

Article

Applicability of Novel Lipid-Lowering Therapy Trial Findings to a Population of Patients Attending a Specialist Lipid Clinic

Daniel Partridge ^{1,*}, Anisha Pattanayak ^{1,†}, Richard Malone ¹ , Patricia O'Connor ² and Cormac Kennedy ² 

¹ School of Medicine, Trinity College Dublin, D08 W9RT Dublin, Ireland; pattanaa@tcd.ie (A.P.); maloneri@tcd.ie (R.M.)

² Department of Pharmacology & Therapeutics, St James's Hospital, D08 W9RT Dublin, Ireland; poconnor@stjames.ie (P.O.); kennec30@tcd.ie (C.K.)

* Correspondence: partridd@tcd.ie

† These authors contributed equally to this work.

Abstract

Background: Hyperlipidaemia is common and most patients can be managed with established oral therapies and lifestyle modifications. However, patients with complex high-risk lipid disorders require specialist input and access to novel therapies to achieve treatment targets. While new agents are progressing through late phase trials, the eligibility criteria of these studies may limit their applicability to real-world settings. **Aim:** Assessing the generalisability of novel lipid-lowering therapy (LLT) trials by mapping their eligibility criteria to a cohort of patients attending a specialist lipid clinic. **Methods:** An ethically approved study was conducted at a specialist clinic in St James's Hospital, Dublin over 6 months, enrolling 370 patients. Demographics, clinical characteristics, lipid profiles, genetic testing results and LLT use were collected. A structured search of clinicaltrials.gov and euclinicaltrials.eu identified phase 3 pharmacological trials registered since 2018. Patient data were then mapped against trial eligibility criteria to estimate the proportion of clinic patients that would have been eligible for each study. **Results:** In total, 38 trials were identified, including 15 different novel LLTs. It was found that the percentage of the cohort ($n = 370$) that would have been eligible for these LLT trials ranged from 0% to 62.4%, with an average eligibility of 19% across the 38 trials. Further analysis of specific patient subgroups and corresponding trial categories was performed. **Conclusions:** The included novel LLTs trials are reasonably applicable to a specialist lipid clinic cohort, suggesting generalisability to a wider group of real-world patients seen in clinics. This study can help guide future trial design by aligning eligibility criteria more closely with real-world patient populations, ensuring safe and effective clinical practice.

Keywords: hyperlipidemia; novel lipid-lowering therapy; clinical trial; eligibility



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1. Introduction

Hyperlipidaemia is a condition that incorporates various genetic and acquired disorders that describe elevated lipid levels [1]. Hyperlipidaemia is common and is a modifiable risk factor for the development of atherosclerosis and subsequent atherosclerotic cardiovascular disease (ASCVD). Most patients with this condition can be managed in primary care with lifestyle changes and standard lipid-lowering medications. However, there are subgroups of patients who require specialist medical care and access to newer pharmacological therapies to attain treatment targets [2,3]. The complexity of lipid metabolism provides

multiple novel targets for treatments and, as a result, there is a pipeline of treatments for lipid disorders that are progressing through the clinical trial process [4,5].

The authorisation process for medicines includes approval of the indications for which the medicine will be licenced [6]. These indications are based on evidence from large randomised controlled trials (RCTs) [6]. The population in which the medicine was assessed in a published RCT provides key information for the medicine's indications. This, in turn, is determined by the trial's eligibility criteria. Eligibility criteria are often exhaustive and therefore their applicability in clinical practice may be limited to small numbers of patients.

This study examines how novel medicines for hyperlipidaemia may translate into practice in a specialist lipid clinic by comparing the characteristics of trial participants to those of patients attending a specialist lipid clinic. Our findings may assist future trial design in facilitating timely translation of important trial results into clinical practice.

2. Materials and Methods

An ethically approved observational study was conducted over a six-month period at a specialist lipid clinic in St James's Hospital, Dublin, and was subsequently reported in accordance with the STROBE checklist for observational research. This checklist is provided as Supplementary Material [7]. Data were collected from 370 adult patients, including demographics, clinical characteristics, lipid profiles, relevant investigations, results of genetic testing, where available, and current or prior use of lipid-lowering therapies. The following seven categories were devised to describe the lipid clinic cohort in terms of treatment groups relevant to the ongoing clinical trials: primary prevention, secondary prevention, definite genetic or definite phenotypic familial hypercholesterolaemia [8], raised lipoprotein (a) (>70 nmol/L), raised triglyceride level (1.7 mmol/L), low/moderate risk of a cardiovascular event and high/very high risk of a cardiovascular event.

