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Review

Polygenic Risk Scores for Personalized Cardiovascular Pharmacogenomics—A Scoping Review

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Abstract: Cardiovascular disease (CVD) is the leading cause of mortality worldwide, often involving a strong genetic background. Polygenic risk scores (PRSs) combine the cumulative effects of multiple genetic variants to quantify an individual's susceptibility to CVD. Pharmacogenomics (PGx) can further personalize treatment by tailoring medication choices to an individual's genetic profile. Even with these potential benefits, the extent to which PRS can be integrated into the PGx of CVD remains unclear. Our review provides an overview of current evidence on the application of PRS in the PGx of CVD, examining clinical utility and limitations and providing directions for future research. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews protocol, we conducted a comprehensive literature search in PubMed, EMBASE, and the Web of Science. Studies investigating the relationship between PRS in predicting the efficacy, adverse effects, or cost-effectiveness of cardiovascular medications were selected. Of the 1894 articles identified, 32 met the inclusion criteria. These studies predominantly examined lipid-lowering therapies, antihypertensives, and antiplatelets, although other medication classes (e.g., rate-control drugs, ibuprofen/acetaminophen, diuretics, and antiarrhythmics) were also included. Our findings showed that PRS is most robustly validated in lipid-lowering therapies, especially statins, where studies reported that individuals with higher PRSs derived the greatest reduction in lipids while on statins. Studies analyzing antihypertensives, antiplatelets, and antiarrhythmic medications demonstrated more variable outcomes, though certain PRSs did identify subgroups with significantly improved response rates or a higher risk of adverse events. Though PRS was a strong tool in many cases, we found some key limitations in its applicability in research, such as the under-representation of non-European-ancestry cohorts in the examined studies and a lack of standardized outcome reporting. In conclusion, though PRS offers promise in improving the efficacy of PGx of CVD by enhancing the personalization of medication on an individual level, several obstacles, such as the need for including a broader ancestral diversity and more robust cost-effectiveness data remain. Future research must (i) prioritize validating PRS in ethnically diverse populations, (ii) refine PRS derivation methods to tailor them for drug response phenotypes, and (iii) establish clear and attainable guidelines for standardizing the reporting of outcomes.

Keywords: cardiovascular disease; polygenic risk scores; pharmacogenomics; cost-analysis

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1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide, responsible for an estimated 17.9 million deaths each year, making up ~32% of all global

fatalities [1]. Many CVDs arise from a combination of lifestyle factors and a mixed genetic background wherein familial risk factors and inherited mutations play a significant role in disease conditions [2,3]. Rather than being explained by single-gene Mendelian-type mutations, most CVDs arise from a complex polygenic background in which many genetic variants, each with a minor individual effect, collectively influence disease onset and progression [4].

Recent advances in Genome-Wide Association Studies (GWASs) have accelerated the discovery of numerous small-effect variants in human populations. The variants are referred to as single-nucleotide polymorphisms (SNPs). An SNP refers to a genetic variation occurring at a specific site in the DNA, where a single nucleotide differs among different individuals in a population [5]. Certain SNPs have been known to show strong association with the onset and progression of various CVDs [4,6–8]. However, the effect size for a single gene variant is typically quite small compared to traditional non-genetic clinical risk factors such as lifestyle, environment, sex, and age [9]. A person's genetic susceptibility to a particular disease may be more accurately reflected by a polygenic risk score (PRS), which is created by integrating numerous SNPs and weighting them according to their effect sizes [10]. Several different methodologies exist to weigh PRSs. Briefly, these include traditional approaches, such as allele counting, which involves weighing each variant by its effect size, and more novel methodologies, including machine learning approaches such as LDPred, which aim to account for linkage equilibrium. All in all, PRS holds immense potential to improve clinical disease models for the prediction and risk stratification of an individual's susceptibility to CVDs [11–13].

Pharmacogenomics (PGx) considers a person's genetic makeup when predicting their response to medications. PGx plays a highly significant role in enhancing drug safety and cost-effectiveness by creating a personalized medicine plan, where pharmacological treatments are tailored based on an individual's genetic profile to reduce adverse drug reactions and optimize therapeutic outcomes [14]. Incorporating PRS into the PGx of CVDs offers a comprehensive analysis of response to pharmacotherapy by capturing the cumulative genetic factors that influence drug response, tolerance, and side-effect profiles [15]. This approach holds potential for identifying patients most likely to benefit from commonly prescribed cardiovascular medications (e.g., statins, antihypertensives, antiplatelets, and rate-control agents) while minimizing risks like adverse events or poor therapeutic response.

Despite growing evidence for the value of PRSs in disease risk prediction, the clinical application of these scores in pharmacogenomic decision-making is limited [16]. The successful implementation of PRS in routine practice will likely hinge on its demonstrated capacity to improve medication selection, enhance safety, and reduce costs through tailored treatment strategies. Currently, there is no comprehensive synthesis of research on integrating PRS into cardiovascular pharmacotherapy. To this end, our scoping review aims to evaluate and summarize the current literature on the use of PRSs in the PGx of CVD. We address the role of PGx in optimizing drug response and the advantage of PRSs in capturing broad genetic risk for personalized treatment. Ultimately, our goal is to inform whether PRS-guided prescribing may enhance patient outcomes, mitigate adverse effects, and provide a cost-effective pathway toward precision cardiovascular care.

2. Methods

The reporting of this scoping review was conducted in accordance with the Preferred Reporting Items For Systematic Reviews and Meta-analysis extension for Scoping Reviews (PRISMA-ScR) statement. A systematic review was the initial intention for this study, but the heterogeneity of the literature and significant variability in the quality of evidence

precluded this, and, therefore, a scoping review was viewed by the authors to be more appropriate. As per the PRISMA-ScR statement, a formal risk of bias assessment was not performed.

2.1. Data Source and Search Strategy

To identify relevant articles, a literature search was performed in the following electronic bibliographical databases, which included publications up to 1 May 2024: PubMed, EMBASE, and the Web of Science on the Cochrane Library. The search strategy was developed with assistance from a medical librarian. Search functions were designed to incorporate three subsections using [AND] Boolean operators. Subsections contained MeSH and field-designated search terms for cardiovascular diseases and polygenic risk scores and pharmacogenomics. The list of search terms used for each of these subsections can be found in the Supplementary Materials (Table S1). A challenge we faced in this approach was the lack of standardized MeSH and field-designated terminology for pharmacogenomics. Hence, we used a detailed list of all the medications of interest instead. These medications were in the four main categories of cardiovascular agents, adrenergic agents, lipid-regulating agents, and heterocyclic compounds. The specific list of medications used can be found in the Supplementary Materials (Table S2). Furthermore, reference lists from previously published reviews and publications were screened for articles not identified through the initial search strategy.

2.2. Inclusion Criteria

All articles identified via the literature search were exported to Covidence (Veritas Health Innovation Ltd., Melbourne, Australia), a systematic review management software. Two study authors (P.N. and J.P.) independently undertook the study selection, with discrepancies resolved by consensus between the two authors. Inclusion criteria included the following: (1) English-language studies; (2) study authors examined the relationship between PRS and adverse effects, efficacy, or cost-effectiveness of medications of interest in the context of heart disease; (3) the articles provided sufficient data for extraction and analysis; (4) they were original research articles published in peer-reviewed journals; (5) the study designs were randomized controlled trials, cohort studies, case–control studies, cross-sectional studies, observational studies, or clinical trials. Of note, there was no restriction on the age of the participants in the included studies, as an individual's genetic profile is set at birth. Studies were excluded if they did not provide sufficient data for analysis or if they were reviews, meta-analyses, conference abstracts, case reports, case series, review articles, editorials, or commentaries.

2.3. Main Outcomes

The main outcomes of this study were the following: (1) the efficacy and benefits of using PRS to predict treatment responses in cardiovascular PGx, (2) the identification of adverse effects associated with cardiovascular therapies when stratified by PRS, and (3) cost considerations related to the implementation of PRS in guiding cardiovascular treatment decisions.

2.4. Data Extraction

Data extraction was conducted by three study authors (P.N., J.P., and A.D.). Information extracted from each study included the title, journal of publication, year of publication, first author, DOI, study objective, cardiovascular disease of study, characteristics of study participants, ancestry of study population, primary study outcome, PRS, number of SNPs used to obtain the PRS, medications that were assessed, main outcome parameters, quantitative variables and statistical methods, PRS performance independently

and when incorporated into an integrated risk model, and main study conclusions. To have a standardized approach to evaluate PRS performance across studies, we recorded statistical findings such as hazard ratio (HR), odds ratio (OR), 95% confidence interval (CI), and measures of model performance such as area under curve (AUC) and C-statistic as they were reported in the studies. These findings were extracted in Google Sheets and then compiled into Summary Tables 1–7.

3. Results

3.1. Study Selection

A study flow diagram is shown in Figure 1. The initial database search identified 1894 articles. Through a de-duplication process, 1016 records were removed. Titles and abstracts of the remaining articles were screened, and 786 were determined to be not relevant to the research question. The full-text review of the remaining 92 articles led to the exclusion of 60 additional studies due to factors such as insufficient endpoints. In total, 32 articles met the inclusion criteria and underwent data extraction and analysis.

