.; Debacker, G.; Kornitzer, M.; Newman, A.B.; Sutton-Tyrrell, K.C.; et al. Development and Validation of an Ankle Brachial Index Risk Model for the Prediction of Cardiovascular Events. *Eur. J. Prev. Cardiol.* **2014**, *21*, 310–320. [CrossRef]
9. Criqui, M.H.; Aboyans, V. Epidemiology of Peripheral Artery Disease. *Circ. Res.* **2015**, *116*, 1509–1526. [CrossRef]
10. Morita, S. Metabolism and Modification of Apolipoprotein B-Containing Lipoproteins Involved in Dyslipidemia and Atherosclerosis. *Biol. Pharm. Bull.* **2016**, *39*, 1–24. [CrossRef]
11. Sanda, G.E.; Belur, A.D.; Teague, H.L.; Mehta, N.N. Emerging Associations Between Neutrophils, Atherosclerosis, and Psoriasis. *Curr. Atheroscler. Rep.* **2017**, *19*, 53. [CrossRef]
12. Aday, A.W.; Lawler, P.R.; Cook, N.R.; Ridker, P.M.; Mora, S.; Pradhan, A.D. Lipoprotein Particle Profiles, Standard Lipids, and Peripheral Artery Disease Incidence. *Circulation* **2018**, *138*, 2330–2341. [CrossRef]
13. Bergiers, S.; Vaes, B.; Degryse, J. To Screen or Not to Screen for Peripheral Arterial Disease in Subjects Aged 80 and over in Primary Health Care: A Cross-Sectional Analysis from the BELFRAIL Study. *BMC Fam. Pract.* **2011**, *12*, 39. [CrossRef]
14. Rosero, E.B.; Kane, K.; Clagett, G.P.; Timaran, C.H. A Systematic Review of the Limitations and Approaches to Improve Detection and Management of Peripheral Arterial Disease in Hispanics. *J. Vasc. Surg.* **2010**, *51*, 27S–35S. [CrossRef]
15. Writing Group Members; Mozaffarian, D.; Benjamin, E.J.; Go, A.S.; Arnett, D.K.; Blaha, M.J.; Cushman, M.; Das, S.R.; de Ferranti, S.; Després, J.-P.; et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* **2016**, *133*, e38–e360. [CrossRef]
16. Forbang, N.I.; Criqui, M.H.; Allison, M.A.; Ix, J.H.; Steffen, B.T.; Cushman, M.; Tsai, M.Y. Sex and Ethnic Differences in the Associations between Lipoprotein(a) and Peripheral Arterial Disease in the Multi-Ethnic Study of Atherosclerosis. *J. Vasc. Surg.* **2016**, *63*, 453–458. [CrossRef]
17. Fowkes, F.G.R.; Rudan, D.; Rudan, I.; Aboyans, V.; Denenberg, J.O.; McDermott, M.M.; Norman, P.E.; Sampson, U.K.A.; Williams, L.J.; Mensah, G.A.; et al. Comparison of Global Estimates of Prevalence and Risk Factors for Peripheral Artery Disease in 2000 and 2010: A Systematic Review and Analysis. *Lancet* **2013**, *382*, 1329–1340. [CrossRef]
18. Duval, S.; Massaro, J.M.; Jaff, M.R.; Boden, W.E.; Alberts, M.J.; Califf, R.M.; Eagle, K.A.; D'Agostino, R.B.; Pedley, A.; Fonarow, G.C.; et al. An Evidence-Based Score to Detect Prevalent Peripheral Artery Disease (PAD). *Vasc. Med.* **2012**, *17*, 342–351. [CrossRef] [PubMed]
19. Ihnat, D.M.; Mills, J.L. Current Assessment of Endovascular Therapy for Infrainguinal Arterial Occlusive Disease in Patients with Diabetes. *J. Vasc. Surg.* **2010**, *52*, 92S–95S. [CrossRef]
20. Lawall, H.; Bramlage, P.; Amann, B. Stem Cell and Progenitor Cell Therapy in Peripheral Artery Disease. A Critical Appraisal. *Thromb. Haemost.* **2010**, *103*, 696–709. [CrossRef]
21. Davies, M.G. Critical Limb Ischemia: Cell and Molecular Therapies for Limb Salvage. *Methodist DeBakey Cardiovasc. J.* **2012**, *8*, 20–27. [CrossRef] [PubMed]
22. Brumberg, R.S.; Back, M.R.; Armstrong, P.A.; Cuthbertson, D.; Shames, M.L.; Johnson, B.L.; Bandyk, D.F. The Relative Importance of Graft Surveillance and Warfarin Therapy in Infrainguinal Prosthetic Bypass Failure. *J. Vasc. Surg.* **2007**, *46*, 1160–1166. [CrossRef] [PubMed]
23. Adam, D.J.; Beard, J.D.; Cleveland, T.; Bell, J.; Bradbury, A.W.; Forbes, J.F.; Fowkes, F.G.R.; Gillepsie, I.; Ruckley, C.V.; Raab, G.; et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL): Multicentre, Randomised Controlled Trial. *Lancet* **2005**, *366*, 1925–1934. [CrossRef] [PubMed]
24. Corrado, E.; Mignano, A.; Coppola, G. Use of Statins in Patients with Peripheral Artery Disease. *Trends Cardiovasc. Med.* **2020**, *30*, 257–262. [CrossRef]
25. Coppola, G.; Novo, S. Statins and Peripheral Arterial Disease: Effects on Claudication, Disease Progression, and Prevention of Cardiovascular Events. *Arch. Med. Res.* **2007**, *38*, 479–488. [CrossRef]
26. Antoniou, G.A.; Fisher, R.K.; Georgiadis, G.S.; Antoniou, S.A.; Torella, F. Statin Therapy in Lower Limb Peripheral Arterial Disease: Systematic Review and Meta-Analysis. *Vascul. Pharmacol.* **2014**, *63*, 79–87. [CrossRef]
27. Pedersen, T.R.; Kjekshus, J.; Pyörälä, K.; Olsson, A.G.; Cook, T.J.; Musliner, T.A.; Tobert, J.A.; Haghfelt, T. Effect of Simvastatin on Ischemic Signs and Symptoms in the Scandinavian Simvastatin Survival Study (4S). *Am. J. Cardiol.* **1998**, *81*, 333–335. [CrossRef]
28. Heart Protection Study Collaborative Group. Randomized Trial of the Effects of Cholesterol-Lowering with Simvastatin on Peripheral Vascular and Other Major Vascular Outcomes in 20,536 People with Peripheral Arterial Disease and Other High-Risk Conditions. *J. Vasc. Surg.* **2007**, *45*, 645–654. [CrossRef]
29. Kumbhani, D.J.; Steg, P.G.; Cannon, C.P.; Eagle, K.A.; Smith, S.C.; Goto, S.; Ohman, E.M.; Elbez, Y.; Sritara, P.; Baumgartner, I.; et al. Statin Therapy and Long-Term Adverse Limb Outcomes in Patients with Peripheral Artery Disease: Insights from the REACH Registry. *Eur. Heart J.* **2014**, *35*, 2864–2872. [CrossRef]
30. Stavroulakis, K.; Borowski, M.; Torsello, G.; Bisdas, T.; CRITISCH collaborators. Association between Statin Therapy and Amputation-Free Survival in Patients with Critical Limb Ischemia in the CRITISCH Registry. *J. Vasc. Surg.* **2017**, *66*, 1534–1542. [CrossRef]