To identify the relevant clinical trials for this research, a structured search was performed using the International Clinical Trials Registry Platform (ICTRP) [9], specifically through clinicaltrials.gov and euclinicaltrials.eu. Search terms included "hyperlipidaemia", "hypercholesterolaemia", "familial hypercholesterolaemia", "hypertriglyceridaemia", "lipoprotein(a)", and "apolipoprotein". Trials were eligible for inclusion if they were Phase 3 studies registered on or after 1 January 2018, involved pharmacological interventions, enrolled at least 200 participants, and were either actively recruiting or completed.

The inclusion and exclusion criteria of each trial were extracted and assessed against the specialist clinic dataset. Each criterion was categorised according to its level of compatibility with available clinic data. This created three categories as follows: criteria that were directly present in the dataset (such as age, lipid values, and comorbidities), criteria partially present but lacking required detail (for example, NYHA classification [10] or time since last hospitalisation), and those not captured in the dataset at all (such as prior malignancy within five years, alcohol or substance misuse, or detailed gynaecological history). Certain universal trial requirements, such as informed consent, contraception adherence, absence of known drug allergies, and willingness to receive subcutaneous or oral medication, were assumed to be satisfied unless explicitly contradicted by the clinical data.

Trials that focused on specific ethnic populations or tested non-novel therapies (such as repurposed statins) were excluded. Trials requiring prior participation in earlier phases were treated as exclusionary unless such participation could reasonably be assumed for general clinical populations. Additionally, criteria related to treatment stability, such as the use of maximally tolerated lipid-lowering therapy or specific medications for a defined period prior to screening, were manually reviewed on a patient-by-patient basis, where applicable data were available. This was to maximise alignment of the lipid clinic

cohort with the trial populations. The final step involved systematically comparing each patient's data with the eligibility criteria of the included trials. This process allowed for the calculation of the proportion of patients who would have met the inclusion and exclusion criteria for each trial. When criteria could not be definitively assessed due to missing or incomplete data, eligibility was conservatively estimated to avoid overestimation.

To facilitate comparison across trials, populations were stratified into primary and secondary prevention. In this study, primary prevention refers to patients without established ASCVD and treated to reduce future risk, while secondary prevention refers to those with a documented ASCVD history including events of myocardial infarction, stroke, etc. Trials that did not focus on a specific prevention subgroup were classified as mixed trials.

Clinical conditions of interest were classified in line with the definitions used in a previous study with the same patient cohort [11], which identified specific populations such as heterozygous familial hypercholesterolaemia (HeFH), elevated lipoprotein (a) [Lp(a)], mixed dyslipidaemia, hypertriglyceridaemia, and statin intolerance. The same categories were used in the current trial dataset for consistency.

Cardiovascular risk categories were also assigned according to the European Society of Cardiology (ESC) SCORE2 criteria, distinguishing low-to-moderate risk from high to very high risk of ASCVD [12].

The novel lipid-lowering therapies were grouped into five categories based on the drug formulation: monoclonal antibody (mAb), antisense oligonucleotide (ASO), small molecule, small interfering RNA (siRNA) and Peptide/Protein. In this study, a small molecule is defined as a low-molecular-weight organic compound, typically less than 1000 Daltons. The Peptide/Protein category encompasses large, complex molecules made of proteins or peptides that have therapeutic effects on the body.

3. Results

The lipid clinic cohort consisted of 370 patients, with a mean age of 49 years (± 14 years). The average BMI of the cohort was 28 and 55% were female. While the majority of patients ($n = 285$) attending the clinic did not have cardiovascular disease at the time of assessment, 23% ($n = 85$) had established cardiovascular disease. There were 127 patients with genetically confirmed or definite phenotypic familial hypercholesterolaemia, defined by a definite Dutch Lipid Clinic Network Score. There were 127 patients with an untreated Lipoprotein(a) level above 70 nmol/L and 134 with a triglyceride level above 1.7 mmol/L. Using the ESC guidelines [12], 217 patients (59%) were classified as having a high or very high risk of a cardiovascular event whilst 152 patients (41%) were at a low or moderate risk of a cardiovascular event. The cohort was stratified into these categories to facilitate comparison across the included trials, as shown in Figure 1.