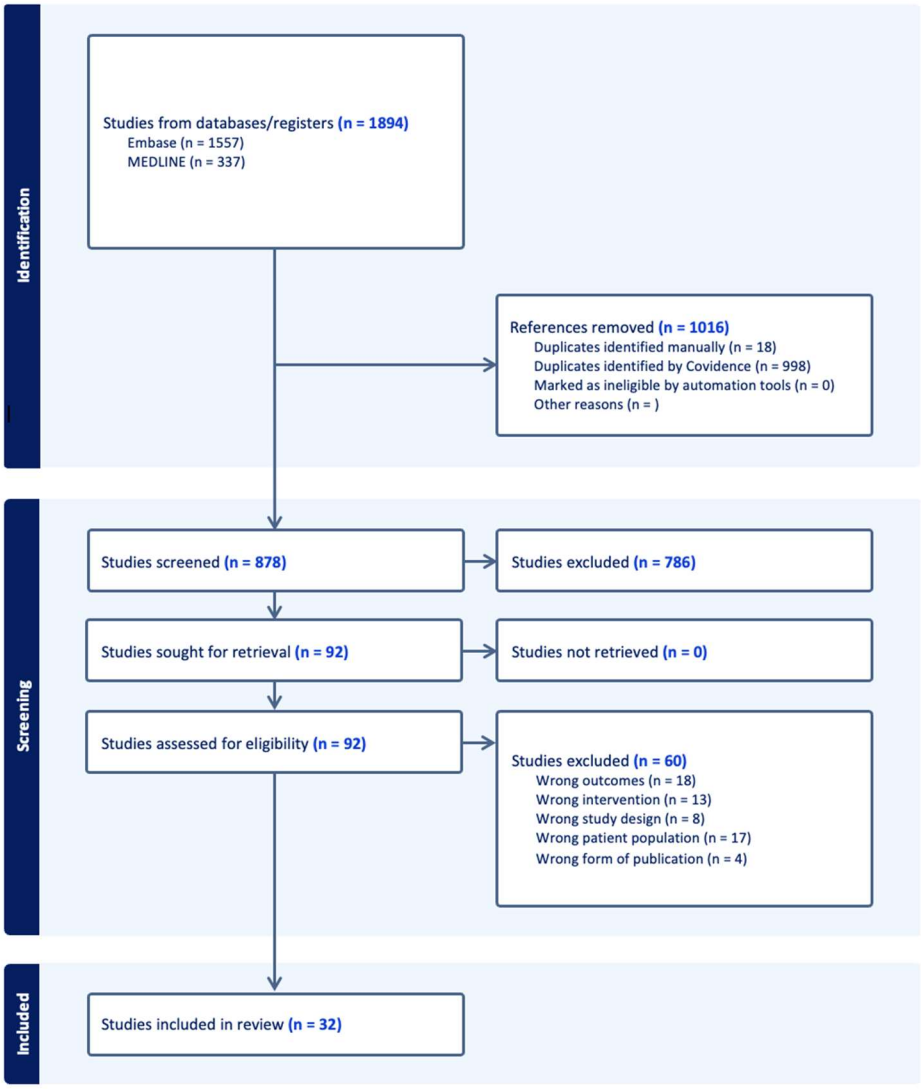

Figure 1. PRISMA flow diagram for review methodology.

3.2. Characteristics of Included Studies

Detailed characteristics of the 32 included studies in our review are presented in Tables 1–7. The studies were published within the year range of 2010 to 2024, with most

articles (28 out of 32) appearing in the last decade. This is likely due to the recent expansion of PRS research within the field of CVD PGx. The sample sizes varied from fewer than 140 participants to large-scale cohorts of over 359,000 individuals. Among the 32 studies, there were a total of 50 PRSs that were investigated. The distribution of PRSs for different drugs and CVDs is provided in Supplementary Table S1.

Table 1. Summary of studies investigating different therapeutics and the ancestry of included participants.

Authors (y)	Refs.	Participant Race/Ancestry	Medication Class
Oni-Orisan A. et al., 2022	[17]	White, Black, Latinx, and East Asian	Lipid-Lowering
Mega et al., 2015	[18]	White	Lipid-Lowering
Natarajan et al., 2017	[19]	White	Lipid-Lowering
Jarmul et al., 2018	[20]	N/A	Lipid-Lowering
Leusink et al., 2016	[21]	White	Lipid-Lowering
Hamrefors et al., 2010	[22]	N/A	Lipid-Lowering
Marston et al., 2020	[23]	White	Lipid-Lowering
Erasmo et al., 2021	[24]	Italian	Lipid-Lowering
Kiflen et al., 2022	[25]	White	Lipid-Lowering
Damask et al., 2020	[26]	White, Asian, Black, and Others	Lipid-Lowering
Mayerhofer et al., 2022	[27]	White	Lipid-Lowering
Pechlivanis et al., 2021	[28]	White	Lipid-Lowering
Zhai et al., 2024	[29]	Chinese	Antihypertensives
Vidal et al., 2022	[30]	Not Mentioned Explicitly—Participants from Lausanne, Switzerland	Antihypertensives
Rouby et al., 2019	[31]	White and Hispanic	Antihypertensives
McDonough et al., 2013	[32]	White and Hispanic	Antihypertensives
Gong et al., 2012	[33]	White and Black	Antihypertensives
Lynch et al., 2012	[34]	White, Black, American Indians/Alaskan Natives, Asians/Pacific Islanders, and Others	Antihypertensives
Tähtisalo et al., 2020	[35]	Finnish	Antihypertensives
Türkmen et al., 2024	[36]	White	Antihypertensives
Åberg et al., 2022	[37]	Finnish	Antihypertensives
Acosta et al., 2023	[38]	White	Antihypertensives
Maroteau et al., 2020	[39]	White and Black	Antihypertensives
Narang et al., 2020	[40]	White	Antihypertensives
Barrett et al., 2016	[41]	White	Rate-Control Agents
Luzum et al., 2023	[42]	White and Black	Rate-Control Agents
Lanfear et al., 2020	[43]	White	Rate-Control Agents
Strauss et al., 2017	[44]	White, Black, and Asian	Antiarrhythmics
Tadros et al., 2019	[45]	White	Antiarrhythmics
Lewis et al., 2020	[46]	White	Antiplatelets
Lacaze et al., 2022	[47]	White	Antiplatelets
Zhang et al., 2023	[48]	White	Anti-Inflammatory

Table 2. Summary of studies on PRS for lipid-lowering therapeutics intervention. Note: Where possible, only the highest PRS group/quintile effect size is reported. No study in this cohort reported AUC/C-statistics. "Discovery GWAS" refers to the dataset used to identify genomic loci associated with PGx outcomes. "Validation/Testing dataset" refers to the population in which the PRS derived from the discovery dataset is tested. In the included studies for our analyses, this dataset represents an external or subset cohort used for validation of the PRS derived from the discovery dataset.

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	Main Findings
Oni-Orisan A. et al., 2022 [1]	N/A	32,736	CHD PRS	164	Statin effectiveness in high PRS, HR = 0.41 (0.31–0.53)	Age, sex, HTN, diabetes, smoking, LDLc levels, ASCVD risk score	Statin effectiveness was highest in the high-PRS group, intermediate in the intermediate group, and lowest in the low PRS group, while ASCVD risk and statin LDLc lowering were similar across all PRS groups.
Mega et al., 2015 [2]	N/A	48,421	CHD PRS	27	Statin effectiveness in high PRS, HR = 0.52 (0.37–0.71)	Age, sex, diabetes status, smoking, race (if applicable), Fx of CHD, HDLc LDLc, HTN	PRS identified individuals at higher risk for incident and recurrent CHD events, with those having a high PRS experiencing the greatest benefit from statin therapy. For primary prevention, high-PRS individuals had a threefold-lower NNT compared to low-risk groups.
Natarajan et al., 2017 [3]	N/A	WOSCOPS (4910), CARDIA (1154), BioImage (4392)	CHD PRS	57	Statin effectiveness in high PRS, HR = 0.56 (0.40–0.78)	Age, sex, DM, smoking, baseline LDLc, baseline HDLc, SBP, antihypertensive medication status, Fx of MI, or stroke	Statin therapy led to greater RR reduction in those at high genetic risk for CHD. High genetic risk was associated with greater burden of subclinical atherosclerosis.

Table 2. *Cont.*

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	Main Findings
Jarmul et al., 2018 [4]	N/A	10,000	Cardiovascular PRS (cPRS)	27	N/A	Age, sex, ASCVD risk factors (SBP, total cholesterol, HDLc, smoking, antihypertensive medication use)	Testing a cPRS is usually not cost-effective for guiding statin therapy in primary ASCVD prevention among low- to intermediate-risk patients. However, in specific cases, cPRS testing may be cost-effective under certain assumptions.
Leusink et al., 2016 [5]	1991	5314	PRS for statin response	50,000 (discovery), 3 (risk score)	N/A	Age, sex, baseline LDLc, population stratification	No new SNPs were linked to statin-induced LDLc reduction. The PRS had a minor but significant effect, with each allele reducing LDLc response by 2%. Since statins effectively lower LDLc regardless of genotype, genetic testing is unlikely to significantly influence statin therapy decisions.
Hamrefors et al., 2010 [6]	N/A	395	LDL + HDL PRS	9	N/A	Age, BMI reduction, baseline blood glucose, % of BMI change	PRS was associated with fluvastatin-induced changes in LDL and HDL in women but not in men. Higher PRS correlated with smaller LDL reductions and greater HDL increases. Additionally, higher LDL + HDL and HDL-specific scores were linked to larger HDL increases in women.