31. Long, C.A.; Mulder, H.; Fowkes, F.G.R.; Baumgartner, I.; Berger, J.S.; Katona, B.G.; Mahaffey, K.W.; Norgren, L.; Blomster, J.I.; Rockhold, F.W.; et al. Incidence and Factors Associated with Major Amputation in Patients with Peripheral Artery Disease: Insights from the EUCLID Trial. *Circ. Cardiovasc. Qual. Outcomes* **2020**, *13*, e006399. [CrossRef]
32. Arya, S.; Khakharia, A.; Binney, Z.O.; DeMartino, R.R.; Brewster, L.P.; Goodney, P.P.; Wilson, P.W.F. Association of Statin Dose with Amputation and Survival in Patients with Peripheral Artery Disease. *Circulation* **2018**, *137*, 1435–1446. [CrossRef]
33. Hsu, C.-Y.; Chen, Y.-T.; Su, Y.-W.; Chang, C.-C.; Huang, P.-H.; Lin, S.-J. Statin Therapy Reduces Future Risk of Lower-Limb Amputation in Patients with Diabetes and Peripheral Artery Disease. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 2373–2381. [CrossRef]
34. Aung, P.P.; Maxwell, H.G.; Jepson, R.G.; Price, J.F.; Leng, G.C. Lipid-Lowering for Peripheral Arterial Disease of the Lower Limb. *Cochrane Database Syst. Rev.* **2007**, *4*, CD000123. [CrossRef]
35. Walldius, G.; Erikson, U.; Olsson, A.G.; Bergstrand, L.; Hådell, K.; Johansson, J.; Kaijser, L.; Lassvik, C.; Mölgaard, J.; Nilsson, S. The Effect of Probucol on Femoral Atherosclerosis: The Probucol Quantitative Regression Swedish Trial (PQRST). *Am. J. Cardiol.* **1994**, *74*, 875–883. [CrossRef]
36. Pastori, D.; Farcomeni, A.; Milanese, A.; del Sole, F.; Menichelli, D.; Hiatt, W.R.; Violi, F. Statins and Major Adverse Limb Events in Patients with Peripheral Artery Disease: A Systematic Review and Meta-Analysis. *Thromb. Haemost.* **2020**, *120*, 866–875. [CrossRef]
37. Kokkinidis, D.G.; Arfaras-Melainis, A.; Giannopoulos, S.; Katsaros, I.; Jawaid, O.; Jonnalagadda, A.K.; Parikh, S.A.; Secemsky, E.A.; Giri, J.; Kumbhani, D.J.; et al. Statin Therapy for Reduction of Cardiovascular and Limb-Related Events in Critical Limb Ischemia: A Systematic Review and Meta-Analysis. *Vasc. Med.* **2020**, *25*, 106–117. [CrossRef]
38. Mondillo, S.; Ballo, P.; Barbati, R.; Guerrini, F.; Ammaturo, T.; Agricola, E.; Pastore, M.; Borrello, F.; Belcastro, M.; Picchi, A.; et al. Effects of Simvastatin on Walking Performance and Symptoms of Intermittent Claudication in Hypercholesterolemic Patients with Peripheral Vascular Disease. *Am. J. Med.* **2003**, *114*, 359–364. [CrossRef]
39. Jones, W.S.; Schmit, K.M.; Vemulapalli, S.; Subherwal, S.; Patel, M.R.; Hasselblad, V.; Heidenfelder, B.L.; Chobot, M.M.; Posey, R.; Wing, L.; et al. *Treatment Strategies for Patients with Peripheral Artery Disease [Internet]*; Agency for Healthcare Research and Quality: Rockville, MD, USA, 2013; Report No.: 13-EHC090-EF.
40. Crismaru, I.; Diaconu, C.C. Lipid-lowering therapy in patients with peripheral artery disease. *E-J. ESC Counc. Cardiol. Pract.* **2015**, *13*, 31.
41. Momsen, A.H.; Jensen, M.B.; Norager, C.B.; Madsen, M.R.; Vestersgaard-Andersen, T.; Lindholt, J.S. Drug therapy for improving walking distance in intermittent claudication: A systematic review and meta-analysis of robust randomised controlled studies. *Eur. J. Vasc. Endovasc. Surg.* **2009**, *38*, 463–474. [CrossRef]
42. Aronow, W.S. Lipid-lowering therapy in high-risk persons. *Compr. Ther.* **2006**, *32*, 68–73. [CrossRef]
43. Harris, S.K.; Roos, M.G.; Landry, G.J. Statin use in patients with peripheral arterial disease. *J. Vasc. Surg.* **2016**, *64*, 1881–1888. [CrossRef] [PubMed]
44. McDermott, M.M.; Spring, B.; Tian, L.; Treat-Jacobson, D.; Ferrucci, L.; Lloyd-Jones, D.; Zhao, L.; Polonsky, T.; Kibbe, M.R.; Bazzano, L.; et al. Effect of Low-Intensity vs. High-Intensity Home-Based Walking Exercise on Walk Distance in Patients with Peripheral Artery Disease: The LITE Randomized Clinical Trial. *JAMA* **2021**, *325*, 1266–1276. [CrossRef] [PubMed]
45. Jansen-Chaparro, S.; López-Carmona, M.D.; Cobos-Palacios, L.; Sanz-Cánovas, J.; Bernal-López, M.R.; Gómez-Huelgas, R. Statins and Peripheral Arterial Disease: A Narrative Review. *Front. Cardiovasc. Med.* **2021**, *8*, 777016. [CrossRef] [PubMed]
46. Di Minno, G.; Spadarella, G.; Cafaro, G.; Petitto, M.; Lupoli, R.; Di Minno, A.; De Gaetano, G.; Tremoli, E. Systematic reviews and meta-analyses for more profitable strategies in peripheral artery disease. *Ann. Med.* **2014**, *46*, 475–489. [CrossRef] [PubMed]
47. Belch, J.J.F.; Brodmann, M.; Baumgartner, I.; Binder, C.J.; Casula, M.; Heiss, C.; Kahan, T.; Parini, P.; Poredos, P.; Catapano, A.L.; et al. Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease. *Vasa* **2021**, *50*, 401–411. [CrossRef] [PubMed]
48. Harwood, A.E.; Pymer, S.; Ingle, L.; Doherty, P.; Chetter, I.C.; Parmenter, B.; Askew, C.D.; Tew, G.A. Exercise training for intermittent claudication: A narrative review and summary of guidelines for practitioners. *BMJ Open Sport Exerc. Med.* **2020**, *6*, e000897. [CrossRef]
49. Cholesterol Treatment Trialists' (CTT) Collaborators; Mihaylova, B.; Emberson, J.; Blackwell, L.; Keech, A.; Simes, J.; Barnes, E.H.; Voysey, M.; Gray, A.; Collins, R.; et al. The Effects of Lowering LDL Cholesterol with Statin Therapy in People at Low Risk of Vascular Disease: Meta-Analysis of Individual Data from 27 Randomised Trials. *Lancet* **2012**, *380*, 581–590. [CrossRef]
50. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/AphA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **2019**, *139*, e1082–e1143. [CrossRef]
51. Singh, N.; Ding, L.; Devera, J.; Magee, G.A.; Garg, P.K. Prescribing of Statins After Lower Extremity Revascularization Procedures in the US. *JAMA Netw. Open* **2021**, *4*, e2136014. [CrossRef]
52. Conte, M.S.; Bandyk, D.F.; Clowes, A.W.; Moneta, G.L.; Namini, H.; Seely, L. Risk Factors, Medical Therapies and Perioperative Events in Limb Salvage Surgery: Observations from the PREVENT III Multicenter Trial. *J. Vasc. Surg.* **2005**, *42*, 456–464. [CrossRef]
53. Hess, C.N.; Cannon, C.P.; Beckman, J.A.; Goodney, P.P.; Patel, M.R.; Hiatt, W.R.; Mues, K.E.; Orroth, K.K.; Shannon, E.; Bonaca, M.P. Effectiveness of Blood Lipid Management in Patients with Peripheral Artery Disease. *J. Am. Coll. Cardiol.* **2021**, *77*, 3016–3027. [CrossRef]