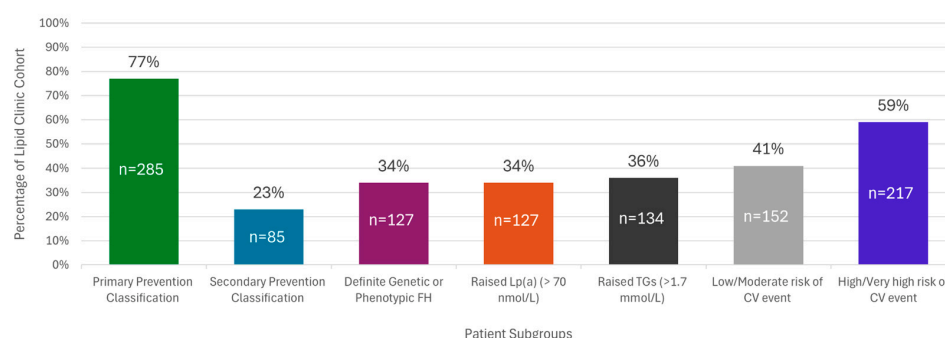


Figure 1. Percentage of patients from the lipid clinic cohort within key subgroups. Distribution of patients across key clinical subgroups, including cardiovascular disease status, lipid phenotypes, and ESC cardiovascular risk categories. FH—familial hypercholesterolaemia. TGs—triglyceride, CV—cardiovascular.

3.1. Identified Clinical Trials and Patient Eligibility

The initial search identified 133 trials. Following screening, 38 trials were included. Reasons for trial exclusion were as follows: evaluation of complementary or alternative medicines, having fewer than 200 participants, limited to paediatric populations, involving existing combination therapies such as ezetimibe plus atorvastatin, restricted to dialysis patients, having unclear mechanisms of drug action, and involving drugs not considered novel, including pitavastatin and ezetimibe.

3.2. Trial Populations

The 38 trials were then summarised based on the patient population on which they focused. Figure 2A shows the distribution of trials by prevention category. Primary prevention trials were the least common (5.3%, $n = 2$) and focused on patients without established ASCVD and being treated to reduce future risk of developing ASCVD. Secondary prevention trials (23.7%, $n = 9$) targeted patients with established ASCVD. The remaining trials (71.1%, $n = 27$) did not specify the cardiovascular disease (CVD) status of the trial population and were classified as mixed.

Figure 2B illustrates the medical conditions targeted by each of the 38 trials. While some trials were condition-specific, the largest category was unspecified/other (42.1%), indicating broad eligibility criteria or focusing on general high-risk lipid disorders.

Figure 2C demonstrates the overall cardiovascular risk categorization of trial populations according to ESC guidelines [12]. Two categories were included: one being low-to-moderate risk; and the other being high-to-very high risk. 60.5% of trials focused on low-to-moderate risk of CVD, and 39.5% of trials focused on high-to-very high risk.