Table 2. *Cont.*

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	Main Findings
Marston et al., 2020 [7]	N/A	14,298	CHD PRS	27	Evolocumab effectiveness in high PRS, HR = 0.75 (0.60–0.94)	Age, sex, HTN, DM, smoking, eGFR, ancestry (using the first 5 PCs)	Individuals with intermediate and high PRS had 1.32- and 1.66-fold-increased hazard for major coronary events, respectively. Patients with high PRS had the greatest benefit from evolocumab, reducing their event rates to levels similar to patients with low genetic risk.
Erasmo et al., 2021 [8]	N/A	370	LDLc PRS	6	N/A	Age, gender, smoking, LDLc levels, and LLT intensity	Monogenic FH patients showed higher baseline LDLc and poorer LLT response compared to polygenic FH and undefined groups.
Kiflen et al., 2022 [9]	NA	96,116	CAD PRS	N/A	N/A	FRS for intermediate CVD risk classification (age, sex, LDLc, non-HDLc, ApoB, additional CVD risk factors)	The most cost-effective strategy was prescribing statins to intermediate-risk individuals with PRS in the top 70%, excluding those in the bottom 1%.
Damask et al., 2020 [10]	184,305	11,953	CAD PRS	6,579,025	Alirocumab effectiveness in high PRS, HR = 0.63 (0.46–0.86)	Ancestry, age, sex, baseline LDLc, lipoprotein(a), Fx of premature CHD, medical characteristics before the index ACS (MI, Percutaneous Coronary Intervention, CABG, and CHF)	Patients with high PRS for CAD had a greater incidence of MACE. Alirocumab treatment resulted in greater absolute and RR of MACE in high-PRS patients compared to lower-PRS patients.

Table 2. *Cont.*

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	Main Findings
Mayerhofer et al., 2022 [11]	40,914	225,195	On-Statin LDL PRS	35	ICH risk in high-statin-response group: HR = 1.16 (1.05–1.28) Statin effectiveness in high-response group: MI, HR = 0.98 (0.96–0.99); PAD, HR = 0.93 (0.87–0.99)	Age, sex, BMI, smoking, history of diabetes, SBP, cumulative statin dose exposure, use of anticoagulation and antiplatelet drugs, PCs 1–10, race, kinship, and genotyping assay	A genetically predicted greater LDL reduction from statins was linked to lower LDL levels and reduced risks of MI and PAD. However, among statin users, a higher predicted statin response was also associated with an increased risk of ICH.
Pechlivanis et al., 2021 [12]	N/A	3157	DM PRS	100	Interaction between DM PRS and statin use on CAC, RR = 1.08 (95% CI: 0.83; 1.41)	Age, sex, baseline CAC, statin intake	There was no significant association between the weighted DM PRS and rapid CAC progression, and no interaction between the PRS and statin use was observed for CAC progression.

ACS, acute coronary syndrome; AMP, amlodipine; ASCVD, atherosclerotic cardiovascular disease; ATL, atenolol; AUC, area under the curve; BMI, body mass index; BPL, Bisoprolol; CABG, coronary artery bypass grafting; CAC, coronary artery calcification; CAD, coronary artery disease; C-statistic, concordance statistic or C-index; CHF, congestive heart failure; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DBP, Diastolic Blood Pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolemia; FRS, Framingham risk score; Fx, family history; GWAS, genome-wide association study; HDL, high-density lipoprotein cholesterol; HR, hazard ratio; HTN, hypertension; HTZ, hydrochlorothiazide; ICH, intracerebral hemorrhage; LDLc, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; LSN, Losasartan; MACE, major adverse cardiovascular event; MI, myocardial infarction; N/A, not available; NNT, number needed to treat; OR, odds ratio; PAD, peripheral artery disease; PC, principal component; PRS, polygenic risk score; RR, relative risk; SBP, systolic blood pressure; SD, standard deviation; SNP, single-nucleotide polymorphism.

Table 3. Summary of studies on PRS for antihypertensive intervention. Note: Where possible, only the highest PRS group/quintile effect size is reported. "Discovery GWAS" refers to the dataset used to identify genomic loci associated with PGx outcomes. "Validation/Testing dataset" refers to the population in which the PRS derived from the discovery dataset is tested. In the included studies for our analyses, this dataset represents an external or subset cohort used for validation of the PRS derived from the discovery dataset.

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	AUC/C-Statistic: PRS Alone	AUC/C-Statistic: PRS + Clinical Risk Factors	Main Findings
Zhai et al., 2024 [13]	N/A	2590	BP PRS	5	Antihypertensive effectiveness in high PRS, OR = 0.91 (0.69–1.22)	Age, sex, baseline SBP, BMI, diabetes, smoking, stroke subtype, baseline National Institutes of Health Stroke Scale score, and time from onset to randomization	N/A	N/A	Early antihypertensive treatment had neutral effects on clinical outcomes in acute ischemic stroke patients across 5 BP-related genetic variants, with no outcome differences between treatment and control groups based on genotype subgroup.
Vidal et al., 2022 [14]	N/A	1097 (baseline), 1126 (1st follow-up), 1020 (2nd follow-up), 809 (3rd follow-up)	SBP PRS	362	N/A	Age, sex, marital status, smoking, education, and BMI	N/A	N/A	There was no link between the PRS and hypertension control, but higher PRSs were associated with increased SBP levels in untreated individuals.
Rouby et al., 2019 [15]	1194	SPS3: 585 eMERGE: 2417	RHTN PRS	3	Variants associated with RHTN despite antihypertensive therapy: rs11749255: OR = 1.60 (1.3–1.9) rs6487504: OR = 1.81 (1.5–2.3) rs324498: OR = 1.62 (1.3–2.0)	Age, sex, BMI, smoking, diabetes, HF, MI, and PVD	N/A	N/A	Associations with RHTN were identified and replicated in the MSX2, IFLTD1, and PTPRD regions. A PRS based on these SNPs was linked to an increased risk of RHTN and was significant in both discovery and replication cohorts.

Table 3. *Cont.*

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	AUC/C-Statistic: PRS Alone	AUC/C-Statistic: PRS + Clinical Risk Factors	Main Findings
McDonough et al., 2013 [16]	1345	4196	CVD PRS	3	Risk of adverse cardiovascular outcomes: high PRS, OR = 1.31 (1.08–1.59) (favouring BB); low PRS: OR = 0.60 (95% CI: 0.42–0.86) (favouring CCB).	Age, sex, MI, HF, DM, and PCs for ancestry	N/A	N/A	SIGLEC12 rs16982743 and rs893184 significantly interacted with treatment strategies for adverse CV outcomes. A PRS including these SNPs and F5 rs4525 was associated with different CV outcomes based on antihypertensive treatment. Patients with a low PRS benefited more from CCBs, while those with a high PRS had better outcomes with BBs.
Gong et al., 2012 [17]	N/A	768	BP PRS	37	N/A	Baseline BP, age, sex, and PCs for ancestry	N/A	N/A	No individual SNPs reached genome-wide significance (6 had $p < 0.05$ and 3 had $p < 0.01$). However, PRS for atenolol and hydrochlorothiazide BP-lowering alleles were significantly associated with BP response.

Table 3. *Cont.*

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	AUC/C-Statistic: PRS Alone	AUC/C-Statistic: PRS + Clinical Risk Factors	Main Findings
Lynch et al., 2012 [26]	39,114	N/A	CHD PRS	78 candidates Chlorthalidone: 5 AMP: 5 Lisinopril: 6 Doxazosin: 6	N/A	Sex, age, race, type 2 diabetes, smoking, LVH, total cholesterol, HDLc, SBP, and DBP	N/A	Chlorthalidone Group: AUC(RF): 0.6529 AUC(RF+PRS): 0.6601 Amlodipine Group: AUC(RF): 0.6429 AUC(RF+PRS): 0.6548 Lisinopril Group: AUC(RF): 0.6584 AUC(RF+PRS): 0.6693 Doxazosin Group: AUC(RF): 0.6516 AUC(RF+PRS):0.6705	Identified treatment-specific PRS that modestly enhanced CHD outcome predictions in hypertensive patients randomized to different antihypertensive drugs. PRS provided a small but statistically significant improvement in CHD prediction within each treatment group.

Table 3. *Cont.*

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	AUC/C-Statistic: PRS Alone	AUC/C-Statistic: PRS + Clinical Risk Factors	Main Findings
Tähtisalo et al., 2020 [20]	N/A	GENRES cohort: (205 AMP, 207 BPL, 206 HTZ 203 LSN) LIFE cohort: 401 Finnish patients on monotherapy for LSN or ATL	HTN PRS	793 for Top_PRS, over 1 million for GW_PRS	N/A	Sex, age, BMI, smoking, antihypertensive medication, daily urinary sodium excretion, and serum creatinine	HTZ AUC SBP response (PRS) = 0.64 AUC DBP response (PRS) = 0.63	N/A	No significant associations were found between PRSs and antihypertensive drug responses after Bonferroni correction. However, higher PRSs were weakly linked to reduced responsiveness to diuretics. Additionally, the GW PRS for SBP correlated with ECG-estimated QRS area and was significantly higher in individuals with drug-resistant HTN compared to those with controlled HTN.

