Utility of polygenic risk scores and pharmacogenetic testing for cardiovascular risk management

Morcillo Serra César[1]*; Espinar Vicario Iñigo[2]; Canepa Leite Juan Pablo[3]; Martí Sánchez David[2]; Ortega Marcos Javier[4]; Jiménez Mena Manuel[4]; Zamorano Gómez José Luis[5]; Gutiérrez Gabriel Sonia[6]; Tomás Martínez José Francisco[7]; Suela Rubio Javier[8]

[1]*Department of Internal Medicine, Sanitas Cima Hospital and Sanitas Medical Direction, Barcelona, Spain.*

[2]*Department of Cardiology, Sanitas Virgen del Mar Hospital, Madrid, Spain.*

[3]*Department of Cardiology, Sanitas Cima Hospital, Barcelona, Spain.*

[4]*Department of Cardiology, Sanitas La Moraleja Hospital, Madrid, Spain.*

[5]*Department of Cardiology, Sanitas La Zarzuela Hospital, Madrid, Spain.*

[6]*Research and Innovation Foundation, Sanitas Hospitals, Madrid, Spain.*

[7]*Department of Hematology, Sanitas Blua Valdebebas, Sanitas La Moraleja and Virgen del Mar Hospital, Madrid, Spain.*

[8]*Genetics Laboratory, Sanitas Hospitals, Madrid, Spain.*

Abstract

Background: Polygenic Risk Scores (PRS) may aid in risk prediction and facilitate earlier interventions for primary prevention. Pharmacogenetic testing has the potential to optimize cardiovascular pharmacotherapy. This study aimed to evaluate the utility of PRS by comparing its results with the SCORE2 risk prediction algorithm and cardiovascular pharmacogenetic testing.

Methods: Cardiovascular risk was assessed using the SCORE2 chart. Patients were classified as having low (<99th percentile, Z-score <2) or high (≥99th percentile, Z-score ≥2) genetic risk based on PRS. The net reclassification risk and treatment changes influenced by pharmacogenetic testing were also evaluated.

Results: A total of 120 patients (mean age: 53.3 years; 66% male) were included. According to SCORE2, 68% were classified as low-moderate risk, 28% as high risk, and 4% as very high risk. Based on PRS, 31 (26% [18-33.7; 95% CI]) of low-moderate risk patients were reclassified as high risk. Treatment modifications occurred in 15 patients (12.5%), with 12 patients (10%) starting statins due to reclassification and 5 patients (4.2%) due to pharmacogenetic findings.

Discussion and conclusion: PRS reclassified 26% of patients assessed using the SCORE2 chart, enabling more patients to qualify for preventative treatment. Genetic testing influenced treatment decisions in 12.5% of patients. PRS and pharmacogenetic testing hold significant potential to enhance cardiovascular risk prediction and therapy optimization.

Introduction

The goal of population-level screening is to identify individuals at elevated disease risk who could benefit from timely interventions. Cardiovascular Disease (CVD) screening poses challenges as approximately half of first coronary events, including sudden deaths, occur in asymptomatic individuals [1]. Ten-year CVD risk stratification is a crucial initial tool that guides clinical evaluation and preventative measures in asymptomatic patients [2]. For high-risk individuals identified through SCORE2 charts, aggressive therapeutic interventions, such as primary prevention strategies, are recommended [3,4]. These strategies can slow disease progression through lifestyle changes and pharmacological treatments.

However, intermediate-risk individuals require further evaluation, as their true risk may be higher or lower depending on additional factors such as coronary artery calcium scoring [5,6]. The emergence of Genome-Wide Association Studies (GWAS) has enabled the development of PRS, which aggregate the small effects of millions of genetic variants across the genome to estimate individual disease risk. PRS provide cost-effective, personalized enhancement of primary prevention [7], complementing traditional clinical tools such as SCORE2 [8].

Despite the lack of official guidelines for integrating PRS into clinical practice, evidence suggests that PRS could soon become a valuable tool for stratifying CVD risk and guiding treatment decisions [9]. For example, PRS combined with existing clinical models has demonstrated improved predictive performance in coronary artery disease (CAD) [10-13]. Furthermore, PRS-guided lipid-lowering treatments for intermediate-risk patients have shown promise in reducing CVD events [14]. Although the 2021 European Society of Cardiology (ESC) guidelines acknowledge the potential of PRS, further validation is required before its widespread clinical application [2]. Drugs with pharmacogenomic evidence are common, yet they are only occasionally used, highlighting critical gaps that hinder precision medicine from becoming the standard of care [15].