54. Colantonio, L.D.; Hubbard, D.; Monda, K.L.; Mues, K.E.; Huang, L.; Dai, Y.; Jackson, E.A.; Brown, T.M.; Rosenson, R.S.; Woodward, M.; et al. Atherosclerotic Risk and Statin Use Among Patients with Peripheral Artery Disease. *J. Am. Coll. Cardiol.* **2020**, *76*, 251–264. [CrossRef]
55. Kiyosue, A.; Honarpour, N.; Kurtz, C.; Xue, A.; Wasserman, S.M.; Hirayama, A. A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk. *Am. J. Cardiol.* **2016**, *117*, 40–47. [CrossRef]
56. Mayne, J.; Dewpura, T.; Raymond, A.; Cousins, M.; Chaplin, A.; Lahey, K.A.; Lahaye, S.A.; Mbikay, M.; Ooi, T.C.; Chrétien, M. Plasma PCSK9 Levels Are Significantly Modified by Statins and Fibrates in Humans. *Lipids Health Dis.* **2008**, *7*, 22. [CrossRef]
57. Sabatine, M.S.; Giugliano, R.P.; Keech, A.; Honarpour, N.; Wang, H.; Liu, T.; Wasserman, S.M.; Scott, R.; Sever, P.S.; Pedersen, T.R. Rationale and Design of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk Trial. *Am. Heart J.* **2016**, *173*, 94–101. [CrossRef]
58. Oyama, K.; Giugliano, R.P.; Tang, M.; Bonaca, M.P.; Saver, J.L.; Murphy, S.A.; Ruzza, A.; Keech, A.C.; Sever, P.S.; Sabatine, M.S.; et al. Effect of Evolocumab on Acute Arterial Events across All Vascular Territories: Results from the FOURIER Trial. *Eur. Heart J.* **2021**, *42*, 4821–4829. [CrossRef]
59. Bonaca, M.P.; Nault, P.; Giugliano, R.P.; Keech, A.C.; Pineda, A.L.; Kanevsky, E.; Kuder, J.; Murphy, S.A.; Jukema, J.W.; Lewis, B.S.; et al. Low-Density Lipoprotein Cholesterol Lowering with Evolocumab and Outcomes in Patients with Peripheral Artery Disease: Insights from the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation* **2018**, *137*, 338–350. [CrossRef]
60. Skeik, N.; Nowariak, M.E.; Smith, J.E.; Alexander, J.Q.; Manunga, J.M.; Mirza, A.K.; Sullivan, T.M. Lipid-Lowering Therapies in Peripheral Artery Disease: A Review. *Vasc. Med.* **2021**, *26*, 71–80. [CrossRef]
61. Schwartz, G.G.; Steg, P.G.; Szarek, M.; Bhatt, D.L.; Bittner, V.A.; Diaz, R.; Edelberg, J.M.; Goodman, S.G.; Hanotin, C.; Harrington, R.A.; et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N. Engl. J. Med.* **2018**, *379*, 2097–2107. [CrossRef]
62. Schwartz, G.G.; Steg, P.G.; Szarek, M.; Bittner, V.A.; Diaz, R.; Goodman, S.G.; Kim, Y.-U.; Jukema, J.W.; Pordy, R.; Roe, M.T.; et al. Peripheral Artery Disease and Venous Thromboembolic Events After Acute Coronary Syndrome: Role of Lipoprotein(a) and Modification by Alirocumab: Prespecified Analysis of the ODYSSEY OUTCOMES Randomized Clinical Trial. *Circulation* **2020**, *141*, 1608–1617. [CrossRef]
63. Bhatt, D.L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Ketchum, S.B.; Doyle, R.T.; Juliano, R.A.; Jiao, L.; Granowitz, C.; et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N. Engl. J. Med.* **2019**, *380*, 11–22. [CrossRef]
64. Budoff, M.J.; Bhatt, D.L.; Kinninger, A.; Lakshmanan, S.; Muhlestein, J.B.; Le, V.T.; May, H.T.; Shaikh, K.; Shekar, C.; Roy, S.K.; et al. Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients with Elevated Triglycerides on Statin Therapy: Final Results of the EVAPORATE Trial. *Eur. Heart J.* **2020**, *41*, 3925–3932. [CrossRef]
65. Virani, S.S.; Morris, P.B.; Agarwala, A.; Ballantyne, C.M.; Birtcher, K.K.; Kris-Etherton, P.M.; Ladden-Stirling, A.B.; Miller, M.; Orringer, C.E.; Stone, N.J. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients with Persistent Hypertriglyceridemia: A Report of the American College of Cardiology Solution Set Oversight Committee. *J. Am. Coll. Cardiol.* **2021**, *78*, 960–993. [CrossRef]
66. Sohn, M.-W.; Meadows, J.L.; Oh, E.H.; Budiman-Mak, E.; Lee, T.A.; Stone, N.J.; Pearce, W.B. Statin Use and Lower Extremity Amputation Risk in Nonelderly Diabetic Patients. *J. Vasc. Surg.* **2013**, *58*, 1578–1585.e1. [CrossRef]
67. West, A.M.; Anderson, J.D.; Meyer, C.H.; Epstein, F.H.; Wang, H.; Hagspiel, K.D.; Berr, S.S.; Harthun, N.L.; DiMaria, J.M.; Hunter, J.R.; et al. The Effect of Ezetimibe on Peripheral Arterial Atherosclerosis Depends upon Statin Use at Baseline. *Atherosclerosis* **2011**, *218*, 156–162. [CrossRef]
68. Ray, K.K.; Wright, R.S.; Kallend, D.; Koenig, W.; Leiter, L.A.; Raal, F.J.; Bisch, J.A.; Richardson, T.; Jaros, M.; Wijngaard, P.L.J.; et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N. Engl. J. Med.* **2020**, *382*, 1507–1519. [CrossRef]
69. Ray, K.K.; Landmesser, U.; Leiter, L.A.; Kallend, D.; Dufour, R.; Karakas, M.; Hall, T.; Troquay, R.P.T.; Turner, T.; Visseren, F.L.J.; et al. Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. *N. Engl. J. Med.* **2017**, *376*, 1430–1440. [CrossRef]
70. Dieplinger, B.; Lingenhel, A.; Baumgartner, N.; Poelz, W.; Dieplinger, H.; Haltmayer, M.; Kronenberg, F.; Mueller, T. Increased Serum Lipoprotein(a) Concentrations and Low Molecular Weight Phenotypes of Apolipoprotein(a) Are Associated with Symptomatic Peripheral Arterial Disease. *Clin. Chem.* **2007**, *53*, 1298–1305. [CrossRef]
71. Gurdasani, D.; Sjouke, B.; Tsimikas, S.; Hovingh, G.K.; Luben, R.N.; Wainwright, N.W.J.; Pomilla, C.; Wareham, N.J.; Khaw, K.-T.; Boekholdt, S.M.; et al. Lipoprotein(a) and Risk of Coronary, Cerebrovascular, and Peripheral Artery Disease: The EPIC-Norfolk Prospective Population Study. *Arter. Thromb. Vasc. Biol.* **2012**, *32*, 3058–3065. [CrossRef]
72. Thompson, G.R.; Catapano, A.; Saheb, S.; Atassi-Dumont, M.; Barbir, M.; Eriksson, M.; Paulweber, B.; Sijbrands, E.; Stalenhoef, A.F.; Parhofer, K.G. Severe Hypercholesterolaemia: Therapeutic Goals and Eligibility Criteria for LDL Apheresis in Europe. *Curr. Opin. Lipidol.* **2010**, *21*, 492–498. [CrossRef] [PubMed]
73. Winters, J.L. Lipid Apheresis, Indications, and Principles. *J. Clin. Apher.* **2011**, *26*, 269–275. [CrossRef] [PubMed]
74. Schatz, U.; Tselmin, S.; Müller, G.; Julius, U.; Hohenstein, B.; Fischer, S.; Bornstein, S.R. Most Significant Reduction of Cardiovascular Events in Patients Undergoing Lipoproteinapheresis Due to Raised Lp(a) Levels—A Multicenter Observational Study. *Atheroscler Suppl.* **2017**, *30*, 246–252. [CrossRef] [PubMed]

75. Roeseler, E.; Julius, U.; Heigl, F.; Spitthoever, R.; Heutling, D.; Breitenberger, P.; Leebmann, J.; Lehmacher, W.; Kamstrup, P.R.; Nordestgaard, B.G.; et al. Lipoprotein Apheresis for Lipoprotein(a)-Associated Cardiovascular Disease: Prospective 5 Years of Follow-Up and Apolipoprotein(a) Characterization. *Arter. Thromb. Vasc. Biol.* **2016**, *36*, 2019–2027. [CrossRef] [PubMed]
76. Leebmann, J.; Roeseler, E.; Julius, U.; Heigl, F.; Spitthoever, R.; Heutling, D.; Breitenberger, P.; Maerz, W.; Lehmacher, W.; Heibges, A.; et al. Lipoprotein Apheresis in Patients with Maximally Tolerated Lipid-Lowering Therapy, Lipoprotein(a)-Hyperlipoproteinemia, and Progressive Cardiovascular Disease: Prospective Observational Multicenter Study. *Circulation* **2013**, *128*, 2567–2576. [CrossRef]
77. Jaeger, B.R.; Richter, Y.; Nagel, D.; Heigl, F.; Vogt, A.; Roeseler, E.; Parhofer, K.; Ramlow, W.; Koch, M.; Utermann, G.; et al. Longitudinal Cohort Study on the Effectiveness of Lipid Apheresis Treatment to Reduce High Lipoprotein(a) Levels and Prevent Major Adverse Coronary Events. *Nat. Clin. Pract. Cardiol.* **2009**, *6*, 229–239. [CrossRef] [PubMed]
78. Weiss, N.; Julius, U. Lipoprotein(a) Apheresis in Patients with Peripheral Arterial Disease: Rationale and Clinical Results. *Clin. Res. Cardiol. Suppl.* **2019**, *14*, 39–44. [CrossRef] [PubMed]
79. Novartis Pharmaceuticals Assessing the Impact of Lipoprotein (a) Lowering with Pelacarsen (TQJ230) on Major Cardiovascular Events in Patients with CVD (Lp(a)HORIZON): NCT04023552. Available online: https://clinicaltrials.gov/ct2/show/NCT04023552 (accessed on 13 May 2022).
80. Fruchart, J.-C.; Nierman, M.C.; Stroes, E.S.G.; Kastelein, J.J.P.; Duriez, P. New Risk Factors for Atherosclerosis and Patient Risk Assessment. *Circulation* **2004**, *109*, III-15–III-19. [CrossRef]
81. Libby, P.; Ridker, P.M.; Maseri, A. Inflammation and Atherosclerosis. *Circulation* **2002**, *105*, 1135–1143. [CrossRef]
82. Shishehbor, M.H.; Bhatt, D.L. Inflammation and Atherosclerosis. *Curr. Atheroscler. Rep.* **2004**, *6*, 131–139. [CrossRef]
83. Libby, P. The Changing Landscape of Atherosclerosis. *Nature* **2021**, *592*, 524–533. [CrossRef]

Journal of
Clinical Medicine

MDPI

Article

Dyslipidemia Treatment and Lipid Control in US Adults with Diabetes by Sociodemographic and Cardiovascular Risk Groups in the NIH Precision Medicine Initiative *All of Us* Research Program

Meleeka Akbarpour [1], Divya Devineni [1], Yufan Gong [2] and Nathan D. Wong [1,*]

[1] Heart Disease Prevention Program, Division of Cardiology, University of California, Irvine, CA 92697, USA
[2] Department of Epidemiology, University of California, Los Angeles, CA 90095, USA
* Correspondence: ndwong@uci.edu

Abstract: Real-world data on lipid levels and treatment among adults with diabetes mellitus (DM) are relatively limited. We studied lipid levels and treatment status in patients with DM across cardiovascular disease (CVD) risk groups and sociodemographic factors. In the *All of Us* Research Program, we categorized DM as (1) moderate risk (≤1 CVD risk factor), (2) high risk (≥2 CVD risk factors), and (3) DM with atherosclerotic CVD (ASCVD). We examined the use of statin and non-statin therapy as well as LDL-C and triglyceride levels. We studied 81,332 participants with DM, which included 22.3% non-Hispanic Black and 17.2% Hispanic. A total of 31.1% had ≤1 DM risk factor, 30.3% had ≥2 DM risk factors, and 38.6% of participants had DM with ASCVD. Only 18.2% of those with DM and ASCVD were on high-intensity statins. Overall, 5.1% were using ezetimibe and 0.6% PCSK9 inhibitors. Among those with DM and ASCVD, only 21.1% had LDL-C < 70 mg/dL. Overall, 1.9% of participants with triglycerides ≥ 150 mg/dL were on icosapent ethyl. Those with DM and ASCVD were more likely to be on high-intensity statins, ezetimibe, and icosapent ethyl. Guideline-recommended use of high-intensity statins and non-statin therapy among our higher risk DM patients is lacking, with LDL-C inadequately controlled.