Table 3. *Cont.*

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	AUC/C-Statistic: PRS Alone	AUC/C-Statistic: PRS + Clinical Risk Factors	Main Findings
Türkmen et al., 2024 [25]	N/A	32,360	SBP PRS DBP PRS Body fat mass PRS Waist/hip PRS Lean mass PRS Serum calcium PRS eGFR PRS Lipoprotein(a) PRS Urinary sodium PRS Liver fibrosis PRS	Varies by trait (e.g., SBP = 240 S, DBP = 297). Refer to Table 1	HF risk despite CCB treatment, HR = 1.14 (1.09–1.19)	Sex, age, and genetic PCs 1–10	N/A	N/A	Genetically predicted body fat mass, lean mass, and lipoprotein(a) were linked to adverse outcomes in hypertensive patients on CCBs. Genetic predisposition to HF also increased the risk of incident HF in these patients. Individual pharmacogenetic effects were modest, but combining high PRS significantly elevated risk.
Åberg et al., 2022 [27]	757,601	33,770	SBP PRS, DBP PRS	SBP PRS (1,072,098) DBP PRS (1,073,588)	Antihypertensive medication and adverse liver outcomes, HR = 0.55 (0.31–0.97)	Sex and age	N/A	N/A	In the highest quintile of the SBP PRS, new initiation of antihypertensive medication was associated with reduced rates of liver-related outcomes.

Table 3. *Cont.*

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	AUC/C-Statistic: PRS Alone	AUC/C-Statistic: PRS + Clinical Risk Factors	Main Findings
Acosta et al., 2023 [23]	5940	1750	SBP PRS, DBP PRS	732	RHTN: Highest quintile SBP PRS, OR = 2.28 (1.61–3.28); Highest quintile DBP PRS, OR = 2.27 (1.62–3.22)	Age, sex, and vascular risk factors	N/A	Uncontrolled BP C-index (RF): 0.61 C-index (RF+PRS): 0.62 Resistant BP C-index (RF): 0.75 C-index (RF+PRS): 0.76	A higher polygenic susceptibility to hypertension is associated with worse BP control in stroke survivors.
Maroteau et al., 2020 [24]	1066	652	F5 Variants PRS	Multiple (11 common and rare nonsynonymous variants in the F5 locus)	ARB-AE/ACE-AE odds with at-least one F5 variant, OR = 2.21 (1.49–3.27)	Sex, age, centre, sequencing batch, PCs 1–10, and covariates associated with intolerance, such as sex and age	N/A	N/A	F5 rs6025 was significantly associated with ACEi-AE and ARB-AE. A combined PRS showed that individuals with at least one variant had significantly higher odds of ACEi-AE or ARB-AE.

Table 3. *Cont.*

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	AUC/C-Statistic: PRS Alone	AUC/C-Statistic: PRS + Clinical Risk Factors	Main Findings
Narang et al., 2020 [29]	N/A	359,876	Gout PRS	10	High PRS for gout odds: Non-users, OR = 2.63 (2.49–2.79). Loop, OR = 2.04 (1.65–2.53). Thiazide, OR = 2.70 (2.26–3.23). Thiazide-like, OR = 2.11 (1.37–3.25)	Age, sex, BMI, HTN, renal failure, and HF	N/A	N/A	Serum urate-associated variants strongly increase gout risk in diuretic users, similar to those not taking diuretics. No nonadditive gene–diuretic interactions were observed.

ACEi, angiotensin-converting enzyme inhibitor; AE, angioedema ARB, Angiotensin Receptor Blocker; AUC, area under the curve; BB, beta-blocker; BMI, body mass index; C-statistic, concordance statistic or C-index; CCB, calcium channel blocker; CHD, coronary heart disease; CI, confidence interval; CV(D), cardiovascular (disease); DBP, Diastolic Blood Pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GWAS, genome-wide association study; HDL(c), high-density lipoprotein (cholesterol); HR, hazard ratio; (R)HTN, (resistant)hypertension; RF, risk factor; LVH, Left Ventricular Hypertrophy; MI, myocardial infarction; N/A, not available; OR, odds ratio; PC, principal component; PRS, polygenic risk score; PVD, Peripheral Vascular Disease; SBP, systolic blood pressure; SD, standard deviation; SNP, single-nucleotide polymorphism.

Table 4. Summary of studies on PRS for rate-control intervention. Note: Where possible, only the highest PRS group/quintile effect size is reported. No study in this cohort reported AUC/C-statistics. "Discovery GWAS" refers to the dataset used to identify genomic loci associated with PGx outcomes. "Validation/Testing dataset" refers to the population in which the PRS derived from the discovery dataset is tested. In the included studies for our analyses, this dataset represents an external or subset cohort used for validation of the PRS derived from the discovery dataset.

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	Main Findings
Barrett et al., 2016 [33]	N/A	142	AVN conduction PRS, resting heart rate PRS, and AF susceptibility PRS	24: AVN conduction (4), resting heart rate (12), or AF susceptibility (8)	N/A	Age, sex, baseline ventricular rate, total weight-based diltiazem dose (mg/kg) received in the first 4 h of treatment, and AF susceptibility PRS	Genetic variants related to AVN conduction, resting heart rate, or AF susceptibility did not significantly predict successful rate-control with IV diltiazem for acute AF.
Luzum et al., 2023 [32]	928	867	BB survival benefit PRS	229: Black patients 18: White patients	rs16844448 × BB survival interaction in Black patients Discovery HR = 73.7 (15.4–353.5) Validation HR = 55.1 (3.4–865.8)	Age, sex, ischemic etiology, AF, stroke, diabetes, BMI, SBP, heart rate, NT pro-BNP, serum creatinine, MAGGIC risk score, BB exposure	Discovery GWAS identified potential genetic variants associated with BB survival benefit in HFrEF patients, but none was validated in an independent dataset. However, rs16844448 in LRP1B showed a suggestive association in Black patients.
Lanfear et al., 2020 [40]	248	1188	BB survival benefit in HFrEF PRP	44	BB exposure: high PRS, HR = 0.84 (0.53–1.3) low PRS, HR = 0.19 (0.04–0.51)	MAGGIC score (without BB), BB propensity score, AF, EF, cardiovascular death, age, sex, creatinine, ischemic etiology, stroke, COPD, PVD, HTN	PRP showed that BBs significantly improved survival in patients with low PRP scores but not in those with high scores. The PRP effectively distinguished patients who received substantial survival benefits from BB from those who did not.

AF, atrial fibrillation; AVN, atrioventricular node; AUC, area under the curve; BB, beta-blocker; BMI, body mass index; C-statistic, concordance statistic or C-index; CHD, coronary heart disease; CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease; EF; ejection fraction; PRS GWAS, genome-wide association study; HDL(c), high-density lipoprotein (cholesterol); HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; HTN, hypertension; N/A, not available; OR, odds ratio; PRP, Polygenic Risk Predictor; PRS, polygenic risk score; PVD, Peripheral Vascular Disease; SBP, systolic blood pressure; SD, standard deviation; SNP, single-nucleotide polymorphism.

Table 5. Summary of studies on PRS for antiarrhythmics. Note: Where possible, only the highest PRS group/quintile effect size is reported. "Discovery GWAS" refers to the dataset used to identify genomic loci associated with PGx outcomes. "Validation/Testing dataset" refers to the population in which the PRS derived from the discovery dataset is tested. In the included studies for our analyses, this dataset represents an external or subset cohort used for validation of the PRS derived from the discovery dataset.

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	AUC/C-Statistic: PRS Alone	AUC/C-Statistic: PRS + Clinical Risk Factors	Main Findings
Strauss et al., 2017 [39]	N/A	22 healthy subjects in drug response study, 216 TdP cases, and 771 controls in Torsade de Pointes study	Genetic QT score	61	N/A	Age, sex, BMI, baseline QTc, electrolyte levels	N/A	N/A	The genetic QT score was associated with drug-induced QTc prolongation and significantly predicted TdP risk, accounting for 12% of TdP risk variability.
Tadros et al., 2019 [41]	N/A	1368	PRSPR, PRSQRS, PRSBrS	PR interval GWAS: 44 QRS GWAS: 26 BrS GWAS: 3	PRSBrS-based odds for ajmaline-induced BrS diagnosis, OR = 1.17 (1.14–1.21)	Age, sex, baseline PR, baseline QRS, presence of Type II or III BrS ECG, family history of BrS	C-statistic (PRSBrS): 0.68 (0.65–0.71)	C-statistic (PRS-BrS + RF): 0.741 (0.710–0.773)	Higher PRSPR, baseline PR, and female sex were linked to a pronounced PR slope, while PRSQRS and age were associated with QRS slope. PRSBrS, baseline QRS duration, presence of Type II or III BrS ECG at baseline, and a family history of BrS independently predicted the occurrence of a Type I BrS ECG.

