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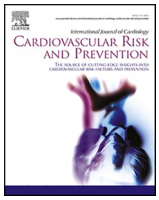

Residual cardiovascular risk, use of standard care treatments, and achievement of treatment goals in patients with cardiovascular disease

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ABSTRACT

Background: Residual risk management in patients with previous cardiovascular disease (CVD) is a relevant issue. Objectives: 1) to assess the residual risk of patients with CVD using the new scores developed to predict recurrent CVD events (SMART score/SMART-REACH model); 2) to determine the use of therapies with cardiovascular benefit and the achievement of therapeutic goals in patients with very high residual risk.

Methods: A multicenter, descriptive, cross-sectional study was performed. Individuals over 18 years of age with CVD were included consecutively. The 10-year risk of recurrent events was estimated using the SMART score and the SMART-REACH model. A value $\geq$ 30% was considered "very high risk".

Results: In total, 296 patients (mean age 68.2 $\pm$ 9.4 years, 75.7% men) were included. Globally, 32.43% and 64.53% of the population was classified as very high risk by the SMART score and the SMART-REACH model, respectively. Among patients classified as very high risk by the SMART score, 45.7% and 33.3% were treated with high-intensity statins and reached the goal of LDL-C <55 mg/dL, respectively. The results were similar when evaluating very high patients according to the SMART-REACH model (high-intensity statins: 59.7%; LDL-C <55 mg/dL: 43.9%). Few very high-risk patients with diabetes were receiving glucose-lowering drugs with demonstrated cardiovascular benefit.

Conclusion: In this secondary prevention population, the residual risk was considerable. Underutilization of standard care treatments and failure to achieve therapeutic goals were evident even in subjects with very high residual risk.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide [1]. Although current treatment regimens have markedly decreased the incidence of cardiovascular risk, many CVD events still occur even with optimal therapy.

Residual CVD risk has been defined as the risk of recurrent vascular events that persists despite treatment or goal achievement for risk factors such as cholesterol bound to low-density lipoproteins (LDL-C), blood pressure, and glycemia [2].

Patients with a clinical manifestation of CVD show substantial variation in cardiovascular prognosis. Major risk factors are long recognized to predict recurrent CVD events and mortality [3]. Likewise, additional biomarkers such as C-reactive protein or the presence of subclinical atheromatosis have also been identified as independent predictors of residual cardiovascular risk [4]. The score-based CVD event recurrence prediction strategy has been previously evaluated [5,6]. However, their utility is limited in contemporary populations who are on statins and other cardioprotective therapies as the standard of care [7].

Recently, two risk scores have been developed for the prediction of recurrent CVD events based on the observational REACH (Reduction of

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Atherothrombosis for Continued Health) and SMART (Secondary Manifestations of Arterial Disease) cohort studies [8,9]. In fact, both estimations are based on easy-to-measure clinical patient characteristics. Both predictive tools can be used for all individual patients with clinical manifest atherosclerotic vascular disease. The SMART risk score estimates individual residual risk for recurrent myocardial infarction, stroke or vascular death in the next 10 years. In addition, the SMART-REACH model estimates individual residual 10-year risk and lifetime risk for recurrent myocardial infarction, stroke or vascular death. The identification of very high-risk patients using these risk stratification tools would favor the use of intensive treatments, novel interventions and improve follow-up strategies. The rationale behind treating very high-risk patients with more intensive interventions is supported by the current evidence that has shown that treatment of higher-risk individuals results in substantially greater reductions in absolute risk.

Therefore, the objectives of this study were: 1) to assess the residual cardiovascular risk of a population with established CVD using the new tools developed for this purpose; 2) determine the use of therapies with proven cardiovascular benefit and the achievement of therapeutic goals in the subpopulation with the highest cardiovascular residual risk.

2. Material and methods

A multicenter, descriptive, cross-sectional study was carried out in five cardiology centers in the Autonomous City of Buenos Aires and Greater Buenos Aires, from June to November 2022. Individuals older than 18 years with diagnosis of CVD (coronary disease, peripheral arterial disease, or cerebrovascular disease). were consecutively included, evaluating clinical and laboratory variables.

The clinical records of the patients included were revised, obtaining information about their history, cardiovascular risk factors and medication received.