This study aimed to assess the utility of PRS and pharmacogenetic testing in cardiovascular risk stratification and treatment by comparing the results of SCORE2 charts with PRS outcomes.

Materials & methods

Study design and participants

This quasi-experimental, cross-sectional study included 120 consecutive outpatients attending four Sanitas hospital cardiology departments in Spain between July 2022 and December 2023, irrespective of referral type. Exclusion criteria included prior CVD diagnosis, diabetes mellitus, and age outside the range of 40-70 years. Based on literature analysis, a sample of 120 participants was selected with a predominance of low-moderate and high CVD risks, to optimize the statistical power for evaluating the utility of PRS. Ethical approval was granted by the local ethics committee, and all participants provided written informed consent.

Data collection and measurements

During outpatient visits, patient history, physical examination findings, and fasting blood samples were collected to assess cardiovascular risk factors. Analyzed variables included age, sex, obesity (BMI>30), smoking habits, hypertension (≥3 readings >140/90 mmHg), hypercholesterolemia (≥2 measurements >250 mg/dL), and diabetes mellitus (fasting glucose ≥126 mg/dL or HbA1c ≥6.5%). Lipid profiles (total cholesterol, triglycerides, HDL-C, LDL-C) were determined using enzymatic assays, and echocardiograms and stress tests were conducted.

Cardiovascular risk was calculated using SCORE2 tables for low-risk European populations, estimating 10-year fatal and non-fatal CVD event risks. Patients were categorized into low-moderate, high and very high-risk groups [3].

A blood sample for genetic testing was collected at hospital centers, transported to the genetics laboratory, and analyzed. Genotyping was performed using array technology (Affymetrix PMDA - Custom Mee with 824.679 SNPs), and a cardiovascular PRS based on 6.6 million genetic variants was developed using the LDPred algorithm in individuals of European ancestry from the UK Biobank [16]. Reports detailing PRS and pharmacogenomic data were uploaded to electronic health records. Pharmacogenomic analyses included relevant genes influencing CVD treatment with real time PCR for the calculation of CYP2D6 CNVs.

Statistical analysis

Baseline characteristics were described using frequencies/percentages for categorical variables. Concordance between SCORE2 and PRS risk classifications was evaluated using the kappa index. Statistical analyses were conducted using SPSS for Windows.

Results

Among the 120 participants (mean age: 53 years; 34% women), the SCORE2 algorithm categorized 68.3% as low-moderate risk, 28.3% as high risk, and 3.4% as very high risk. PRS analysis identified 72 patients (60%) as low-risk and 48 (40%) as high-risk (PRS score >3). Based on PRS, 31 (25.8% [18 to 33.7 with 95% confidence interval]) patients initially classified as low-moderate risk by SCORE2 were reclassified as high-risk. Treatment modifications were observed in 15 patients (12.5%), including statin initiation in 12 patients (10%) following PRS reclassification. For the remaining 16 patients reclassified as high risk, only lifestyle changes were recommended. Treatment changes were observed in 5 patients (4.2%) based on pharmacogenomic data. Specifically, the treatments most frequently changed by patients, in descending order, were statins, aspirin, angiotensin II antagonists, diuretics, beta-blockers, empagliflozin, amiodarone, and novel oral anticoagulants. All patients with treatment changes showed good pharmacological tolerance. For the 21 patients at high or very high risk according to SCORE2 but with a low-risk PRS, at the discretion of their cardiologists, treatment was not de-escalated.

Relevant cardiovascular risk factors and echocardiographic and stress test findings are shown in (Table 1).