AUC, area under the curve; BMI, body mass index; BrS, Brugada syndrome; CI, confidence interval; C-statistic, concordance statistic or C-index; HR, hazard ratio; N/A, not available; OR, odds ratio; PRS, polygenic risk score; PRSBrS, PRS for Brugada syndrome; PRSPR, PRS for PR interval; PRSQRS, PRS for QRS interval; RF, risk factor; SD, standard deviation; SNP, single-nucleotide polymorphism; TdP, Torsade de Pointes.

Table 6. Summary of studies on PRS for antiplatelets. Note: Where possible, only the highest PRS group/quintile effect size is reported. No study in this cohort reported AUC/C-statistics. "Discovery GWAS" refers to the dataset used to identify genomic loci associated with PGx outcomes. "Validation/Testing dataset" refers to the population in which the PRS derived from the discovery dataset is tested. In the included studies for our analyses, this dataset represents an external or subset cohort used for validation of the PRS derived from the discovery dataset.

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	Main Findings
Lewis et al., 2020 [42]	N/A	3391	ADP-stimulated platelet reactivity PgxRS	31 candidates,6 included in PgxRS	Age, sex, site, BMI, smoking, diabetes, proton pump inhibitor use	8 or more risk alleles odds: CVE OR = 1.78 (1.14–2.76) Cardiovascular death OR = 4.39 (1.35–14.27)	Multiple polymorphisms influence clopidogrel response. A PgxRS predicts cardiovascular events and death in patients with more alleles linked to higher platelet reactivity. Clopidogrel users with eight or more risk alleles have significantly increased odds of such events and mortality.
Lacaze et al., 2022 [43]	N/A	12,815	LPa PRS	43	Age, sex, smoking, alcohol, BMI, previous regular aspirin use, HTN, diabetes, CKD, NSAID use	MACE risk: rs3798220-C carriers (Aspirin group), HR = 0.54 (0.17–1.70) High LPa-PRS (aspirin group), HR = 1.41 (0.90–2.23)	Aspirin may reduce MACE risk in individuals with elevated LPa genotypes, particularly rs3798220-C carriers and those in the highest PRS quintile. However, there was no significant interaction between aspirin use and the highest LPa-PRS quintile for MACE. While aspirin increased clinically significant bleeding overall, it did not significantly raise bleeding risk among rs3798220-C carriers or those in the top LPa-PRS quintile.

AUC, area under the curve; BMI, body mass index; C-statistic, concordance statistic or C-index; CI, confidence interval; CKD, Chronic Kidney Disease; CVE, cardiovascular event; HTN, hypertension; LPa, lipoprotein(a); MACE, major adverse cardiovascular event; NSAID, Non-Steroidal Anti-Inflammatory Drug; N/A, not available; OR, odds ratio; PgxRS, pharmacogenomic polygenic response score; SBP, systolic blood pressure; SD, standard deviation; HR, hazard ratio.

Table 7. Summary of one study PRS for analgesics. Note: Where possible, only the highest PRS group/quintile effect size is reported. No study in this cohort reported AUC/C-statistics. "Discovery GWAS" refers to the dataset used to identify genomic loci associated with PGx outcomes. "Validation/Testing dataset" refers to the population in which the PRS derived from the discovery dataset is tested. In the included studies for our analyses, this dataset represents an external or subset cohort used for validation of the PRS derived from the discovery dataset.

Authors (y)	Discovery GWAS (*n*)	Validation/Test Dataset (*n*)	PRS	SNPs in PRS	HR/OR (95% CI)	Clinical Factors Included in Model	Main Findings
Zhang et al., 2023 [44]	N/A	212,968	Alzheimer's disease PRS	25	Paracetamol All-Cause Dementia risk, HR = 1.18 (1.10–1.26) Ibuprofen All-Cause Dementia risk, HR = 1.06 (0.97–1.16)	Age, sex, race, BMI, socioeconomic deprivation, smoking, alcohol, income, education, physical activity, healthy diet scores, albumin, C-reactive protein, dementia family history, HTN, diabetes, CVD, self-reported joint pain, self-reported arthritis, aspirin use, APOE ε4 dosage, and PRS of Alzheimer's disease	Regular paracetamol use was linked to a higher risk of new-onset dementia, whereas ibuprofen was not. PRS did not significantly affect the association between either drug and the incidence of all-cause dementia.

AUC, area under the curve; C-statistic, concordance statistic or C-index; CI, confidence interval; CVD, cardiovascular disease; HTN, hypertension; N/A, not available; OR, odds ratio; PRS, polygenic risk score; SD, standard deviation; HR, hazard ratio.

In the included articles, 12 focused primarily on PRSs associated with lipid-lowering therapies, particularly statins and PCSK9 inhibitors, probably due to the increased interest in using genetic information to refine dyslipidemia management. Another 12 studies centred on antihypertensive medications such as beta-blockers, diuretics, calcium channel blockers, or angiotensin-converting enzyme inhibitors (ACEis). The remaining eight publications addressed a variety of drug classes, including rate-control agents (three), anti-inflammatory medications (one), and antiplatelets (two), as well as antiarrhythmic agents (two).

The size of the PRSs was also heterogenous and ranged from a small number of candidate-gene polymorphisms (fewer than 10 SNPs) to genome-wide scores comprising more than six million variants. This heterogeneity could be due to both the differences between studies in PRS derivation methods and the diversity of research aims between studies. Most of the studies included at least one clinical outcome related to cardiovascular risk or drug efficacy, such as blood pressure control, incidence of major adverse cardiovascular events (MACEs), or treatment-related adverse effects (Tables 2–7). Additionally, 2 of the 32 articles explored the cost-effectiveness of integrating PRSs into clinical decisions for a statin prescription (Table 2).

During our analyses, we found that overall, the studies lacked a notable representation of non-European-ancestry cohorts. Although a small number of articles did include participants of Black, Hispanic, and Asian race or ethnicity, the majority of studies conducted their discovery or replication analyses in populations of European descent. We identified that ten studies incorporated ethnic groups beyond just predominantly Caucasian and European populations within their cohorts. Most of these studies were in the antihypertensives group (six). A single study in this group exclusively examined a cohort of individuals of Chinese ancestry. A summary of participant ancestries by each study is provided in Table 1.

Among the 32 studies, 20 explicitly reported either a hazard ratio (HR) or an odds ratio (OR) with a confidence interval for the PRS estimation of drug effects or for the integrated prediction of CVD risk or adverse events while on a drug. However, out of the included studies, only four reported measures of model performance, such as the area under the curve (AUC) or a C-statistic, with the majority not reporting these metrics.

In summary, the varying study designs, populations, and outcome measures precluded any formal meta-analysis. On a broader scale, we noted that the findings demonstrated the potential of leveraging PRS insights to enhance medication selection and improve patient outcomes in CVD. However, as illustrated in Tables 1–6, there were instances where incorporating a PRS did not result in a clinically significant benefit. Thus, establishing a definitive consensus on the predictive accuracy of the published PRSs proved challenging, irrespective of the CVD and medication under analysis.

3.3. Lipid-Lowering Medications

Lipid-lowering therapies, including statins and PCSK9 inhibitors, continue to serve as central interventions for mitigating atherosclerotic cardiovascular disease (ASCVD) risk. Twelve studies published a PRS relevant to lipid-lowering treatment response (Table 2). Overall, we noticed the trend that PGx was able to predict lipid-lowering treatment response in most studies. However, the studies had many limitations in their approach. Although many cohorts included primarily European-ancestry participants, a few studies assessed multi-ethnic or diverse populations [17,26]. Among 32,736 participants, Oni-Orisan et al. observed that individuals classified as having high genetic risk achieved the greatest reduction in ASCVD events with statin therapy (HR = 0.41 [95% CI, 0.31–0.53]), showcasing the potential of PRS-based stratification for optimizing therapy [17]. From a cost-effectiveness standpoint, routine genetic testing generally may not be warranted in

low- or intermediate-risk groups [20], although targeted use in higher-risk populations could be beneficial [25].

Adverse effects from statins were also reported in cases such as in Mayerhofer et al., 2022, who found that individuals genetically predisposed to lower low-density lipoprotein (LDL) levels demonstrated a reduced short-term risk of myocardial infarction (MI) yet increased intracerebral hemorrhage over the long term [27].

PCSK9 inhibitors offered comparable benefit trends for patients with a high PRS [23,26]. An interesting study found that, in familial hypercholesterolemia populations, those with polygenic hypercholesterolemia experienced more favourable LDL reductions compared to monogenic FH when treated with both statins and PCSK9 inhibitors [24].

3.4. Antihypertensives (Calcium Channel Blockers (CCBs), Beta-Blockers (BBs), Thiazide Diuretics)

Antihypertensives are a diverse class of medications that act through different physiological mechanisms to lower BP and reduce the risk of complications. Twelve articles assessed the interaction between antihypertensive medications and various PRSs (Table 3). We identified significant heterogeneity within this cohort of studies, including participants from Black, Asian, Hispanic, and other diverse ethnic groups. Overall, we found mixed results with a few studies noting minimal predictive power in PGx's ability to report treatment responses, whereas some reported that PGx was able to successfully predict side effects and treatment responses.