The blood levels of glucose, total cholesterol, cholesterol bound to high-density lipoproteins (HDL-C), triglycerides, C-reactive protein, lipoprotein(a) [Lp(a)], and creatinine were measured according to standardized biochemical tests. The LDL-C was calculated through Friedewald's formula [10], while non-HDL-C was estimated by the following equation: total cholesterol − HDL-C. The glomerular filtration rate (GFR) was estimated according to the CKD-Epidemiology Collaboration equation (CKD-EPI) [11].

The 10-year risk of recurrent events (myocardial infarction, stroke, or vascular death) was estimated using the SMART score and the SMART-REACH model [8,9]. When some variables are not available, the calculator imputes the population median instead. Patients were considered to be at very high risk when the score was equal to or greater than 30%.

2.1. Statistical analysis

Continuous data between two groups were analyzed using a Student's *t*-test if the variables were normally distributed or with a Wilcoxon–Mann–Whitney test otherwise. Categorical data analysis was performed using a chi-squared test. Continuous variables are summarized as mean ± standard deviation (SD) or median (25–75 interquartile range) according to their distribution, while categorical variables are given as percentages.

Pearson's test was used to establish the correlation between both scores to calculate CVD residual risk. The concordance between different scores was analyzed using Cohen's kappa index and the Bland-Altman graph plot for graphical representation. Mild or poor, acceptable, or discreet, moderate, substantial or very good concordance was defined depending on kappa below 0.20, between 0.21 and 0.40, 0.41 and 0.60, 0.61 and 0.80 and between 0.81 and 1, respectively.

A value of $p < 0.05$ was considered statistically significant. STATA 13.0 software packages were used for statistical analysis.

3. Results

A total of 296 patients (mean age 68.2 ± 9.4 years, 75.7% men) were included in the study. Globally, the prevalence of type 2 diabetes mellitus in the population was 31.4% and 72.6% of patients were hypertensive. Furthermore, 17.9% of the patients did not have controlled blood pressure and 10.5% continued smoking. The average LDL-C was 66.7 ± 27.6 mg/dL and the median fasting triglyceride level was 113.5 mg/dL (27.4% of the patients had a triglyceride level >150 mg/dL). The baseline characteristics of the population are described in Table 1.

In total, 96.62% of the population received statins (high intensity statins: 61.48%; moderate/low intensity statins: 35.14%). The type and dose of statins used are shown in Table 2.

Regarding non-statin lipid-lowering medication, 45.27%, 3.38% and 5.74% received ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors or fibrates, respectively. Only two patients received ezetimibe as monotherapy, the rest received it in combination with statins. Importantly, 61.49% and 36.82% of the population achieved the goal of C-LDL <70 mg/dL and <55 mg/dL, respectively.

The medians (IQR) of the SMART score and SMART-REACH model were 21.95% (13.4–35.95) and 34.95% (24.95–45.0), respectively. Likewise, 32.43% and 64.53% of the population was classified as very high risk by the SMART score and the SMART-REACH model, respectively.

Patients at very high risk according to the SMART score and SMART-REACH model were older, had more frequent hypertension and type 2 diabetes, and had a lower GFR compared to subjects classified as not very high risk. In addition, patients at very high risk according to the REACH score were more frequently men and had lower levels of LDL-C and non-HDL-C. The characteristics of the population with or without very high risk can be seen in Table 1 supplementary.

Table 1
Characteristics of the population.

Continuous variables[a]	Total population n = 296
Age, years	68.2 (9.4)
Time to first event, years	5.6 (2–11)
Systolic blood pressure, mmHg	125.5 (14.3)
Total cholesterol, mg/dL	136.3 (33.1)
LDL-C, mg/dL	66.7 (27.6)
HDL-C, mg/dL	43.7 (10.8)
Triglycerides, mg/dL	113.5 (88–160)
Non HDL-C, mg/dL	92.6 (31.8)
Creatinine, mg/dL	1.1 (0.6)
Glomerular filtration rate, mL/min	75.6 (20.2)
Glycosylated hemoglobin (HbA1c), %[b]	6.9 (1.2)
C-reactive protein, mg/dL[c]	1.5 (1.4)
Lipoprotein(a), mg/dL[c]	26 (14–65)
Apolipoprotein B, mg/dL[d]	64.4 (19.9)
Categorical variables, %	
Male gender	75.7
Type 2 diabetes	31.4
Hypertension	72,6
Current smoking	10.5
Triglycerides >150 mg/dL	27.4
Coronary heart disease	10.9
Acute coronary syndrome	55,7
Myocardial infarction	39,2
Coronary revascularization	78,7
Peripheral vascular disease	14.2
Cerebrovascular disease	14.5
Heart failure	12.2
Atrial fibrillation	9.8
Familial hypercholesterolemia	8.1

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol.
[a] Mean or median (standard deviation or interquartile range).
[b] Patients with type 2 diabetes.
[c] n = 109.
[d] n = 93.