(Figure 1) shows the correlation between cardiovascular risk by PRS and SCORE2. The kappa index between SCORE2 and PRS is 0.25, indicating low concordance.
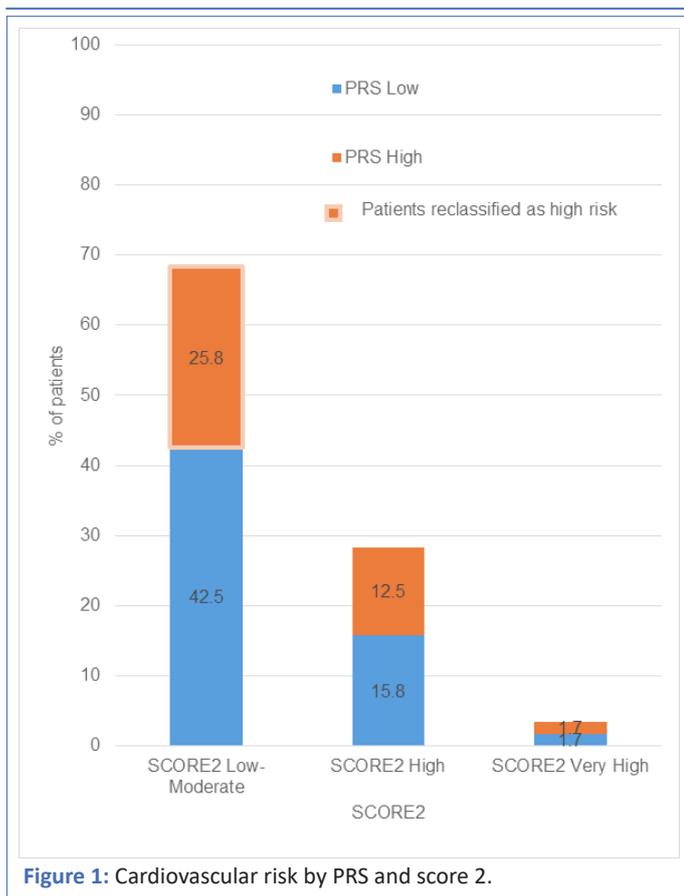
Figure 1: Cardiovascular risk by PRS and score 2.

Table 1: Clinical characteristics of patients.

Clinical characteristics of patients (120)	Value
Males	79(66%)
Age	53(51.9-54.7)
BMI >30	13(11%)
Smoking	23(19%)
Hypertension	42(35%)
Hypercholesterolemia	74(62%)
Hypertriglyceridemia	22(18%)
Positive Stress Test	3(2.5%)
Echocardiogram with LVH	11(9%)
Score 2 Low-Moderate Risk	82(68%)
Score 2 High Risk	34(28%)
Score 2 Very High Risk	4(4%)

Discussion

Our study demonstrates that the measurement of PRS reclassified 26% of patients, initially evaluated using the SCORE2 chart, as high risk. This significant reclassification aligns with findings from Marston et al. who reported similar results in their study of 330,201 patients from the UK Biobank. In their analysis, CAD PRS effectively identified patients with borderline and intermediate clinical risk who would benefit from statin therapy. Specifically, when CAD PRS was added to the clinical CVD risk score in individuals younger than 50 years, 20% of those at borderline risk were reclassified into the intermediate-risk group, warranting initiation of statin therapy. Conversely, 20% of patients with borderline or intermediate risk were reclassified as low risk, thus eliminating the need for unnecessary treatment [17].

In our sample, 21(17%) patients with a SCORE2 of high or very high risk were reclassified to low risk according to the PRS result, which could have avoided unnecessary therapy. Conversely, 31(26%) patients with a SCORE2 of low risk were reclassified to high risk according to the PRS, who would benefit from specific therapy. This reclassification highlights the potential of PRS to refine risk stratification and guide more personalized treatment decisions.

Another study, also using UK Biobank data, demonstrated that absolute CVD risk, determined through a clinical risk score, and relative genetic risk, determined by a PRS, provide independent and complementary information. When these components were combined into a simple multiplicative model, the precision of predicting incident CVD was significantly improved. This model reclassified 9.55% of intermediate-risk patients into the high-risk group, increasing the number of individuals in this category by 56.6% [15]. This finding underscores the value of integrating genetic risk with traditional clinical assessments to enhance predictive accuracy.

Although integrated risk tools that combine clinical scores with PRS have been shown to improve risk reclassification across multiple ethnicities and ancestries [18], the high percentage of reclassification observed in some studies like ours contrasts with others, which report rates between 2.5% and 8.7% [19]. Approximately 10% of incident CAD cases are misclassified as low risk by traditional risk calculators and are correctly reclassified as high risk using PRS [20]. This discrepancy suggests that PRS may offer a more precise risk assessment, particularly for individuals who fall into intermediate-risk categories.