Keywords: dyslipidemia; diabetes mellitus; LDL-cholesterol; triglycerides; statins; treatment

Citation: Akbarpour, M.; Devineni, D.; Gong, Y.; Wong, N.D. Dyslipidemia Treatment and Lipid Control in US Adults with Diabetes by Sociodemographic and Cardiovascular Risk Groups in the NIH Precision Medicine Initiative *All of Us* Research Program. *J. Clin. Med.* **2023**, *12*, 1668. https://doi.org/10.3390/jcm12041668

Academic Editors: Marijana Tadic and Jianjun Li

Received: 5 January 2023
Revised: 27 January 2023
Accepted: 15 February 2023
Published: 20 February 2023

1. Introduction

Atherosclerotic cardiovascular diseases (ASCVD) are major causes of morbidity and mortality in people with diabetes mellitus (DM) [1]. Dyslipidemia remains a significant ASCVD risk factor in those with DM. In the US Diabetes Collaborative Registry [2], among the 74,393 patients with DM, 48.6% had controlled levels of low-density lipoprotein-cholesterol (LDL-C) but only 62% were on a moderate- or high-intensity statin. Hypertriglyceridemia (HTG) also remains common in patients with DM. Among 1448 U.S. adults aged 20 years and over with diabetes in the US National Health and Nutrition Examination Survey, approximately 40% had triglyceride levels of ≥ 150 mg/dL, regardless of statin use; and even among statin users with LDL-C < 70 mg/dL, one-third had borderline or elevated levels [3]. Moreover, clinical trials have shown that statin therapy, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor use, and fish oil therapy using pure icosapent ethyl all reduce ASCVD risk, including among those with DM [4–6].

US and other international guidelines recommend statin therapy for all adults with DM, with high-intensity statins for those at higher risk and icosapent ethyl (pure EPA fish oil) for those at higher risk who have elevated triglycerides [5,7]. US and European guidelines for the management of dyslipidemias now include the use of PCSK9 inhibitors for very high-risk ASCVD patients (with or without DM) who are not adequately controlled for LDL-C on a maximum tolerated dose of statin and ezetimibe [8–10].

Data on the extent of dyslipidemia and lipid target attainment, as well as on the use of statin and newer non-statin therapies, are limited among recent real-world cohorts of diverse patient populations. The aim of our study was to examine disparities in lipid control and use of statin and newer lipid therapies according to sociodemographic and ASCVD risk groups in a large cohort of patients with DM representative of the diversity of the United States. Key objectives were to examine differences in (1) LDL-C and triglyceride control by sociodemographic and ASCVD risk groups, and (2) the use of statin, ezetimibe, PCSK9 inhibitor, and icosapent ethyl by sociodemographic and ASCVD risk groups.

2. Materials and Methods

2.1. All of Us Research Program

The mission of the *All of Us* Research Program is to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care [11]. The *All of Us* Research Program is an ongoing program that aims to invite 1 million adults across the United States. There are currently over 541,000 participants that have been recruited from 590+ sites. Over 50% of these participants represent racial and ethnic minorities, and over 80% of them are underrepresented in biomedical research [11].

This work was performed on data collected using the *All of Us* Researcher Workbench, a cloud-based platform where approved researchers can access and analyze data [11]. The data currently includes surveys, electronic health records (EHR) data, and physical measurements (PM). Participants could choose not to answer specific questions. PM recorded at enrollment include systolic and diastolic blood pressure, height, weight, heart rate, waist and hip measurement, wheelchair use, and current pregnancy status. EHR data was linked for those participants who consented [11]. All participants provided informed consent to participate in the *All of Us* research program. The current analysis utilized de-identified data.

2.2. Study Sample

On the researcher workbench, we created a cohort of 81,332 participants aged $\geq$ 18 years enrolled between 2018 and 2022 with DM based on $\geq$1 of the following from recorded personal or medical history: DM, DM without complications, type 2 DM, different diseases/conditions due to DM, secondary DM, on insulin treatment or DM medication, HbA1c $\geq$ 6.5%, fasting glucose $\geq$ 126 mg/dL, or non-fasting glucose $\geq$ 200 mg/dL. We excluded participants with Type 1 DM and variables with missing values in our analysis from participants. Ethnicity within our cohort included non-Hispanic White, non-Hispanic Black, Hispanic or Latino, Asian, and other. We categorized our ASCVD risk groups as moderate risk based on $\leq$1 CVD risk factor, high risk with $\geq$2 CVD risk factors, and DM with known ASCVD. Risk factors included were age $\geq$60 years, hypertension (blood pressure $\geq$ 130/80 mmHg or being on antihypertensive therapy), low-density lipoprotein cholesterol (LDL-C) $\geq$ 160 mg/dL, cigarette smoking, and high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL for males and <50 mg/dL for females (Table 1). We also analyzed these parameters across health insurance status, education, and income categories.

Table 1. Demographic characteristics of participants with Type 2 DM.

Variable	Total (n = 81,332)
Age (years)	62.0 ($\pm$14.1)
Male	31,887 (40.6%)
Female	46,661 (59.4%)
Non-Hispanic White	42,532 (52.3%)
Non-Hispanic Black	18,100 (22.3%)
Hispanic or Latino	13,986 (17.2%)

Table 1. *Cont.*

Variable	Total (n = 81,332)
Asian	1445 (1.8%)
Other Race/Ethnicity	5269 (6.5%)
Health Insurance	74,838 (95.6%)
Income	
Less than 10 k	11,678 (19.6%)
10–25 k	11,793 (19.8%)
25–35 k	5994 (10.1%)
35–50 k	6262 (10.5%)
50–75 k	7990 (13.4%)
75–100 k	5673 (9.5%)
More than 100 k	10,046 (16.9%)
Education	
Less than a high school degree or equivalent	9527 (12.2%)
Twelve or GED	17,147 (21.9%)
Some College	22,394 (28.6%)
College Graduate/Advanced Degree	29,104 (37.2%)
BMI (kg/m^2)	32.5 ($\pm$12.2)
Smoking Status	
Non-Smoker	43,071 (54.7%)
Former Smoker	23,383 (29.7%)
Current Smoker	12,229 (15.5%)
Systolic Blood Pressure (mm Hg)	129.5 ($\pm$14.2)
Diastolic Blood Pressure (mm Hg)	76.9 ($\pm$9.1)
Triglycerides (mg/dL)	145.7 ($\pm$85.1)
LDL-C (mg/dL)	100.9 ($\pm$31.3)
HDL-C (mg/dL)	50.1 ($\pm$15.2)
Diabetes Risk and ASCVD Status	
$\leq$1 Diabetes Risk Factors without ASCVD	24,787 (31.1%)
$\geq$2 Diabetes Risk Factors without ASCVD	24,112 (30.3%)
Diabetes with ASCVD	30,682 (38.6%)
Diabetes Risk Factors	
Age $\geq$60 years	50,768 (62.4%)
Hypertension	42,315 (54.9%)
LDL-C $\geq$160 mg/dL	1835 (3.4%)
Smoking History	12,229 (15.5%)
HDL-C < 50 mg/dL in females	14,861 (18.3%)
HDL-C < 40 mg/dL in males	8641 (10.6%)

Individual categories do not add up to total sample size due to missing data as follows: 2784 persons did not indicate their sex, 3050 persons did not indicate their health insurance status, 21,896 persons did not indicate their income status, 3160 persons did not indicate their education level, 2649 persons did not indicate their smoking status, 1751 persons did not indicate their diabetes risk and/or ASCVD status.

2.3. Definitions and Measurements

We extracted information on each subject on demographics, survey data, cholesterol, LDL-C, and triglyceride levels, as well as use of statins and PCSK9 inhibitor use. ASCVD was defined based on all listed manifestations of coronary artery disease, cerebrovascular disease (excluding hemorrhagic stroke), and peripheral arterial disease. Statin use was defined as a documented prescription (generic or branded) of atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and/or simvastatin. Statin intensity was categorized into those at high and low/moderate intensities according to US guidelines [12]. Ezetimibe and icosapent ethyl use was also captured, and PCSK9 inhibitors included evolocumab and alirocumab. We additionally obtained survey data on health insurance status, types of health insurance, BMI, education level, cigarette smoking status, and income.

2.4. Statistical Analyses

R programming was used for statistical analysis, utilizing the *All of Us* Research Program participants to project estimates to the US population. The Chi-squared test of proportions was used to compare icosapent ethyl and statin use according to risk group, sex, and ethnicity. We examined the percentage of people on low-, moderate-, and high-intensity statin therapy, and at LDL-C levels less than 70 mg/dL, 70–99 mg/dL, and 100 mg/dL or greater. The percentage of people on icosapent ethyl and with triglyceride levels less than 100 mg/dL, 100–149 mg/dL, 150 mg/dL to 199 mg/dL, and 200 mg/dL and greater were also analyzed using the Chi-squared test of proportions. We then performed logistic regressions that assessed the relation of demographic factors to high-statin, ezetimibe, PCSK9 inhibitor, and icosapent ethyl uses. Multiple logistic regressions were used to assess the relation of predetermined sociodemographic factors, risk groups, and individual risk factors, with odds ratios (ORs) and 95% confidence intervals calculated. The p-values shown represent the significance levels across the strata of interest (e.g., sex, ethnicity, or DM risk group).