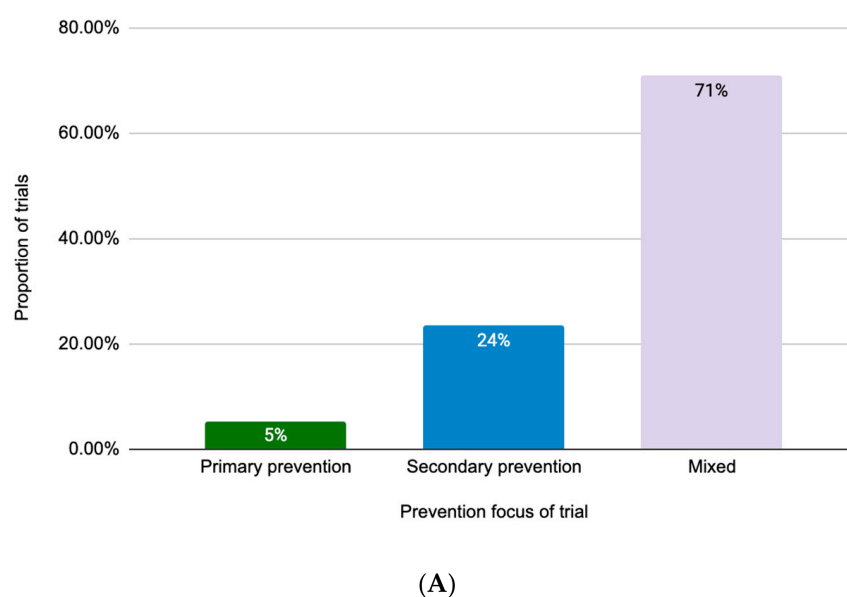
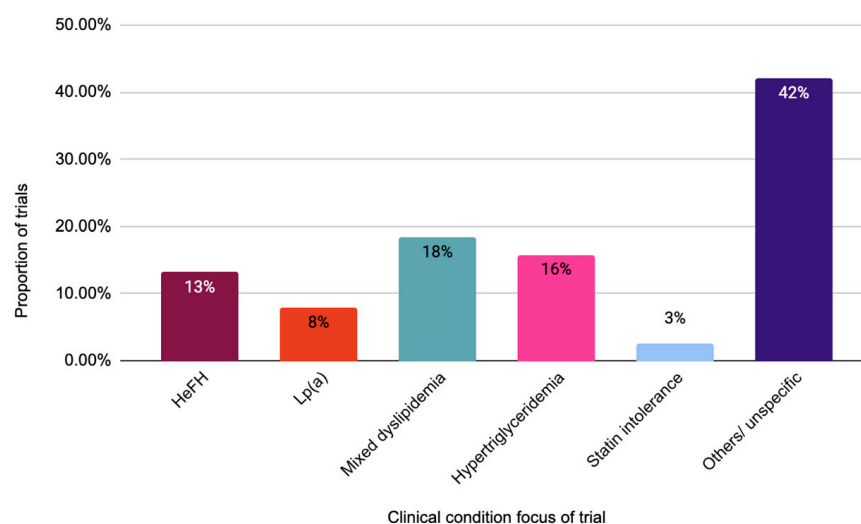
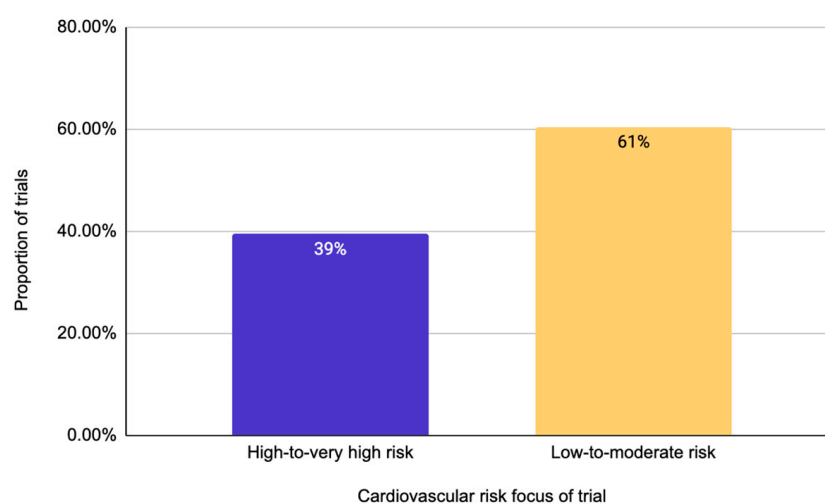


Figure 2. Cont.



(B)



(C)

Figure 2. (A): Proportion of included trials by prevention focus. Distribution of the 38 trials according to whether they focused on primary prevention, secondary prevention, or did not specify prevention status. (B): Proportion of included trials by clinical condition of interest. Distribution of the 38 trials according to the clinical indications targeted, including heterozygous familial hypercholesterolaemia, elevated lipoprotein(a), mixed dyslipidemia, hypertriglyceridaemia, statin intolerance and unspecified categories. (C): Proportion of included trials by cardiovascular risk focus. Distribution of the 38 trials according to the cardiovascular risk categories targeted (high-to-very high risk versus low-to-moderate), based on ESC definitions.