Table 2
Statin therapy in the population.

Statin	n						Total, n (%)
	2 mg	5 mg	10 mg	20 mg	40 mg	80 mg	
Simvastatin			1	6	1		8 (2.8)
Atorvastatin			16	36	50	22	124 (43.36)
Rosuvastatin		4	30	59	55		148 (51.75)
Fluvastatin						3	3 (1.05)
Pitavastatin	3						3 (1.05)

The correlation between the SMART score and SMART-REACH model was good (r = 0.743). The agreement between the SMART score and the SMART-REACH model to identify high-risk patients was discreet (kappa = 0.393). The graphical representation can be seen in Fig. 1.

When analyzing patients classified as "very high risk" by the SMART score, 45.7% were treated with high-intensity statins, while the goal of LDL-C <55 mg/dL was reached in one third of the subjects. The results were slightly better when evaluating patients at "very high risk" according to the SMART-REACH model (use of high-intensity statins: 59.7%; LDL-C <55 mg/dL: 43.9%). Interestingly, few patients with type 2 diabetes classified as "very high risk" by both predictive tools were receiving glucose-lowering drugs with demonstrated cardiovascular benefit, such as glucagon-like peptide-1 receptor agonists (GLP-1a) or sodium–glucose cotransporter-2 inhibitors (SGLT-2i).

Among patients classified as very high risk by the SMART score, 22.9% and 12% had uncontrolled blood pressure and continued smoking, respectively. The results were similar when evaluating very high patients according to the SMART-REACH model (uncontrolled blood pressure: 19.4%; smoking: 10.5%). Preventive therapies and therapeutic targets in patients classified as very high risk according to both scores are shown in Fig. 2.

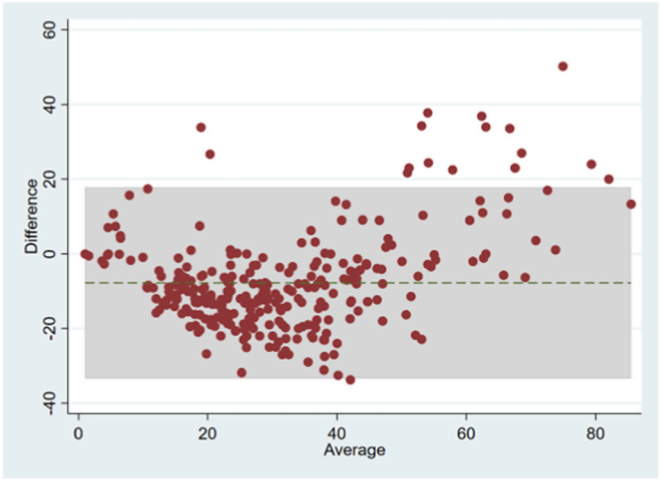

Fig. 1. Bland-Altman graph plot showing the concordance between the SMART score and the SMART-REACH model. The dotted line shows the average difference between both scores (−7.7%) and the shaded box shows the 95% limits of agreement (−33.3% to +17.8%).