3. Results

Our analysis includes 81,332 participants diagnosed with DM based on our inclusion criteria. Overall, 31.1%, 30.3%, and 38.6% were at moderate risk, high risk, or with ASCVD, respectively. Our sample also comprised 22.3% non-Hispanic Black, 17.2% Hispanic or Latino, 52.3% non-Hispanic White, and 1.8% Asian participants, as well as 40.6% males and 59.4% females. Overall, 4.4% did not have health insurance, and 34.1% had a high school education or less (Table 1).

Table 2 shows how the use of different therapies for dyslipidemia varied by risk and demographic groups. Within risk groups, sex, and ethnicity, there were significant differences in the use of statins. Approximately 33.5% of people who have DM and ASCVD were not using any statins. High-intensity statin use also varied among groups, ranging from 5.9% in those at lower risk to 18.2% in those with DM and ASCVD ($p < 0.05$). Furthermore, across all risk groups, use of PCSK9 inhibitors and icosapent ethyl was universally low, being highest at 1.3% and 1.7%, respectively, in those with both DM and ASCVD. Approximately 1.9% of participants with TG levels greater than or equal to 150 mg/dL were on icosapent ethyl. A total of 5.1% of participants were on ezetimibe ($p < 0.05$).

Table 2. Lipid treatment and control in US adults with DM according to risk group, sex and ethnicity.

Proportion (%)	Total (*n* = 81,332)	≤1 DM Risk Factors w/o ASCVD (*n* = 24,780)	≥2 DM Risk Factors w/o ASCVD (*n* = 24,119)	DM with ASCVD (*n* = 30,682)	Female (*n* = 46,661)	Male (*n* = 31,887)	Non-Hispanic White (*n* = 42,532)	Non-Hispanic Black (*n* = 18,100)	Hispanic or Latino (*n* = 13,986)	Asian (*n* = 1445)	Other Race/ Ethnicity (*n* = 5269)
Statin Category											
No statin use	49.8%	68.5%	50.5%	33.5% *	54.2%	43.2% *	46.2%	53.9%	54.5%	51.8%	51.9%
Low intensity	6.6%	4.7%	6.9%	7.9% *	6.6%	6.5% *	7.6%	4.8%	6.0%	5.3%	6.1% *
Moderate intensity	31.8%	20.9%	32.7%	40.4% *	29.4%	35.7% *	35.1%	28.5%	26.8%	32.8%	30.8% *
High intensity	11.8%	5.9%	9.9%	18.2% *	9.8%	14.6% *	11.2%	12.8%	12.6%	10.2%	11.2% *
Ezetimibe Use (*n* = 4136)	5.1%	2.1%	3.2%	9.1% *	4.7%	5.6% *	6.6%	3.0%	2.8%	5.4%	5.8% *
PCSK9 Inhibitor Use (*n* = 495)	0.6%	0.1%	0.2%	1.3% *	0.6%	0.7%	0.8%	0.2%	0.3%	0.1%	1.1% *
Icosapent Ethyl Use (*n* = 846)	1.0%	0.5%	0.8%	1.7% *	0.5%	1.8% *	1.3%	0.3%	0.9%	2.1%	1.4% *
Among those with TG ≥ 150 mg/dL	1.9%	0.1% †	0.5%†	1.1% †	0.9%	2.3%	2.5%	0.3%	0.5%	2.1%	1.1%
LDL-C Category											
<70 mg/dL	16.0%	10.6%	13.3%	21.1% *	11.5%	22.5% *	15.7%	16.6%	15.3%	16.1%	17.3% *
70–99 mg/dL	34.6%	32.9%	31.2%	38.1% *	32.2%	38.2% *	35.9%	34.0%	31.0%	34.9%	35.2% *
≥100 mg/dL	49.5%	56.5%	55.5%	40.9% *	56.3%	39.3% *	48.4%	49.4%	53.7%	49.0%	47.5% *
Triglyceride Category											
<100 mg/dL	31.6%	41.8%	24.8%	30.4% *	32.6%	30.0% *	30.7%	41.4%	21.5%	28.2%	32.1% *
100–149 mg/dL	32.8%	32.1%	33.0%	33.1% *	33.6%	31.7% *	32.9%	32.9%	32.5%	32.0%	32.7% *
≥150 mg/dL	35.6%	26.1%	42.2%	36.5% *	33.7%	38.3% *	36.4%	25.7%	46.0%	39.7%	35.1% *

† p value < 0.01, * p value < 0.001 across risk, sex, or ethnic groups. Individual categories do not add up to total sample size due to missing data as follows: 2784 persons did not indicate their sex and 1751 persons did not indicate their diabetes risk and/or ASCVD status.

Overall, 50.6% of our participants had LDL-C levels < 100 mg/dL, although only 16.0% were <70 mg/dL (Table 2). Figure 1 shows the proportion of participants with LDL-C < 70 mg/dL, 70–99 mg/dL, and ≥100 mg/dL according to sociodemographic and ASCVD risk groups. A total of 55.5% of those with ≥ 2 risk factors had LDL-C ≥ 100 mg/dL, whereas 40.9% of those with DM and ASCVD had LDL-C ≥ 100 mg/dL (with only 21.1% having LDL-C < 70 mg/dL). A total of 56.3% of females had LDL-C ≥ 100 compared to 39.3% of males. Of the participants who had health insurance, 49.5% had LDL-C ≥ 100 mg/dL, compared to 53.2% of participants who had no insurance and had LDL-C ≥ 100 mg/dL.

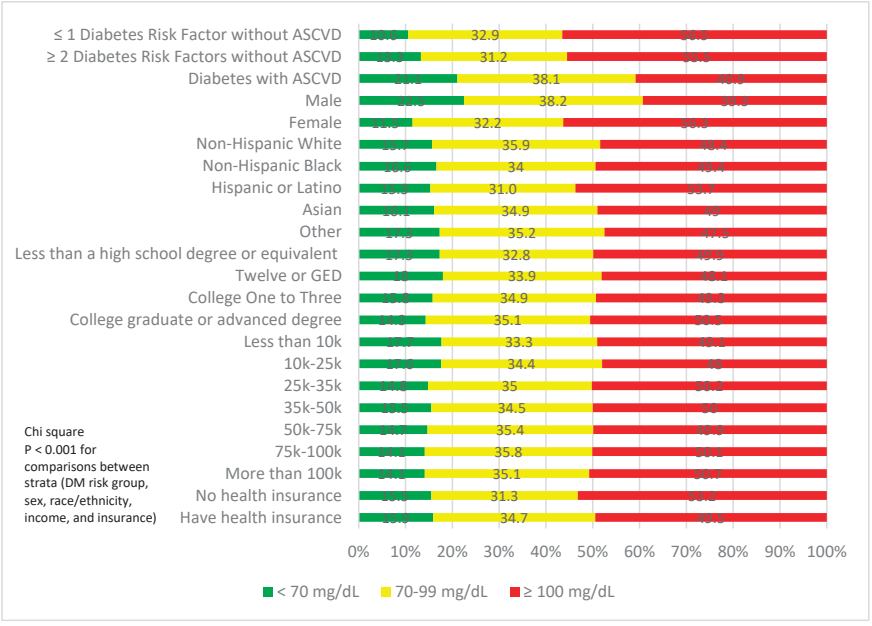

Figure 1. Proportion of subjects at ideal, borderline, or poor LDL-C control by ASCVD risk group, sex, ethnicity, education, income, and health insurance. $p < 0.001$ across risk, sex, ethnicity, education, income, and health insurance status categories.

Overall, 64.4% had triglyceride levels < 150 mg/dL, and only 31.6% had levels < 100 mg/dL (Table 2). Figure 2 shows the proportion of participants with triglyceride levels of <100 mg/dL, 100–149 mg/dL, 150–199 mg/dL, and ≥200 mg/dL by sociodemographic and risk groups. A total of 21.3% of participants with 2 or more risk factors had triglyceride levels ≥ 200 mg/dL, whereas 17.9% of those with DM and ASCVD had triglyceride levels ≥ 200 mg/dL. A total of 15.6% of females had triglyceride levels ≥ 200 mg/dL compared to 19.6% of males. Additionally, 16.9% of participants with health insurance had triglyceride levels ≥ 200 mg/dL, compared to 25.1% of those without health insurance.

Table 3 shows significant differences in the prevalence of high-intensity statin, ezetimibe, PCSK9 inhibitor, and icosapent ethyl use across health insurance, education, and income. For those with health insurance, 27.5% were on high-intensity statins, compared to 23.7% without health insurance. Ezetimibe use was greater in those with health insurance at 5.3% compared to 1.4% in those without health insurance, as was PCSK9 inhibitor use (0.6% and 0.1%, respectively). Moreover, 3.1%, 0.2%, and 0.5% of participants with less than a high school degree were on ezetimibe, PCSK9 inhibitors, and icosapent ethyl, respectively. For those with a college or advanced degree, this was 6.4%, 0.8%, and 1.0%, respectively. Ezetimibe use was more common in those at higher versus lower income levels.