3.3. Associated Patient and Trial Subgroups

The patient and trial subgroups were analysed to assess the percentage of patients that would have been eligible for at least one corresponding phase 3 lipid-lowering therapy trial. This analysis showed that 44% of primary prevention patients would have been eligible for at least one of the primary prevention trials and 82% of secondary prevention patients would have been eligible for at least one of the secondary prevention trials. With regard to Lp(a) trials, 95% of patients with an Lp(a) level greater than 70 nmol/L would have been eligible for at least one of the Lp(a) trials. In the fourth and final subgroup analysed, 64% of patients with genetically confirmed or definite phenotypic familial hypercholesterolaemia

would have been eligible for at least one of the familial hypercholesterolaemia trials. These findings are shown in Figure 3 below.

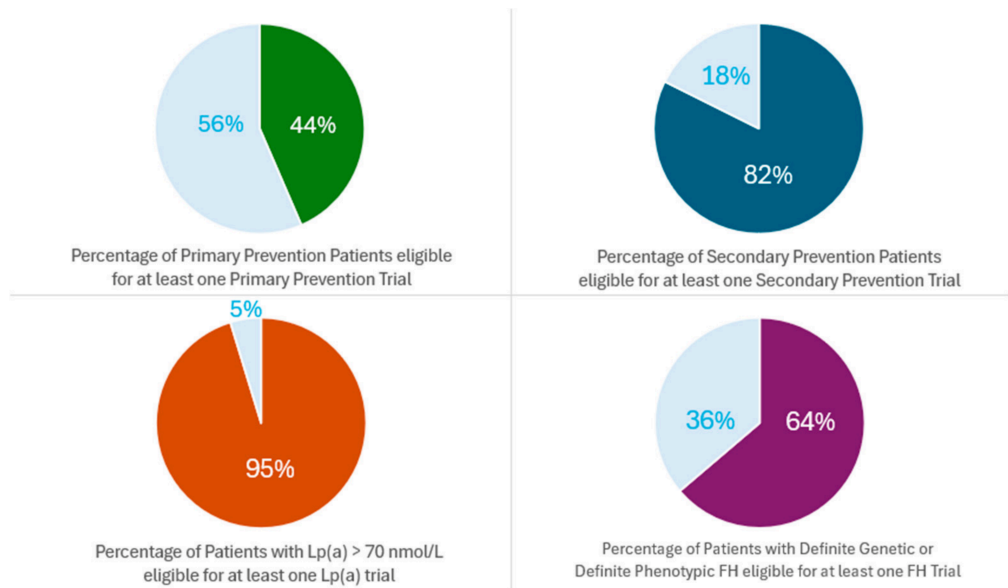


Figure 3. Eligibility of clinical subgroups for corresponding phase 3 trials. Percentage of patients within each clinical subgroup who met the eligibility criteria for at least one corresponding phase 3 lipid-lowering therapy trial. Results are shown for the following categories: primary prevention; secondary prevention; definite genetic or phenotypic familial hypercholesterolaemia and elevated lipoprotein(a) [Lp(a)].

3.4. Whole Lipid Clinic Cohort

The 38 trials covered 15 different novel lipid-lowering therapies. The percentage of the lipid clinic cohort (*n* = 370) that would have been eligible for these lipid-lowering therapy trials ranged from 0% (in four trials) up to 62.4%. Figure 4 presents the percentage of the cohort that would have been eligible for each trial.