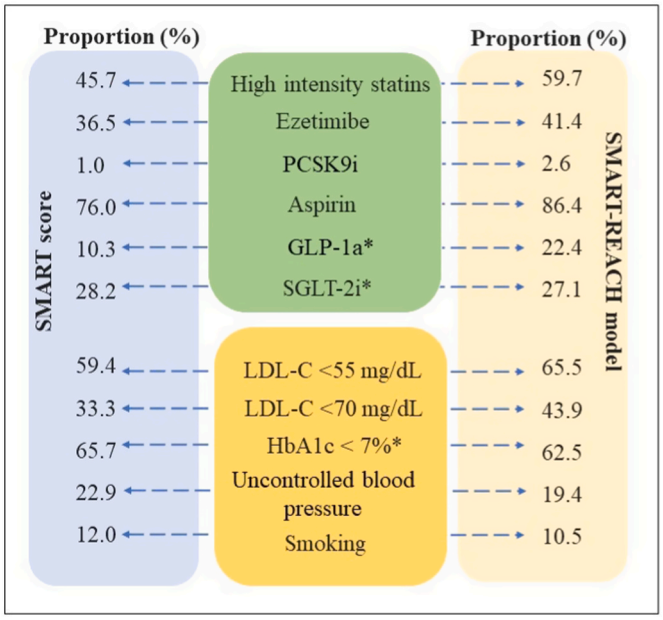

Fig. 2. Preventive therapies and therapeutic goals in patients classified as very high risk according to both scores. GLP-1a: Glucagon-like peptide-1 receptor agonists; LDL-C: low density lipoprotein cholesterol; PCSK9i: Proprotein convertase subtilisin/kexin type 9 inhibitors; SGLT-2i: Sodium–glucose cotransporter-2 inhibitors.*Patients with type 2 diabetes.

4. Discussion

Previous clinical guidelines recommend the use of risk prediction scores in patients without vascular disease or diabetes since those at high cardiovascular risk are more likely to benefit from preventive strategies [12,13]. On the other hand, the traditional approach is to classify all patients with established vascular disease as 'very high risk'. However, this universal and simplified approach ignores the fact that the individual level of cardiovascular risk may vary in these patients and limits the option for a more personalized management in secondary prevention [14].

The 2018 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines recommend that CVD patients be categorized into 1 of 2 groups: not at very high risk or at very high risk. Very high-risk patients have a history of multiple major CVD events or 1 major CVD event and multiple high-risk conditions. Selecting the candidate subpopulation to receive additional lipid-lowering agents, such as PCSK9 inhibitors, is the main objective of this recommendation

[15]. This was later reaffirmed by a panel of experts who developed a consensus on the use of non-statin lipid-lowering therapies [16], considering the use of additional drugs such as ezetimibe, PCSK9 inhibitors, inclisiran, or bempedoic acid, especially in subjects classified as very high risk. On the other hand, the current European guidelines for cardiovascular prevention suggest that after initial risk factor treatment and the achievement of risk factor treatment goals, the individual residual risk for recurrent CVD could be calculated [17]. Taking these guidelines into account, patients at very high risk of recurrent CVD events may benefit from the use of novel but less established preventive treatments such as dual antithrombotic pathway inhibition, icosapent ethyl, or anti-inflammatory therapy with colchicine.

This study showed that the proportion of subjects with very high risk was considerable. In fact, one third and two thirds of the population was classified as very high risk according to the SMART score and the SMART-REACH model, respectively. Consistent with our findings, Colantonio et al. reported that 55.3% of a sample of US adults with a history of cardiovascular disease were stratified as very high cardiovascular risk when applying the 2018 ACC/AHA guidelines [18]. As expected, the proportion of very high-risk patients is higher in patients with acute coronary syndrome [19,20].

Another finding of our study was that the agreement between the two scores used was discreet. Interestingly, these results are similar to those reported in other studies that analyzed scores in primary prevention [21,22]. Although both scores include the traditional risk factors and the type of CVD, there are some differences when calculating them. On one hand, the SMART score includes C-reactive protein levels. On the other hand, the SMART-REACH model considers some other comorbidities such as heart failure or the presence of atrial fibrillation. In addition, this score considers the type and dose of statin, non-statin lipid-lowering medications, and hypoglycemic drugs with proven cardiovascular benefit.

Therefore, our findings confirm that, depending on the selection of different residual risk-assessment methods, risk estimation can change and consequently preventive therapies prescription rate.

This study showed that many subjects in secondary prevention were not receiving high-intensity statins (≈38%). Strikingly, this proportion was more considerable when analyzing patients classified as very high risk by both scores (≈54% and 40% according to SMART and SMART-REACH scores, respectively). The underutilization of high-intensity statins observed in our study coincides with recent reports. Mitani et al. showed in a large Japanese cohort in which only 33.1% of the very high-risk secondary prevention patients received high-intensity statins [23]. In addition, the maximum dose of intensive statins was used in <1% the patients. Similarly, a recent retrospective observational study conducted in Wales showed that only 44% of patients with coronary heart disease, diabetes, and LDL-C levels ≥55 mg/dL received high intensity statins [24].