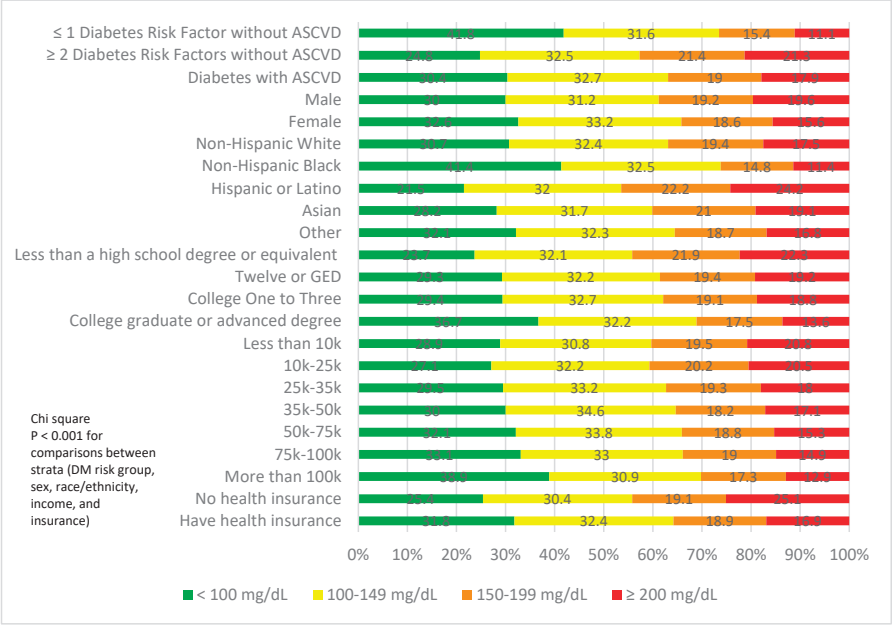

Figure 2. Proportion of subjects at ideal, borderline, or poor triglyceride control by ASCVD risk group, sex, ethnicity, education, income, and health insurance. $p < 0.001$ across risk, sex, ethnicity, education, income, and health insurance status categories.

Table 3. Prevalence of high-intensity statin, ezetimibe, PCSK9 inhibitor, and icosapent ethyl treatments in Adults with DM across health insurance, education, and income.

Proportion (%)	High-Intensity Statin Use	Ezetimibe Use	PCSK9 Inhibitor Use	Icosapent Ethyl Use
Health Insurance (*n* = 74,838)	27.5% *	5.3% *	0.6% *	1.0%
No Health Insurance (*n* = 3469)	23.7% *	1.4%	0.1% *	1.1%
Less than a high school degree (*n* = 9527)	31.1% *	3.1% *	0.2% *	0.5% *
Twelfth Grade or GED (*n* = 17,147)	28.1% *	4.2% *	0.5% *	0.9% *
College (*n* = 22,394)	26.6% *	4.9% *	0.6%*	1.1% *
College Graduate or Advanced degree (*n* = 29,104)	25.8% *	6.4% *	0.8% *	1.0% *
Income Less than 10 k (*n* = 11,678)	26.9% *	2.8% *	3.0%	0.5% *
10–25 k (*n* = 11,793)	30.8% *	4.5% *	0.2% *	1.0% *
25–35 k (*n* = 5994)	26.8% *	5.2% *	0.7% *	1.1% *
35–50 k (*n* = 6262)	26.7% *	5.7% *	0.5% *	1.6% *
50–75 k (*n* = 7990)	25.6% *	5.8% *	0.7% *	1.3% *
75–100 k (*n* = 5673)	25.0% *	6.8% *	0.8% *	1.4% *
More than 100 k (*n* = 10,046)	24.9% *	7.2% *	0.9% *	1.1% *

* $p < 0.001$ across health insurance, education, or income categories. (Participants may be on one or more medication class.)

Multiple logistic regression (Table 4) showed males to be significantly more likely to be on icosapent ethyl (OR = 2.98 [2.03, 4.48]) and high-intensity statins (OR = 1.73 [1.62, 1.85])

compared to females. Non-Hispanic Black participants were significantly less likely to be on icosapent ethyl (OR = 0.22 [0.12, 0.38]) and ezetimibe (OR = 0.62 [0.54, 0.72]) than non-Hispanic White participants, but were more likely to be on PCSK9 inhibitors and high-intensity statins. High-intensity statin use was significantly more likely in participants with hypertension (OR = 1.13 [1.07, 1.19]), and those with LDL-C $\geq$ 160 mg/dL (OR = 1.63 [1.43, 1.86]). Ezetimibe use was significantly more likely in participants $\geq$60 years (OR = 1.27 [1.05, 1.54]) and among those with health insurance (OR = 1.52 [1.03, 2.35]). Hispanic or Latino participants were significantly less likely to be taking ezetimibe. Those with DM and ASCVD were significantly more likely to be on a high-intensity statin (OR = 3.66 [3.37, 3.97]) and ezetimibe (OR = 3.12 [2.66, 3.67]) as well as icosapent ethyl (OR = 2.21 [1.44, 3.47]).

Table 4. Multiple logistic regression of indicators for high-intensity statin, ezetimibe, PCSK9 inhibitor, and icosapent ethyl.

Variable	High-Intensity Statin Use Odds Ratio [95% CI]	Ezetimibe Use Odds Ratio [95% CI]	PCSK9 Inhibitor Use Odds Ratio [95% CI]	Icosapent Ethyl Use Odds Ratio [95% CI]
Age (Per Year)	1.02 [1.016, 1.023]	1.02 [1.017, 1.03]	1.02 [0.99, 1.04]	1.00 [0.99, 1.03]
Gender: Male	1.73 [1.62, 1.85]	0.98 [0.87, 1.099]	1.17 [0.84, 1.63]	2.98 [2.03, 4.48]
BMI (Per kg/m^2)	1.00 [0.999, 1.003]	1.00 [0.998, 1.004]	0.995 [0.992, 1.00]	1.006 [1.003, 1.009]
Age $\geq$60 years	1.09 [0.99, 1.20]	1.27 [1.05, 1.54]	0.47 [0.27, 0.79]	1.38 [0.85, 2.28]
HTN	1.13 [1.07, 1.19]	0.91 [0.82, 1.00]	1.13 [0.86, 1.47]	0.92 [0.71, 1.18]
LDL-C $\geq$ 160 mg/dL	1.63 [1.43, 1.86]	3.02 [2.48, 3.66]	0.15 [0.10, 0.23]	0.63 [0.19, 1.50]
Smoking History	1.11 [1.03, 1.19]	0.87 [0.74, 1.02]	1.07 [0.71, 1.69]	0.61 [0.37, 0.96]
HDL-C < 50 mg/dL in females	1.47 [1.37, 1.58]	1.16 [1.02, 1.32]	1.34 [0.93, 1.96]	2.19 [1.41, 3.45]
HDL-C < 40 mg/dL in males	1.27 [1.17, 1.37]	1.05 [0.91, 1.21]	0.99 [0.67, 1.49]	1.92 [1.43, 2.58]
Ethnicity: Non-Hispanic Black	1.30 [1.21, 1.39]	0.62 [0.54, 0.72]	2.49 [1.60, 4.04]	0.22 [0.12, 0.38]
Hispanic or Latino	1.34 [1.24, 1.45]	0.70 [0.59, 0.84]	1.57 [0.98, 2.64]	0.97 [0.64, 1.43]
Asian	0.96 [0.78, 1.17]	0.88 [0.61, 1.24]	4.87 [1.08, 8.59]	2.30 [1.20, 4.01]
Other	1.05 [0.93, 1.19]	1.05 [0.85, 1.28]	0.65 [0.41, 1.07]	1.17 [0.69, 1.88]
Have health insurance	0.79 [0.69, 0.90]	1.52 [1.03, 2.35]	0.22 [0.01, 0.99]	0.60 [0.32, 1.29]
Income: 10–25 k	0.97 [0.89, 1.05]	1.13 [0.94, 1.35]	0.58 [0.33, 0.98]	0.89 [0.54, 1.48]
25–35 k	0.76 [0.69, 0.84]	1.17 [0.95, 1.45]	0.61 [0.32, 1.14]	1.16 [0.66, 2.03]
35–50 k	0.76 [0.69, 0.84]	1.17 [0.95, 1.44]	0.75 [0.39, 1.42]	1.41 [0.84, 2.39]
50–75 k	0.70 [0.64, 0.77]	1.18 [0.97, 1.44]	0.68 [0.37, 1.22]	1.22 [0.74, 2.05]
75–100 k	0.69 [0.62, 0.77]	1.46 [1.19, 1.80]	0.55 [0.29, 1.02]	1.04 [0.60, 1.83]
>100 k	0.71 [0.65, 0.78]	1.53 [1.27, 1.85]	0.53 [0.29, 0.92]	1.15 [0.71, 1.92]
Diabetes Risk Group				
Diabetes with $\geq$2 Risk Factors	1.18 [1.08, 1.30]	1.11 [0.92, 1.34]	0.80 [0.41, 1.51]	1.18 [0.73, 1.96]
Diabetes with ASCVD	3.66 [3.37, 3.97]	3.12 [2.66, 3.67]	0.14 [0.08, 0.24]	2.21 [1.44, 3.47]

Reference Groups: Gender—-female; age $\geq$60 years-age $\leq$60 years age; HTN-no HTN, LDL-C $\geq$ 160 mg/dL-LDL-C $\leq$ 160 mg/dL; smoking history: no smoking history; HDL-C < 50 mg/dL in females; HDL-C > 50 mg/dL in females; HDL-C < 40 mg/dL in males; HDL-C > 40 mg/dL in males; race: non-Hispanic White; health insurance: none; income: < 10 k, DM risk group < 1 DM risk factor.