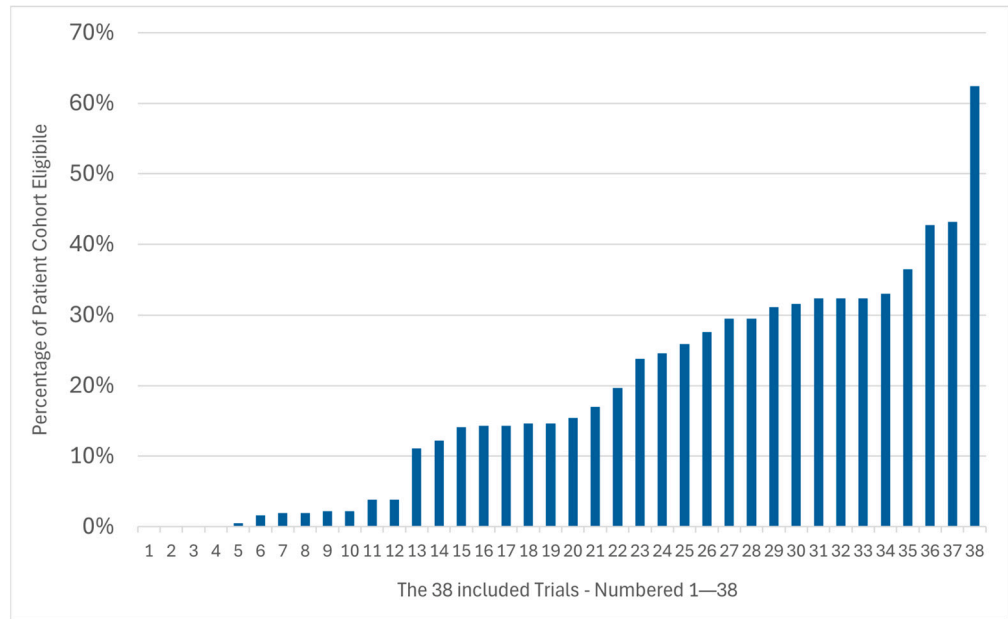


Figure 4. Eligibility of the patient cohort across the included phase 3 trials. The percentage of patients from the lipid clinic cohort (*n* = 370) meeting the eligibility criteria for each of the 38 included trials (numbered 1—38).

3.5. Drug Modalities Under Investigation

The 38 trials were then categorised into five different groups of drug classification. These are: monoclonal antibodies, antisense oligonucleotides, small molecules, small interfering RNAs and Peptides/Proteins. The monoclonal antibody trials looked at the use of certain Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors. The antisense oligonucleotide trials investigated the use of pelacarsen and olezarsen whilst the small molecule trials investigated the use of obicetrapib, pemafibrate and certain PCSK9 inhibitors. The siRNA trials looked at the use of plogasiran, inclisiran and olpasiran. Finally, the Peptide/Protein trials assessed the use of lerodalcibep and Enlicitide chloride. Figure 5 shows the number of trials per drug classification.

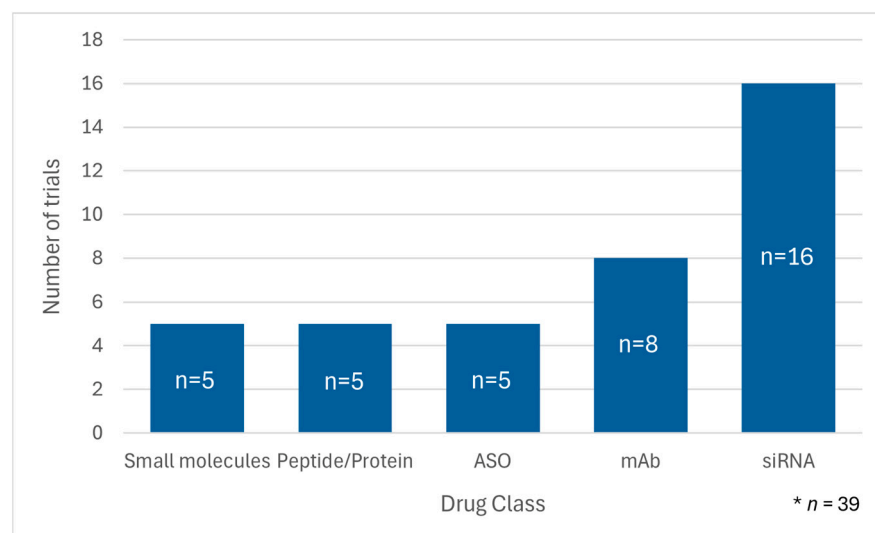


Figure 5. Breakdown of trials ($n = 38$) by drug classification. Breakdown of the 38 trials according to drug class, including antisense oligonucleotides (ASO), small molecules, Peptide/Protein therapies, monoclonal antibodies (mAb) and small interfering RNA (siRNA). * Trial NCT04790513 involved two drug classifications (Peptide/Protein and mAb), examining Lerodalcibep, Evolocumab and Alirocumab, hence the total = 39.