PRS are based on inherited genetic variations, established at conception, and can thus be used early in life to guide lifestyle modifications. In contrast, pooled cohort equations have only been validated for individuals aged 40 years and older. PRS also offer the advantage of estimating lifetime risk trajectories, rather than focusing on 5- or 10-year windows as most clinical risk scores do. Since genetic risk is constant throughout life, PRS can be particularly valuable for younger individuals who have not yet developed clinical risk factors, such as hypertension or dyslipidemia, which are heavily influenced by lifestyle. Consequently, PRS could facilitate earlier interventions aimed at primary prevention [21]. For this reason, some authors recommend screening for PRS at birth or during childhood.

PRS information has the potential to motivate risk-reducing health behaviors, such as initiating medication, undergoing screening, or making lifestyle changes [22]. Emerging evidence highlights the positive behavioral impact of CAD PRS information. Studies on the disclosure of CAD PRS results have shown increased perception of personal control, heightened information-seeking behaviors [23], and the adoption of favorable health practices [24]. Moreover, shared decision-making in response to PRS findings has resulted in more frequent statin prescriptions [25]. Cross-sectional studies suggest that a favorable lifestyle can mitigate the increased risk associated with a high CAD PRS [26]. For example, individuals with a high PRS can reduce their lifetime risk of CAD by up to 50% through adherence to recommended lifestyle modifications [27].

In addition, elevated genetic risk is associated with earlier disease onset, even in the absence of traditional risk factors. Thus, PRS have the potential to enhance the accuracy of early and targeted primary prevention, particularly for chronic diseases that develop over decades.

While most evidence suggests that combining PRS with non-genetic risk factors maximizes clinical utility, PRS alone may be sufficient for individuals with extremely high scores. For instance, individuals in the top 8% of the CAD PRS distribution have a risk comparable to that of individuals with a monogenic familial hypercholesterolemia mutation [28]. Based on equivalent risk principles, it can be argued that individuals with PRS-based risk levels similar to monogenic risks should qualify for comparable preventative therapies. While CAD PRS enhances risk stratification for future CVD, individuals with both high clinical risk factors and elevated CAD PRS derive greater benefit (i.e., greater risk reduction) from statin therapy than those at lower PRS [29,30]. Furthermore, among patients with acute coronary syndrome and elevated lipid levels who received optimized statin therapy, a high CAD PRS was associated with a higher risk of recurrent cardiovascular events. These patients also experienced greater risk reduction when treated with PCSK9 inhibitors [31,32].

In our study, 12.5% of patients modified their treatment based on genetic testing results, either due to the PRS findings or pharmacogenomics, with good pharmacological tolerance. Pharmacogenomics holds the potential to optimize cardiovascular pharmacotherapy and improve outcomes for patients with cardiovascular disease. Robust evidence supports genetic associations with drug dosage requirements and the risk of adverse effects [33]. The drugs with the strongest pharmacogenomic evidence include warfarin, clopidogrel, and statins, with accumulating data on genetic contributions to β-blocker response. Current guidelines recommend the use of pharmacogenetic testing to optimize warfarin dosing, select appropriate antiplatelet therapy after percutaneous coronary intervention, and predict the risk of statin-induced myopathy [34].

Limitations

This study should be interpreted with caution due to certain limitations, such as the small sample size, and challenges associated with the deployment of PRS. Patients or physicians may misunderstand the uncertainties inherent in PRS-based risk estimates. Effective and clear risk communication by trained professionals is essential to minimize potential psychosocial effects. Additionally, individuals of non-European ancestry may receive inaccurate risk estimates due to the underrepresentation of these populations in large prospective genomic cohorts, potentially exacerbating healthcare disparities [35]. Furthermore, despite the demonstrated usefulness of PRS as a prognostic tool in Anglo-Saxon populations, its implications in other settings remain unclear. Mediterranean countries, for instance, have a lower baseline risk of CVD, and it is necessary to evaluate the prognostic value of elevated PRS in these populations. Studies are needed to assess the predictive capacity of PRS in quantifying coronary events and to evaluate the utility of preventive pharmacological interventions based on PRS findings in these regions.

Conclusion

Measurement of PRS reclassified 26% of patients as high risk when evaluated using the SCORE2 chart, potentially making more patients eligible for preventative treatment. Additionally, 12.5% of patients modified their treatment based on genetic testing, with good pharmacological tolerance. PRS and pharmacogenetic testing hold significant promise for personalized medicine, optimizing cardiovascular risk prediction and pharmacotherapy.

Declarations

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