4. Discussion

We demonstrated continuing gaps in lipid treatment and inadequate control of LDL-C and triglycerides in an important current real-world cohort of US adults with DM. We analyzed these gaps across ASCVD risk groups and key underserved demographic groups of participants within the NIH Precision Medicine Initiative's *All of Us Study* who have been underrepresented in health research. We found that LDL-C and triglyceride levels remain inadequately controlled, including among people with ASCVD, who despite

having the strongest recommendations for treatment, remain suboptimally treated with high-intensity statins, ezetimibe, PCSK9i, and icosapent ethyl. Among participants with both DM and ASCVD, only 21.1% had LDL-C < 70 mg/dL and 36.5% had triglyceride levels ≥ 150 mg/dL, respectively. Additionally, ezetimibe, PCSK9i, and icosapent ethyl, while not widely used, were most prevalent among those with a college degree or higher, and PCSK9i was most used in those with health insurance.

Furthermore, ezetimibe, PCSK9 inhibitor, and icosapent ethyl use were highest among non-Hispanic White populations compared to other minority racial/ethnic groups. These results are concerning because Hispanic or Latino populations and non-Hispanic Black populations had the highest proportions with LDL-C levels ≥ 100 mg/dL, and Hispanic or Latino populations and Asian populations had the highest proportion of uncontrolled triglyceride levels of 150 mg/dL or higher. Others have also shown minority groups are more likely to have high triglyceride levels and low HDL-C dyslipidemia [13]. In the US Diabetes Collaborative Registry [2], we recently showed Black persons to be less likely to be at LDL-C target (42.7%) compared to White persons (49.3%). Moreover, from analysis of electronic health record data from a large healthcare system [14], among those with diabetes, Black persons had a 36% lower likelihood of being prescribed a statin compared to White persons in adjusted analysis. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study similarly showed underutilization of statins in non-Hispanic Black populations compared to non-Hispanic White populations [15].

Clinical trials have documented the efficacy of statin and ezetimibe therapy as well as PCSK9 inhibitors and icosapent ethyl, including among persons with DM. In 14 randomized statin trials, which included 18,686 people, researchers found that people with DM who were on statins for an average of 4.3 years had a 21% decrease in major vascular events and a 9% decrease in mortality compared to those who were not on statins [4]. Further reduction of LDL-C not satisfactorily achieved by high-intensity statins can be achieved by ezetimibe or PCSK9 inhibitors [4]. In the IMPROVE-IT trial comparing the addition of ezetimibe to statins alone in persons with a recent acute coronary syndrome, in subgroup analyses, those with DM (in addition to the recent acute coronary syndrome) compared to those without DM had a substantially greater reduction in risk of the primary composite cardiovascular endpoint [16]. In the Fourier trial of evolocumab in persons with prior ASCVD, pre-specified subgroup analyses showed that among the 11,031 (40%) patients with DM, there was a similar 17% risk reduction of the primary cardiovascular endpoint compared to the 13% risk reduction in those without DM (interaction term not significant) [5]. Another study found that the rosuvastatin/ezetimibe combination is safe and effective in patients with hypercholesterolemia or dyslipidemia with or without DM and with or without cardiovascular disease [17,18]. The drug combination enabled higher proportions of patients to achieve recommended LDL-C goals than rosuvastatin monotherapy, without additional adverse events [17,18].

However, despite statin use, people with well-controlled LDL still have residual ASCVD risk associated in part with elevated triglycerides that may be lowered by omega-3 fatty acids, such as icosapent ethyl [5] or fibrate therapy. In the REDUCE-IT trial testing the efficacy of icosapent ethyl in persons with prior ASCVD or DM and multiple risk factors with triglycerides of 135–499 mg/dL on statin therapy, those with vs. without DM had a similar risk reduction in the primary endpoint (23% vs. 27%, with the interaction term not significant) [8]. The recently reported RESPECT-EPA trial [19], while of borderline significance for the primary endpoint, did achieve the secondary endpoint, with relative risk reductions due to icosapent ethyl therapy consistent with REDUCE-IT. However, the recently reported PROMINENT trial [20] involving pemafibrate failed to demonstrate any benefit from this therapy in reducing ASCVD risk in persons with DM who had elevated triglycerides and low HDL-C, and instead showed increased LDL-C levels in the treated group.

Recent real-world evidence from population studies in those with DM shows use of lipid-lowering therapy is still limited, and acceptable LDL-C levels are often not achieved. While our recent report from the National Health and Nutrition Examination Survey 2013-

2016 did show more than 80% of those with DM were on lipid-lowering therapy, only 57% (among those without ASCVD) had an LDL-C < 100 mg/L and only 26% of those who had both DM and CVD had an LDL-C < 70 mg/dL [21]. Moreover, our recent report from the Diabetes Collaborative Registry showed that 49% of those with DM were at LDL cholesterol targets < 100 mg/dL or < 70 mg/dL if with ASCVD, with two-thirds of these on moderate or high-intensity statins [2]. Our results from the *All of Us* cohort show lower levels of lipid treatment, as well as lower levels at appropriate LDL-C levels, likely due to the greater proportions of underrepresented and/or inadequately insured persons in our cohort.

We have previously demonstrated in US adults with DM that despite statin therapy, triglycerides of ≥150 mg/dL are still present in 40%, and even if LDL-C < 100 mg/dL in those on statin therapy, more than a third of such persons still have triglycerides ≥ 150 mg/dL, warranting the consideration of additional triglyceride reducing therapies [3]. We found icosapent ethyl use to be only 1.9% among participants with triglyceride levels greater than or equal to 150 mg/dL. This low use is consistent with other recent real-world data. A recent study by Derington et al. created cohorts using the National Health and Nutrition Examination Surveys (NHANES) 2009–2014 and the Optum Research Database (ORD) to see how many participants were eligible to receive icosapent ethyl [22]. They estimated 3.6 million US adults to be eligible and observed that the 5-year first event (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, or coronary revascularization) rate without IPE was 19.0% compared to 13.1% with 5 years of IPE treatment, preventing 212,000 events. They also projected that the total 5-year event rate (first and recurrent) could be reduced from 42.5% to 28.9% with 5 years of IPE therapy, preventing around 490,000 events, which would amount to approximately USD 2.6 billion in net annual cost. In addition, because icosapent ethyl was approved for ASCVD risk reduction by the FDA recently in December of 2019, it is not surprising that uptake is low in the current study, especially given the wide range of demographic groups included in the *All of Us* research program.

While our results show those with both DM and ASCVD were most likely to be on high-intensity statins, ezetimibe, and icosapent ethyl compared to people with DM who did not have ASCVD, their use was still suboptimal. High-intensity statins are recommended for those with DM and ASCVD [23,24], with further non-statin therapy indicated for further LDL-C lowering. Only 18.2% of our patients with DM and ASCVD were on high-intensity statins, and only 9.1%, 1.3%, and 1.7% were on ezetimibe, PCSK9 inhibitors, and icosapent ethyl, respectively.

Our study has some strengths and limitations. The participants in this study reflect the diversity of the United States and the data are available in near-real time, which is valuable when trying to understand current lipid treatment and control patterns. While the data are extracted from an on-line platform for analysis, these data are from the NIH Precision Medicine Initiative *All of Us* Research Program that does have standardized methods for data collection regarding surveys and blood measurements. However, like with most research studies, participation is voluntary and thus the sample studied, while large, is not necessarily representative of the US population. Moreover, this is a cross-sectional study and we do not have multiple measures of medication use to assess adherence nor multiple laboratory measures to examine the effects of individual therapies, which would require a clinical trial design. There are also other limitations in using electronic health records (EHR) data, where there may be inconsistencies across study sites in capturing prescription and diagnostic data. Additionally, assuming the absence of a diagnostic code as an absence of disease may lead to information and/or selection bias. Further, it has been demonstrated that one key source of bias in EHRs is "informed presence" bias, where those with more medical encounters are more likely to be diagnosed with various conditions [25,26]. Lastly, as our study population is enriched in underserved and disadvantaged persons, results may differ compared to results from health claims data from insured persons.

5. Conclusions

In summary, our cross-sectional analysis demonstrates important disparities in lipid control, as well as in the use of statins, ezetimibe, PCSK9 inhibitors, and icosapent ethyl in US adults with DM across sociodemographic and DM risk groups. Guideline-recommended use of high-intensity statins and ezetimibe among our higher risk DM patients is lacking, with many having inadequately controlled LDL-C levels. Moreover, icosapent ethyl use remains low, even among those with high TG levels. Continued provider and patient education needs to be prioritized—especially among those at highest risk. However, systematic approaches, including the use of EHR and other automated interventions, are needed to address both remaining clinical inertia and significant remaining gaps between evidence-based guidelines and actual care received.