4. Discussion

This study adds to the limited body of evidence assessing the real-world applicability of LLT trials. It systematically examined 38 trials across 15 emerging lipid-lowering agents that were still in late phase development, providing a general overview of the evolving therapeutic landscape. The study compared information on emerging lipid-lowering therapies trials with a group of 370 patients attending a specialist lipid clinic. Across the 38 included trials, the percentage of patients from the St James's Hospital lipid clinic who would have been eligible ranged from 0% to 62.4%, with an average eligibility of 19%. Of the included trials, 5.3% focused on primary prevention and 23.7% targeted secondary prevention. A large proportion of the trials (42.1%) did not focus on a specific medical condition, suggesting broader eligibility criteria. Overall, 60.5% of the trials involved participants at low-to-moderate cardiovascular risk. Sixteen trials investigated small interfering RNA (siRNA) agents, eight investigated monoclonal antibodies and Peptides/Proteins, small molecules, and antisense oligonucleotides (ASO) were represented by five trials each.

The additional subgroup analysis showed that eligibility varied across clinical populations. While only 43.5% of primary prevention patients were eligible for at least one corresponding phase 3 trial, eligibility was substantially higher among secondary prevention patients (82%), patients with elevated Lp(a) (95%), and those with definite genetic

or phenotypic FH (64%). These findings suggest that the current evidence base is more representative of certain high-risk populations than others, with primary prevention patients remaining comparatively underrepresented in contemporary phase 3 lipid-lowering therapy trials.

LLT clinical trials typically apply strict inclusion and exclusion criteria, often focusing on high-risk patients with ASCVD as these patients are at a high risk of recurrence. The statistical power of such trials is increased in higher risk populations as CV events are more likely to occur in these groups. A greater number of events occurring translates to a higher event rate. This can result in a shorter, less expensive trial and one that is more likely to show a statistically significant difference in the treatment group. However, once a therapy becomes available in the clinical world, it is often prescribed to a broader and more heterogeneous patient group than those enrolled in the original trials. It is important to note that among the broader patient group, many would have a high CV risk due to factors such as diabetes or subclinical disease.

This study looks to address a gap in the current literature on how the eligibility criteria of novel LLT trials can affect their generalisability. Averitt et al. highlighted that while strict inclusion and exclusion criteria in randomised controlled trials (RCTs) improve internal validity of the trials, the external validity is usually compromised, therefore limiting applicability to patients commonly seen in routine care [13]. Similarly, Schuitema et al. applied eligibility criteria from eight lipid-lowering RCTs to a large real-world cohort of patients with established ASCVD ($n = 8537$) [14]. They found that patient eligibility depended on the specific trial and disease subtype considered. Trial eligible and ineligible patients differed in baseline characteristics like age, comorbidities, and lipid levels; however, they did not differ when considering long-term risks of recurrent cardiovascular events and all-cause mortality, suggesting that exclusion criteria may not always accurately reflect the benefits and risks of treatment.

Aeschbacher-Germann et al. (2022) similarly observed that restrictive exclusion criteria in lipid trials often exclude people with common diseases, such as moderate to severe kidney disease, heart failure or patients with immunosuppression [15]. The study emphasised the need to balance internal and external validity and to consider more flexible eligibility criteria where appropriate. Zafrir et al. showed that RCTs are more generalisable if the sample cohort has patients with characteristics close to that of real-world patients [16]. Their study of PCSK9 inhibitor use in a real-world lipid clinic showed comparable efficacy and safety outcomes to those seen in related RCTs. However, the study emphasised the need to consider additional practical barriers such as cost, adherence and treatment access, all of which could affect the translation of trial outcomes into everyday practice.

Beyond LLT trials, Nicolucci et al. (2019) examined the generalisability of four cardiovascular outcome trials of SGLT2 inhibitors in a real-world Italian cohort with type 2 diabetes [17]. The proportion of patients meeting trial eligibility criteria varied greatly (11.7–55.9%), and only a small fraction of eligible patients was actually prescribed SGLT2 inhibitors in clinical practice, highlighting a persistent gap between trial eligibility and real-world implementation.