Few studies observed minimal or no genotype-based differences in treatment response, such as Zhai et al., who found that in a cohort of 2,590 Chinese individuals, early antihypertensive treatment had a neutral effect on clinical outcomes among patients with acute ischemic stroke according to five BP-associated genetic variants [29]. However, some studies reported notable gene-by-treatment effects. For instance, Gong et al. found that the efficacy of atenolol and hydrochlorothiazide in controlling systolic and diastolic BP was modulated by a BP PRS [33].

Interestingly, a study by McDonough et al. found that a PRS including SNPs rs16982743, rs893184, and rs4525 in F5 was associated with differential cardiovascular outcomes based on antihypertensive treatment strategy [32]. They found that PRS combining these SNPs showed that patients with a low PRS benefited more from calcium channel blockers, while those with a high PRS had better outcomes with beta-blockers, which points strongly towards the importance of genotyping and PRS acquisition for tailored prescription response [32].

Studies also analyzed the roles of genes in causing side effects against certain antihypertensives [39,40]. For example, in a large European-ancestry cohort (n = 359,876), Narang et al. evaluated a 10-SNP gout PRS across multiple diuretic-use categories (non-users, loop diuretics, thiazide diuretics, and thiazide-like diuretics) [40]. Elevated genetic risk was consistently associated with higher odds of gout, irrespective of diuretic type (e.g., loop diuretics OR = 2.04 [95% CI: 1.65–2.53], thiazides OR = 2.70 [95% CI: 2.26–3.23], thiazide-like OR = 2.11 [95% CI: 1.37–3.25], non-users OR = 2.63 [95% CI: 2.49–2.79]) [40]. Of note, no significant gene–diuretic interactions were detected, suggesting that serum urate-associated genetic predisposition to gout remains comparable in both diuretic users and non-users [40].

3.5. Rate-Control Medications

Rate-control medications are used to manage heart rate in conditions like atrial fibrillation (AF) by slowing the conduction of electrical impulses through the heart, thus improving cardiac efficiency and reducing symptoms. Three articles evaluated the interaction between rate-control medications and PRS (Table 4). Of these, two studies specifically

examined White populations only [41,43], while the third included individuals from both White and Black populations [42]. Overall, as with antihypertensives, we found mixed results with studies having conflicting findings on PGx's predictive power.

Barrett et al. found that a candidate SNP approach assessing atrioventricular node (AVN) conduction, resting heart rate, and AF susceptibility did not reliably predict rate-control outcomes in acute AF patients treated with intravenous diltiazem [41]. In a separate analysis of beta-blocker survival benefit in patients with heart failure with reduced ejection fraction (HFrEF), Luzum et al. identified potential genetic variants of interest in a discovery-based GWAS but failed to replicate these findings in an independent dataset [42]. One variant (rs16844448 in the LRP1B gene) showed a suggestive association in Black patients, underscoring the potential importance of ancestry-specific effects [42].

By contrast, Lanfear et al. (2020) successfully developed a 44-SNP Polygenic Response Predictor (PRP) for beta-blockers in HFrEF [43]. However, only patients with low PRP scores experienced a substantial survival benefit (HR = 0.19 [95% CI: 0.04–0.51]), whereas those with high PRP scores showed no significant improvement (HR = 0.84 [95% CI: 0.53–1.3]) [43].

3.6. Antiarrhythmics

Antiarrhythmic drugs are used to manage and prevent abnormal heart rhythms by modulating ion channels, altering cardiac conduction pathways, or influencing autonomic regulation of the heart to restore normal rhythm. There were two articles discussing antiarrhythmic medications (Table 5) [44,45]. Overall, the two studies found that PGx was able to predict genetic predisposition to drug induced side effects.

In a study of drug-induced QTc prolongation, Strauss et al. (2017) evaluated a 61-SNP genetic QT score in healthy subjects of multiple ancestries and ethnicities (European, Black, and Asian) [44]. The score explained a substantial proportion of interindividual variability in QTc response to dofetilide (30%), quinidine (23%), and ranolazine (27%), and it predicted 12% of the variation in risk for Torsade de Pointes [44]. These results suggest that genetic predisposition may aid in identifying individuals at higher risk for QT-related adverse drug effects [44].

Separately, Tadros et al. (2019) examined three PRS for PR interval (PRSPR), QRS duration (PRSQRS), and Brugada syndrome (PRSBrS) in a European-ancestry cohort [45]. The PRSBrS was independently associated with an ajmaline-induced Brugada diagnosis (OR = 1.17 [95% CI: 1.14–1.21]; C-statistic = 0.68), and incorporating additional clinical factors (family history of BrS, baseline QRS duration, and Type II/III BrS ECG) improved risk discrimination (C-statistic = 0.74) [45]. Thus, combining genotype-based scores with established clinical markers may enhance the prediction of arrhythmia susceptibility.

3.7. Antiplatelets

Antiplatelet drugs, such as aspirin and clopidogrel, inhibit platelet aggregation by blocking key pathways in platelet activation, thereby reducing the risk of thrombotic events. Two articles evaluated the interaction between rate-control medications and PRS (Table 6). A general trend of mixed results was found in this cohort of studies as well.

In a cohort of 3391 Caucasian participants, Lewis et al. examined a pharmacogenomic polygenic response score (PgxRS) comprising six genetic variants related to clopidogrel response [46]. Patients carrying at least eight risk alleles had a significantly higher odds of cardiovascular events (OR = 1.78 [95% CI: 1.14–2.76]) and cardiovascular death (OR = 4.39 [95% CI: 1.35–14.27]), thus hinting at the important role for genetic screening to identify individuals at heightened risk on clopidogrel therapy [46].

Lacaze et al. studied a 43-SNP lipoprotein(a) (LPa) PRS in 12,815 European-ancestry participants. Aspirin appeared to reduce the risk of MACE in carriers of the rs3798220-C variant (HR = 0.54 [95% CI: 0.17–1.70]) [47]. Although aspirin use was associated with a greater incidence of clinically significant bleeding risk overall, neither rs3798220-C carriers nor individuals in the highest PRS quintile had a significant increase in bleeding risk [47].

3.8. Acetaminophen and Ibuprofen

A single study examined the effects of two over-the-counter anti-inflammatory drugs (acetaminophen and ibuprofen) and gene interactions on the development of dementia (Table 7). In a large cohort of 212,968 predominantly British White participants, Zhang et al. assessed dementia risk in relation to the regular use of paracetamol (acetaminophen) and ibuprofen [48]. Paracetamol use was associated with an increased risk of developing all-cause dementia (HR = 1.18 [95% CI: 1.10–1.26]) [48]. By contrast, ibuprofen was not linked to a statistically significant increase in dementia risk (HR = 1.06 [95% CI: 0.97–1.16]) [48]. Moreover, the PRS of Alzheimer's disease did not significantly influence the relationship between regular use of paracetamol and ibuprofen and the incidence of all-cause dementia (both P-interactions > 0.05) [48].

4. Discussion

Phulka et al. have demonstrated that PRS can be a strong predictor for cardiometabolic diseases through a scoping review that summarized the current state and future of genetic testing and PRS [49]. Building on this knowledge, we conducted a scoping review to understand and synthesize current research on the role of PRS in predicting the efficacy, safety, and cost-effectiveness of various cardiovascular medications. Our review included 32 studies published between 2010 and 2024. The cardiac therapeutics we included in our review were lipid-lowering agents, antihypertensives, antiplatelets, rate-control agents, analgesics, and antiarrhythmics. Our analyses concluded that the studies for the most part demonstrated that PRSs were able to stratify patients based on their genetic risk, thereby influencing treatment outcomes across various therapeutic classes. For example, PRS for CHD was shown to significantly modulate the benefits of statin therapy [19]. We saw a pattern for statin-associated PRS, whereby individuals with high genetic risk for CHD experienced greater risk reductions when treated with statins, indicating the potential of PRS to personalize treatment and improve outcomes [17]. This effect was observed in diverse populations, including those of European, Latin, and East Asian ancestry [17]. Studies also investigated the economic implications of integrating PRS into clinical practice [20,25]. Using PRS to guide statin therapy was found to be cost-effective in specific scenarios where the cost of obtaining a PRS would outweigh further downstream costs [20,25]. We also found that the cost-effectiveness varied based on factors such as age, sex, and baseline cardiovascular risk [20]. This means that though PRS could be potentially beneficial from a public health spending point of view, its widespread integration into society would need more robust data supporting its longitudinal cost-effectiveness in larger and multi-ethnic cohorts.

In the context of antihypertensive therapy, certain genetic markers were associated with resistant hypertension, suggesting that PRS could be used to identify patients who may require more aggressive or alternative treatment strategies [31]. We also saw more representation of non-Caucasian/European ancestries in this cohort of research. A few investigations observed minimal or no genotype-driven differences in drug response, such as Tähtisalo et al., who reported that no statistically significant associations were found between PRSs and antihypertensive drug responses after applying Bonferroni correction [35]. However, most reports identified significant gene-by-treatment interactions. For example,

McDonough et al. observed that a three-SNP gene risk score determined whether patients fared better on calcium channel blockers or beta-blockers [32].

The utility of PRS was tested in other drug classes and adverse effects as well. In terms of adverse effects, for instance, PRS was able to predict the likelihood of developing gout in patients on diuretics [40] and the risk of ACE-induced angioedema [39]. This result speaks to the potential applicability of PRS in predicting patient populations likely to develop iatrogenic drug-associated side effects.