Author Contributions: Conceptualization, N.D.W.; methodology, M.A., D.D., Y.G. and N.D.W.; software, M.A., D.D. and Y.G.; validation, M.A., D.D. and N.D.W.; formal analysis, M.A., D.D. and Y.G.; investigation, M.A., D.D. and N.D.W.; resources, N.D.W.; data curation, N.D.W.; writing—original draft preparation, M.A., D.D. and N.D.W.; writing—M.A. and N.D.W.; visualization, N.D.W.; supervision, N.D.W.; project administration, N.D.W.; funding acquisition, N.D.W. All authors have read and agreed to the published version of the manuscript.

Funding: The *All of Us* Research Program is supported by the National Institutes of Health, Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD 026552; 1 OT2 OD026553; 1 OT2 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276.

Institutional Review Board Statement: Our project involved use of de-identified data so does not meet the definition for human subjects research, therefore is exempt from IRB review.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All data utilized in this study are available from the *All of Us* Research Program at https://allofus.nih.gov/ (accessed on 15 February 2023).

Acknowledgments: The authors thank the participants and investigators of the *All of Us* Research Program. In addition, the *All of Us* Research Program would not be possible without the partnership of its participants. Research reported in this manuscript was supported by the *All of Us* Research Program of the National Institutes of Health under award number OT-PM-16-003. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of Interest: Wong reports research funding not related to this study from Novartis, Novo Nordisk, and Lilly. The other authors declare no conflict of interest.

References

1. Leon, B.M.; Maddox, T.M. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World J. Diabetes* **2015**, *6*, 1246–1258. [CrossRef] [PubMed]
2. Fan, W.; Song, Y.; Inzucchi, S.E.; Sperling, L.; Cannon, C.P.; Arnold, S.V.; Kosiborod, M.; Wong, N.D. Composite cardiovascular risk factor target achievement and its predictors in US adults with diabetes: The Diabetes Collaborative Registry. *Diabetes Obes. Metab.* **2019**, *21*, 1121–1127. [CrossRef] [PubMed]
3. Fan, W.; Philip, S.; Granowitz, C.; Toth, P.P.; Wong, N.D. Residual Hypertriglyceridemia and Estimated Atherosclerotic Cardiovascular Disease Risk by Statin Use in U.S. Adults With Diabetes: National Health and Nutrition Examination Survey 2007-2014. *Diabetes Care* **2019**, *42*, 2307–2314. [CrossRef] [PubMed]
4. Cholesterol Treatment Trialists' (CTT) Collaborators; Kearney, P.M.; Blackwell, L.; Collins, R.; Keech, A.; Simes, J.; Peto, R.; Armitage, J.; Baigent, C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: A meta-analysis. *Lancet* **2008**, *371*, 117–125. [CrossRef]

5. Bhatt, D.L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Ketchum, S.B.; Doyle, R.T., Jr.; Juliano, R.A.; Jiao, L.; Granowitz, C.; et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N. Engl. J. Med.* **2019**, *380*, 11–22. [CrossRef]
6. Sabatine, M.S.; Leiter, L.A.; Wiviott, S.D.; Giugliano, R.P.; Deedwania, P.; De Ferrari, G.M.; Murphy, S.A.; Kuder, J.F.; Gouni-Berthold, I.; Lewis, B.S.; et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: A prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol.* **2017**, *5*, 941–950. [CrossRef] [PubMed]
7. Ganda, O.P.; Bhatt, D.L.; Mason, R.P.; Miller, M.; Boden, W.E. Unmet Need for Adjunctive Dyslipidemia Therapy in Hypertriglyceridemia Management. *J. Am. Coll. Cardiol.* **2018**, *72*, 330–343. [CrossRef]
8. Schwartz, G.G.; Steg, P.G.; Szarek, M.; Bhatt, D.L.; Bittner, V.A.; Diaz, R.; Edelberg, J.M.; Goodman, S.G.; Hanotin, S.; Har-rington, R.A.; et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N. Engl. J. Med.* **2018**, *379*, 2097–2107. [CrossRef]
9. Gallego-Colon, E.; Daum, A.; Yosefy, C. Statins and PCSK9 inhibitors: A new lipid-lowering therapy. *Eur. J. Pharmacol.* **2020**, *878*, 173114. [CrossRef]
10. Sabatine, M.S.; Giugliano, R.P.; Keech, A.C.; Honarpour, N.; Wiviott, S.D.; Murphy, S.A.; Kuder, J.F.; Wang, H.; Liu, T.; Wasserman, S.M.; et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N. Engl. J. Med.* **2017**, *376*, 1713–1722. [CrossRef]
11. The All of Us Research Program. 2021. Available online: https://allofus.nih.gov/ (accessed on 9 October 2021).
12. Force, U.P.S.T.; Mangione, C.M.; Barry, M.J.; Nicholson, W.K.; Cabana, M.; Chelmow, D.; Coker, T.R.; Davis, E.M.; Donahue, K.E.; Jaén, C.R.; et al. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA* **2022**, *328*, 746–753. [CrossRef]
13. Frank, A.T.; Zhao, B.; Jose, P.O.; Azar, K.M.; Fortmann, S.P.; Palaniappan, L.P. Racial/ethnic differences in dyslipidemia patterns. *Circulation* **2014**, *129*, 570–579. [CrossRef] [PubMed]
14. Dorsch, M.P.; Lester, C.A.; Ding, Y.; Joseph, M.; Brook, R.D. Effects of Race on Statin Prescribing for Primary Prevention With High Atherosclerotic Cardiovascular Disease Risk in a Large Healthcare System. *J. Am. Heart Assoc.* **2019**, *8*, e014709. [CrossRef]
15. Schroff, P.; Gamboa, C.M.; Durant, R.W.; Oikeh, A.; Richman, J.S.; Safford, M.M. Vulnerabilities to Health Disparities and Statin Use in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *J. Am. Heart Assoc.* **2017**, *6*, e005449. [CrossRef] [PubMed]
16. Giugliano, R.P.; Cannon, C.P.; Blazing, M.A.; Nicolau, J.C.; Corbalán, R.; Špinar, J.; Park, J.G.; White, J.A.; Bohula, E.A.; Braunwald, E.; et al. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation* **2018**, *137*, 1571–1582. [CrossRef] [PubMed]
17. Boutari, C.; Karagiannis, A.; Athyros, V.G. Rosuvastatin and ezetimibe for the treatment of dyslipidemia and hypercholesterolemia. *Expert Rev. Cardiovasc. Ther.* **2021**, *19*, 575–580. [CrossRef]
18. Lazarte, J.; Hegele, R.A. Dyslipidemia Management in Adults With Diabetes. *Can. J. Diabetes* **2020**, *44*, 53–60. [CrossRef]
19. Available online: https://www.acc.org/Latest-in-Cardiology/Articles/2022/11/01/22/00/sun-7pm-respect-epa-aha-2022 (accessed on 1 February 2023).
20. Das Pradhan, A.; Glynn, R.J.; Fruchart, J.C.; MacFadyen, J.G.; Zaharris, E.S.; Everett, B.M.; Campbell, S.E.; Oshima, R.; Amarenco, P.; Blom, D.J.; et al. Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. *N. Engl. J. Med.* **2022**, *387*, 1923–1934. [CrossRef] [PubMed]
21. Andary, R.; Fan, W.; Wong, N.D. Control of Cardiovascular Risk Factors Among US Adults With Type 2 Diabetes With and Without Cardiovascular Disease. *Am. J. Cardiol.* **2019**, *124*, 522–527. [CrossRef] [PubMed]
22. Derington, C.G.; Bress, A.P.; Herrick, J.S.; Fan, W.; Wong, N.D.; Andrade, K.E.; Johnson, J.; Philip, S.; Abrahamson, D.; Jiao, L.; et al. The potential population health impact of treating REDUCE-IT eligible US adults with Icosapent Ethyl. *Am J Prev Cardiol.* **2022**, *10*, 100345. [CrossRef]
23. Grundy, S.M.; Stone, N.J.; Blumenthal, R.S.; Braun, L.T.; Heidenreich, P.A.; Lloyd-Jones, D.; Orringer, C.E.; Saseen, J.J.; Smith, S.C.; Sperling, L.S.; et al. High-Intensity Statins Benefit High-Risk Patients: Why and How to Do Better. *Mayo Clin. Proc.* **2021**, *96*, 2660–2670. [CrossRef] [PubMed]
24. American Diabetes Association Professional Practice Committee; Draznin, B.; Aroda, V.R.; Bakris, G.; Benson, G.; Brown, F.M.; Freeman, R.; Green, J.; Huang, E.; Isaacs, D.; et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. *Diabetes Care* **2022**, *45* (Suppl. S1), S125–S143. [CrossRef]
25. Gianfrancesco, M.A.; Goldstein, N.D. A narrative review on the validity of electronic health record-based research in epidemiology. *BMC Med. Res. Methodol.* **2021**, *21*, 234. [CrossRef] [PubMed]
26. Pareek, M.; Mason, R.P.; Bhatt, D.L. Icosapent ethyl: Safely reducing cardiovascular risk in adults with elevated triglycerides. *Expert Opin. Drug Saf.* **2022**, *21*, 31–42. [CrossRef] [PubMed]

MDPI
St. Alban-Anlage 66
4052 Basel
Switzerland
www.mdpi.com

Journal of Clinical Medicine Editorial Office
E-mail: jcm@mdpi.com
www.mdpi.com/journal/jcm

Academic Open
Access Publishing

mdpi.com

ISBN 978-3-0365-9872-7