The clinical benefit of the addition of ezetimibe was demonstrated in a large randomized trial [25]. Additionally, a recent study showed that among patients with CVD, moderate-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy for the composite CVD outcomes [26]. However, the use of ezetimibe in secondary prevention patients continues to be very low [27]. Despite a significant proportion of very high patients not reaching the recommended lipid goals, the use of ezetimibe observed in our study was limited (≈37% and 41% according to SMART and SMART-REACH scores, respectively). Likewise, the use of PCSK9 inhibitors in our study was extremely low, despite the proven cardiovascular benefit [28,29] and the current guidelines recommendations [16,17]. We believe that our findings reflect the high cost and access issues related to these drugs. The deficient prescription of lipid-lowering drugs is directly associated with the poorly achieved therapeutic goals. Our study showed that ≈33% and 44% of patients classified as high risk by the SMART score and the SMART-REACH model, respectively, had an LDL-C <55 mg/dL. Again, these findings are consistent with recently reported data [30].

Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events was significantly lower among those who received icosapent ethyl than among those who received placebo [31]. Since in our study approximately 27% of the population had triglycerides >150 mg/dL, this medication could be indicated in many of our patients. However, this therapy is not available in Argentina to date.

Importantly, the optimization of medical treatment to reduce residual risk is not limited to lipid-lowering treatment.

For example, in patients with type 2 diabetes, SGLT-2 inhibitors and GLP-1 receptor agonists reduced cardiovascular and renal outcomes [32]. In addition, absolute benefits are determined by individual risk profiles and underlying pathology of the patients. In line with other publications [24,33], the proportion of subjects with diabetes at very high cardiovascular risk treated with these drugs was very low in our study.

On the other hand, approximately 1 out of 10 patients continued smoking and 2 out of 10 patients persisted with inadequate levels of blood pressure. These findings were similar or worse in the group with high residual risk. Previous studies have shown that despite the recommendation to stop smoking after being diagnosed with CVD, many patients continued smoking [34]. Moreover, quitting smoking is associated with a substantial reduction in risk of all-cause mortality and myocardial infarction among patients with CVD [35]. Therefore, our finding supports the need for physicians involved in the follow-up of these patients to offer appropriate smoking cessation interventions. On the other hand, large epidemiological studies clearly demonstrate that the control of blood pressure in patients with CVD remains poor with large proportions not achieving the targets defined in the prevention guidelines [36]. This finding is clinically relevant, since a 5 mmHg reduction of systolic blood pressure reduced the risk of major cardiovascular events by about 10% for patients with previous CVD [37].

This study has certain limitations. Given the study design, the possibility of bias cannot be ruled out. On the other hand, the scores used in this study have not been validated in Argentina. However, external validation was performed for SMART score in pooled trial cohorts of vascular patients from Europe, Israel, USA, Canada, Mexico, Africa, Australia, and New Zealand [15]. In addition, external validity of the SMART-REACH model was tested in the SMART population and in North America [38]. Additionally, the cut-off points of the scores to define the very high-risk stratum was arbitrary. However, our decision was based on the World Health Organization CVD risk charts, which categorize individuals with a score ≥30% as very high risk [39,40]. In addition to calculating the 10-year residual cardiovascular risk, the SMART-REACH model allows to estimate life expectancy without recurrent cardiovascular events. This information was not analyzed in our study. On the other hand, although most of the data needed to calculate the scores was available, this was not the case for C-reactive protein. In this case, the calculator imputed the population median instead in 63.2% of the cases. Finally, the present study aimed to estimate the residual risk by using predictive tools. To determine if these scores calibrate and discriminate correctly in our population, new prospective investigations must be developed.

5. Conclusion

In this population of patients with established CVD, the residual risk was considerable. Underutilization of standard care treatments and failure to achieve therapeutic goals were evident even in subjects with very high cardiovascular risk. Considering the very high residual risk in many secondary prevention patients, it is necessary to intensify personalized preventive strategies and evaluate the utilization of novel therapies.

Author contributions

DS, WM and LB: Conceptualization, Methodology, Software. **GM, WM, DS, JD, DL and LV**: Data curation, Writing- Original draft preparation. **JP, FB and AI**: Visualization, Investigation. **WM**: Supervision. **WM TE and MH**: Software, Validation. **WM DS and LB:** Writing-Reviewing and Editing.

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Ethics considerations

The study was conducted in compliance with the recommendations for medical research contained in the Declaration of Helsinki, Good Clinical Practice standards, and the applicable ethical regulations. The protocol was reviewed and approved. by the Institutional Ethics Board.

Availability of data and material

The data underlying this article are available in the article and in its online supplementary material.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2023.200198.

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