For rate-control drugs, some studies revealed no significant associations such as Barrett et al.'s finding of minimal genetic influence on diltiazem response [41]. On the contrary, Lanfear et al. successfully validated a 44-SNP beta-blocker response predictor in heart failure patients [43].

Antiarrhythmic-specific PRS predicted drug-induced QTc prolongation risk [44] and susceptibility to Brugada syndrome [45]. In addition, for antiplatelet therapy, elevated polygenic risk correlated with significantly higher odds of cardiovascular events and mortality in clopidogrel users [46], while PRS influenced aspirin-related major cardiovascular event risk [47].

Lastly, in terms of analgesics, a study found that the regular use of paracetamol was significantly associated with an increased risk of developing dementia, whereas the regular use of ibuprofen did not show a significant association with new-onset dementia [48]. However, the PRS failed to capture this nuance and did not significantly highlight the relationship between the use of paracetamol and the incidence of all-cause dementia [48]. This shows that PRS may not be the most effective tool for assessing dementia risk related to analgesic use.

Summing our findings, PRS definitely has the potential to enhance the personalization of cardiovascular care by predicting treatment responses and minimizing adverse effects. However, the application of PRS in clinical practice requires further validation and standardization, particularly across diverse populations, to fully realize its potential. Furthermore, the validation of PRS is conducted in a primarily Caucasian population, which thus reduces its applicability to other ethnic groups.

4.1. Nature Versus Nurture: A Clinician's Dilemma

PRS can help predict variable drug responses to CVDs by accounting for the cumulative effect of genetic variants that each exert small yet meaningful influences on drug metabolism and efficacy. This contrasts with traditional models for dosing, which account for age, sex, ethnicity, eGFR, and BMI. While these models serve as a good estimate for physicians to prescribe and dose drugs, a key limitation is that these models are inherently generalized to the population and do not account for the fact that differential gene expression might influence how a drug is metabolized [50]. PRS can not only stratify those at higher risk due to genetic predisposition, but it can also provide predictions on the efficacy of drugs for CVDs. For example, Oni-Orisan et al. observed that individuals in the highest-risk strata experienced a significantly greater reduction in ASCVD events when taking statins [17]. Among these individuals at higher genetic risk, PRS-based insights can inform clinicians about who may respond more favourably to intensive lipid-lowering therapies, such as high-intensity statins or PCSK9 inhibitors, improving both efficacy and potentially long-term outcomes.

In light of this evidence, we believe that the best strategy for optimal prediction is to combine PRS with a clinical model of drug efficacy to enhance the selection of the right drug class, dosage, and target population. A study by Harpe et al. found that combining traditional European and US risk prediction models with PRS improved the reclassification risk of ASCVD incidence for intermediate-risk subjects [51]. Similar results are found in

other studies as well. For example, O'Sullivan et al. found that combining PRS and clinical risk predictors improved the prediction for the risk of stroke in individuals with atrial fibrillation [52].

Thus, by complementing established risk factors rather than replacing them, PRS can refine our understanding of who will benefit most from CV therapies and potentially reduce adverse outcomes through individualized intervention strategies. Furthermore, predicting which patients are more likely to benefit from cardiovascular drugs or experience adverse reactions, PRS could transform clinical practice by enabling a more tailored approach to therapy.

4.2. PRS-PGx and Healthcare Costs in a Clinical Context

The predictive ability of PRS can have significant implications for healthcare systems, as the ability to target therapies to those who will derive the most benefit can reduce unnecessary treatments and associated costs [25]. Kiflen and colleagues found that when statins are prescribed to the right population (individuals in the PRS of the top 70% are eligible for statins while the lowest 1% are excluded), healthcare costs can save an estimated CAD 172,906 per quality-adjusted life-year [25]. A systematic review conducted by Zhu and colleagues in 2019 found that 67% of the included studies found PGx to be a cost-effective method for the treatment of CVD [53]. The Canadian Institute on Health Information reported that Canada's healthcare spending is increasing per year, with approximately CAD 372 billion spent in 2024 [54]. In a country with rapidly increasing population numbers and a publicly funded healthcare system, these savings could mean the reallocation of much-needed funds to other strained services, such as ER beds. Our review found that though PRS can be cost-effective, challenges remain in translating PRS findings into routine clinical use. The cost and accessibility of genetic testing are substantial barriers, especially in low-resource settings where healthcare systems may not be equipped to implement widespread genetic screening.

4.3. Challenges in Using PRS in Cardiovascular Pharmacogenomics

Even though the potential for PRS in improving treatment outcomes and reducing healthcare spending looks promising, as highlighted in our review, several obstacles are likely to hinder its broader application in CVD PGx. The most obvious one is the lack of uniform data validating the utility of PRS for PGx, as highlighted in our review. For example, even though many studies provided data supporting PRS-PGx for certain drug classes such as statins, we still had numerous studies reporting weak predictive power for PRS-PGx. For example, the study conducted by Tähtisalo et al. found no significant associations between PRSs and antihypertensive drug responses [35]. This raises the question of how broadly PRS can be applied across different therapeutic areas within cardiovascular medicine. Another significant challenge is the variability in PRS performance across populations. Many of the studies we reviewed were conducted in predominantly European-ancestry populations, which could mean that PRS-PGx might lack external validity in other ethnic or racial groups. Given that genetic variations differ significantly between populations, PRS developed in one group may not accurately predict outcomes in another, and this could further exacerbate health disparities if not carefully addressed. Efforts to derive and validate PRS in large multi-ethnic cohorts are underway. For example, a recent 2024 study by Smith and colleagues aimed to validate their derived CHD PRS in a diverse cohort—including individuals from South Asian, African, Hispanic, East Asian, and European ancestries—and found that even after using a large database of multi-ethnic individuals, the predictive power of PRS was limited in individuals of African ancestries [55]. Similarly, another recent study by Grau et al. also tried to validate PRS for 14 medical conditions in a

multi-ethnic cohort [56]. They found that though PRS was able to predict these diseases, the PRS performance was optimal in European populations, and there was substantial decay in performance in other ethnicities [56]. Larger-scale government involvement is also currently in progress. For example, Health Data Research UK recently shared that a Canadian–UK team is testing new artificial intelligence and machine learning methods to build PRS that work better across diverse ancestral groups. They are using large, multi-ethnic datasets from the UK, Canada, the US, Japan, Bangladesh, and China to ensure diversity in PRS derivation and validation [57].

Even in a hypothetical scenario where current efforts to derive multi-ethnic PRSs are successful, other challenges might hinder their application in the real world. Firstly, the healthcare infrastructure itself poses additional challenges as genetic testing can be costly and inaccessible to some patients, potentially exacerbating disparities in health services [58]. This could also lead to geographical disparities. For example, if we are able to introduce genetic screening prior to issuing a prescription in major urban healthcare systems but not in rural ones due to cost constraints, the existing disparities between the two might become worse for individuals who have limited resources and access to genetic testing. Moreover, the computational and bioinformatics resources needed to store, process, and interpret vast amounts of genetic data can potentially exceed the capacity of many healthcare systems [58]. Also, the likelihood of a potential privacy leak of genetic data is another concern that needs to be addressed as PRS becomes more integrated into healthcare systems.

Interestingly, the clinical validation of integrating genomic data in mainstream healthcare has been assessed before. For example, a study by Ayatollahi and colleagues found that integrating genomic data into electronic health records (EHRs) would serve as a robust method for individualized medicine application, but they mentioned that several technical factors such as the configuration of EHRs to handle genomic data and non-technical factors such as user preferences and security must be addressed before implementation [59]. Therefore, the security of data is a highly important factor, as privacy leaks regarding an individual's genetic risk stratification might lead to employment or insurance discrimination.

Education and communication are also key concerns. Many clinicians have limited training in interpreting PRS results and may need targeted educational programs to apply these insights effectively [58,60,61]. Conversely, communicating PRS findings to patients requires careful strategies to avoid confusion or undue anxiety. Patients must also be able to understand what PRS testing entails and how it might influence their therapy. A recent cross-sectional study by Brar et al. demonstrated that 79% of patients had never heard of polygenic testing, highlighting a significant gap in patient awareness [62]. Thus, clinicians must learn to convey PRS results in a clear, accessible manner to enable fully informed patient engagement in personalized medicine, which would allow widespread implementation.

Thus, despite promising findings, a significant translational gap remains. Cost barriers, a lack of patient and physician awareness, technical difficulties in EMR integration, and potential privacy leaks must be addressed prior to widespread integration.

4.4. Strengths and Limitations

Our study has several strengths. Firstly, we adhered to the strict PRISMA methodology and coupled this with a peer-reviewed search and data extraction strategy. This allowed us to maintain a strict and rigorous selection process that ensured the inclusion of only high-quality evidence. Secondly, adopting a scoping review approach was an ideal methodology in this topic, given the broad spectrum of cardiovascular therapeutics under investigation. This methodology allowed us to conduct a comprehensive synthesis of emerging high-quality data while also allowing us to provide directions for future studies.