Studies across oncology, HIV, transplantation and lung cancer consistently show that trial eligibility criteria frequently exclude large proportions of patients seen in clinical practice. In advanced non-small cell lung cancer, Al-Baimani et al. reported that up to 73% of real-world patients would have been trial-ineligible, yet many still benefited from treatment when prescribed the medication in clinics or hospitals, suggesting eligibility criteria may be too restrictive [18]. Gandhi et al. showed in their review of HIV RCTs, that there was a discrepancy between the trial protocol eligibility criteria and the eligibility criteria outlined in subsequent publications. This adds further complexity to evaluating

the external validity of these trials [19]. Ayaz-Shah et al. identified gaps in transplant immunosuppression trials, where the eligibility criteria used, often did not reflect real-world patient cohorts [20]. In oncology, Karim et al. found most real-world patients would not be eligible for standard trials, and Sam et al. showed that even among eligible melanoma patients, many did not receive the trial-proven therapies in practice, highlighting a gap between evidence generated in trials and what happens in real-world care [21,22]. These studies further show that strict eligibility criteria frequently limit real-world applicability across various specialties.

4.1. Future Avenues

This study is a retrospective review of LLT trials and compares their eligibility criteria to an established patient cohort attending a specialist lipid clinic. Future studies would ideally identify the trial eligibility criteria prior to the collection of patient data, thereby employing a prospective methodology. This approach would ensure that the patient data in future studies will be aligned with the trial eligibility criteria and facilitate a more accurate measure of generalisability.

The methodology employed in this research suggests a role for Artificial Intelligence (AI) to assist in similar future studies, as data collection and cross comparison of medical information may be achieved in a quicker, more efficient process compared to the manual data interpretation that was employed in this study. AI would be of particular benefit in recognising patterns in patient clinical characteristics and categorising each patient into specific clinical subgroups for analysis. The technology may also aid in screening for any errors in the data interpretation and subsequent analysis. Patient data protection would need to be ensured and therefore ensuring transparency in any potential AI system's design, operation, and outcomes is essential for their safe and effective deployment [23].

4.2. Study Limitations

Clinical data was gathered from 370 individuals attending a specialist clinic and therefore represents a relatively small snapshot of the generalisability of these novel LLT trials to the wider population with dyslipidaemia. Future studies would benefit from increasing the number of included patients in order to gain a better understanding of the generalisability of such trials.

Patient data on certain eligibility criteria was either unavailable or incomplete. These included the New York Heart Association classification, time since last hospitalisation, prior malignancy within 5 years and alcohol or substance misuse. Future prospective studies would benefit from collecting clinical data on variables in accordance with the identified trial eligibility criteria as this would better enable comparability and thus assessment of the applicability of the trial results.

Certain trial eligibility criteria were not a reflection of the patient cohort characteristics but rather a technical diagnostic method deemed necessary for the trial. For example, one trial (NCT06347016) outlined that triglyceride levels needed to be "collected at two separate and consecutive visits at least seven days apart and no more than 17 days apart during the screening period." Such specific criteria could not be satisfied in a retrospective study.

These limitations could be addressed by future large, prospective studies. In these studies, a focus should be on including a larger number of patients with clinical data more closely aligned with the identified trial eligibility criteria.

5. Conclusions

This study assesses the applicability of novel lipid-lowering therapy trial results to real-world patient populations. We found that the included novel lipid-lowering therapy trials

are reasonably applicable to a specialist lipid clinic cohort, suggesting generalisability to a wider group of patients. Eligibility varied considerably across trials, reflecting heterogeneity in target populations, therapeutic classes and their mechanisms of action. These findings provide a unique insight into trial eligibility criteria as they span different novel lipid-lowering therapies across 38 trials.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/lipidology3030022/s1>, STROBE checklist.

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Informed Consent Statement: The Tallaght Hospital Research Ethics Committee waived the requirement for informed consent.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to patient privacy restrictions as the data were collected from patients attending a specialist lipid clinic.

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