Our study also had limitations. Our review was restricted to English-language studies only, and this might have potentially excluded relevant research published in other languages, which might have provided more insights and definitive conclusions. Furthermore, even though strict adherence to inclusion criteria allowed us to uphold methodological quality, it might have also led to the exclusion of studies that otherwise presented relevant clinical insights but lacked specific reporting items. In addition, we found that the included studies had significant heterogeneity in how they reported their outcomes, which made it impractical for us to conduct a formal meta-analysis. Although the scoping review methodology offered a broad overview of the evidence, these limitations point out the need for more standardized reporting practices to enable strong, quantitative assessments of PRS performance in future research.

4.5. Future Directions

We believe that the goal of our review has been accomplished, as we aimed to provide a synthesis of existing knowledge on the PRS in PGx of CVDs. However, we understand that the clinical implementation of PRS faces significant hurdles, such as the need for standardized regulatory frameworks, robust data protection laws, and the creation of a user-friendly technical interface for clinicians as well as patients, who are the key players in the process. These challenges can be addressed by following a structured and timewise approach that addresses all obstacles in a step-by-step manner. To improve the efficacy and generalizability of PRS for PGx, we have created a framework for short-, medium-, and long-term priorities that future research should focus on.

4.5.1. Short-Term Priorities (Within 2–5 Years)

Future studies should focus on creating a standardized protocol for reporting PRS for PGx of CVD. To improve the efficacy and generalizability of PRS for PGx, more studies are needed that better represent multi-ethnic GWAS cohorts. We believe that studies should report a standardized reporting method that will then allow future reviews to conduct meta-analyses, which were limited in our review. To achieve this goal, we recommend that future researchers report an HR/OR or AUC/C-statistic for evaluation if PRS + clinical risk factors improve predictions as compared to clinical risk factors alone. In addition, a clear description of how PRS is derived will enhance reproducibility and transparency. The harmonization of PRS can also be achieved via consistent thresholds of SNP inclusion. Furthermore, multi-national consortia must take leadership in publishing best-practice guidelines to ensure less inter-study reporting heterogeneity. We believe that this would allow future reviews to conduct meta-analyses, which was limited in our study.

In tandem with protocol standardization, we also believe that a significant effort is needed in conducting multi-ancestry pilots. Most current GWAS databanks consist of European/Caucasian populations. Creating large-scale multi-ethnic databanks would allow researchers to evaluate PRS performance in diverse ancestral groups and would help clarify the applicability of PRS beyond predominantly European cohorts. This will also allow future studies to use these databanks to then evaluate their PRSs in different cohorts and see whether the validity still stands.

An emerging methodology for PRS genesis involves integrating transcriptome data into PRS. For instance, Cai and colleagues demonstrated that transcriptome-based "Sum Transcriptome-Polygenic Risk Scores" models significantly outperformed conventional PRS in predicting various UK Biobank phenotypes, such as atrial fibrillation, while also enhancing predictive accuracy for ischemic stroke [63]. Similarly, Liang and colleagues observed that a polygenic transcriptomic risk score demonstrated higher portability in African-descent populations, where traditional PRS performance often declines most sharply [64].

In sum, these findings highlight the importance of exploring the integration of functional gene expression profiles into PRS, rather than relying solely on genotype-based methods.

4.5.2. Medium-Term Priorities (Within 5–10 Years)

Once a multi-ancestry databank, along with standard reporting guidelines for PRS' efficacy in CVD PGx, is created, we can conduct a derivation comparison. This will involve a head-to-head comparison of PRSs for PGx to see which ones have the best predictability. This will allow us to configure a gold standard for PRS derivation. Several PRS derivation methods exist; however, most of these are for disease-based PRS. A study by Zhai and colleagues in 2022 advocated for a change in disease PRS to PGx PRS approaches, as conventional PRS methods derived from disease GWASs often fail to account for genotype-by-treatment interaction effects, which are critical in PGx [65]. Furthermore, they found that using Bayesian regression in PGx formation and creating a "PRS-PGx-Bayes" demonstrated a superior prediction accuracy and captured genotype-by-treatment effects effectively to predict treatment-related LDL reduction [65]. With more studies testing different PRS derivation models and focusing on pharmacogenomic PRS, we can garner more robust data on the efficacy of PRS for PGx.

We also assert that this timeframe is feasible for validating a combined PRS–PGx–clinical factors model. A combined model that reflects both polygenic burden and shared genetic/environmental factors may reduce false reassurance when either PRS or family history alone is deemed low-risk.

4.5.3. Long-Term Priorities (Within 10–15 Years)

Finally, real-world adoption requires practical tools for healthcare providers (HCPs). Most clinics lack streamlined workflows to handle large-scale genetic data, and many HCPs are unfamiliar with interpreting PRS alongside other clinical metrics [58,60,61]. Slunecka et al. suggest that user-friendly methods of PRS visualization such as risk charts, and simplified visual outputs can act as foundational tools for both patients and clinicians to improve their comprehension of PRSs [58]. Significant research needs to be conducted and validated within student doctor populations as well as practising clinicians to elucidate which tools and user interfaces would yield the best comprehensibility of PRS for both the physician and the patient. Furthermore, widespread implementation would also require robust genetic testing infrastructure and guidelines for data privacy and equitable access.

Moreover, most studies have conducted cost–benefit analysis in a simulated population and scenarios. Long-term cost–benefit analysis must also be conducted in real-world healthcare scenarios after implementation of PGx is complete.

4.6. Potential Strategies to Streamline Implementation

The early implementation of PRS must be performed in a strategic manner. To do so, we would first require a PRS–PGx–clinical factors combination approach. Most EMR systems show the Framingham risk scores (FRSs) for patients by incorporating clinical risk factors such as age, sex, LDL levels, etc. Embedding point-of-care alerts or dashboards that integrate PRS with clinical tools could guide clinicians to prescribe the most effective medication and dosage in real time, making decision-making more efficient. In tandem, creating continuing education modules to help physicians learn about interpreting PRSs in combination with clinical tools would be very important. These modules could focus on providing PRS basics, interpretation, and application in cardiovascular PGx and should also include real-world case studies to illustrate clinical decision-making. A study conducted in British Columbia analyzing the efficacy of continuing education modules for end-of-life (EOL) care found that physicians who completed the module reported increased confidence

in EOL-related skills (e.g., initiating conversations and developing action plans) compared to the baseline [66]. We believe that this could be the case for PRS-PGx modules as well.

Furthermore, our review highlighted drug classes whose efficacies are strongly predicted by PRSs. Focusing on a targeted rollout approach where initial PRS adoption on drug classes with strong evidence for genetic stratification (e.g., statins) can streamline workflows and demonstrate early success. If positive outcomes are noted in terms of clinical outcomes and healthcare costs, such pilots can then garner further institutional and payer support for broader implementation. Currently, such implementation is not standard of care. Only in very few circumstances is genomic testing the standard of care, such as in the prescription of abacavir (an HIV medication), where HLA-B*57:01 is required prior to initiation due to the risk of severe immune-mediated reactions [67]. Thus, it might not be feasible to roll out PRS for every cardiovascular therapeutic, and using a single drug approach first might be required.

In addition, creating and implementing small-scale pilot programs in specialized clinics for CVDs (such as lipid clinics and heart failure clinics) to test the effectiveness of PRS-guided approaches to therapeutics would be warranted. This would give us data on both patient outcomes and the cost-effectiveness of PRS for PGx. This step is highly crucial, as although we noted that PRS can meaningfully stratify risk within large populations, recent findings, such as a study by Abramowitz et al. in 2025, highlight that individual-level risk estimates might be inconsistent [68]. Thus, addressing PRS performance variability at an individual level is necessary to strengthen clinical applicability. As a result, small pilot programs are required to ensure that clinicians are able to successfully interpret PRS results in conjunction with environmental factors such as diet and financial status, as well as clinical metrics such as LP(a) and total LDL cholesterol levels. In essence, these programs should serve as a learning opportunity for clinicians to view a high PRS as a prompt for more rigorous screening or earlier pharmacological interventions, but not in isolation from patient lifestyle, comorbidities, and shared decision-making preferences. Such models can also provide a "real-world" example of cost-effectiveness data of using PRS in clinical settings. Currently, almost all research on the cost-effectiveness of PRS is based on simulation models. However, a small pilot program would allow researchers to capture the real-world cost implications of this practice. If successful, these pilot programs can pave the way for a more widespread introduction. Furthermore, if validated, PRS may find its way in guideline-directed medical therapy refinement by identifying subgroups with heightened responsiveness or the risk of adverse effects. This can pave the path for its introduction into official cardiology-based organizations such as the American College of Cardiology (ACC) and the American Heart Association (AHA).

5. Conclusions

In conclusion, our review showcases that PRS holds significant promise for improving PGx for CVDs. Though its utility was supported in certain scenarios, such as statin response prediction, its current application is limited by challenges related to population diversity, cost, accessibility, and ethical considerations, such as accessibility-based health disparities and potential privacy concerns. Furthermore, future research should focus on validating PRS in large-scale multi-ethnic cohorts, comparing PRS derivation methodologies, and employing strategies to begin small-scale implementation into clinical workflow settings.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/scipharm93020018/s1, Table S1: Summary of Polygenic Risk Score (PRS) studies by clinical category and condition in cardiovascular research; Table S2: Summary of pharmacogenomic studies by medication category in cardiovascular conditions.

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