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EDITORIAL COMMENT

Coronary artery disease and genetics: Steps toward a tailored approach

Doença coronária e genética: passos em direção a uma abordagem personalizada

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Despite advances in medical technology and treatment, coronary artery disease (CAD) remains a significant public health issue in Portugal.[1] In 2020, CAD was responsible for 10 924 deaths in the country, highlighting the considerable impact this disease has on the population.[2] Addressing the root causes of CAD in Portugal, such as lifestyle factors and genetic predisposition, will be critical to improve the health outcomes of individuals and communities.

Traditional risk factors such as hypertension, dyslipidemia, diabetes, and smoking have long been established as the primary causes of CAD.[3] However, the role of genetic factors in CAD susceptibility is subject of considerable research. Recent studies have shown that the genetic risk may be considered the first risk factor, establishing a lifelong baseline risk profile that can be influenced by clinical, environmental, and stochastic factors.[4]

Genome-wide association studies (GWAS), by systematically comparing single-nucleotide polymorphisms (SNPs) between individuals with and without CAD, can identify genes related to CAD susceptibility.[5] Since the first GWAS in 2007, 321 loci have been associated with CAD in a significant fashion genome-wide.[6,7] To date, many of these candidate causal genes have been related to the pathogenesis of CAD through multiple mechanisms such as immune response and inflammation, lipid metabolism, proliferation and transcriptional regulation, neovascularization and angiogenesis.[8] However, it is noteworthy that most of the novel risk alleles confer relatively small odds ratios, so the main applicability of GWAS is through the development of polygenic risk scores (PRS).[5]

PRS are calculated as weighted sums of SNPs that enable an individual's lifelong risk of developing CAD to be estimated.[5] The use of PRS is a promising approach to personalized medicine that has the potential to improve the accuracy of risk prediction and inform targeted interventions to prevent or manage CAD. PRS have potential applications in population-based screening for CAD, particularly as healthcare-associated biobanks and direct-to-consumer genetic testing become more widespread. Several studies in middle-aged patients have shown that a high PRS for CAD is associated with an increased risk of developing the disease and can provide risk discrimination that is comparable to that of traditional clinical risk factors.[9]

In addition, PRS could also have important implications for the prevention of recurrent CAD events through appropriate treatment, such as lipid-lowering therapy. While there is a general consensus that all patients who have experienced

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symptomatic CAD should receive lipid-lowering therapy, the target for low-density lipoprotein cholesterol (LDL-C) levels varies depending on the patient's individual risk profile. Recent research suggests that among individuals with CAD, a high PRS is predictive of recurrent events, and post-hoc analyses of patients with appropriate indications for lipid-lowering therapy who were already receiving statins found that those with a high PRS for CAD had greater reductions in relative as well as absolute risk from proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies compared to placebo. This suggests that PRS for CAD could be combined with traditional clinical risk factors to guide LDL-C thresholds and optimize treatment for patients with CAD.[5]

However, before PRS can be incorporated into clinical practice, several potential pitfalls need to be considered. Firstly, most GWAS have been conducted in the European populations, which means that the resulting PRS may not be generalizable to other populations. Variations in ancestry, environmental factors, and other factors can significantly impact the accuracy and generalizability of PRS. Therefore, caution should be exercised when applying PRS to populations with different genetic backgrounds and environmental exposures.[10]

Moreover, although PRS have shown promise, they have not yet been widely adopted in clinical practice, and their clinical utility for predicting CAD risk is not yet established. Further research is needed to determine the best approach to integrate PRS into clinical practice and to develop evidence-based guidelines for their use.[10]

The study by Santos et al in this issue of the *Journal* was conducted at the renowned Dr Maria Isabel Mendonça Research Center in the Madeira archipelago.[11] It is based on the large GENEMACOR case–control study, which included 3139 individuals (1723 patients with a previous acute coronary syndrome and 1416 controls) and investigated the association between traditional CAD risk factors, 33 CAD-related genetic variants and the development of CAD.[12] This study demonstrated that the addition of a multiplicative PRS to a traditional risk factor-based model significantly, albeit modestly, increased the discriminative power of the model from 0.73 to 0.75 ($p<0.0001$).[12] The authors also identified eight genetic variants associated with an increased likelihood of developing CAD, including the transcription factor 21 gene (*TCF21*) rs12190287 G>C polymorphism (odds ratio 1.260; 95% confidence interval: 1.094–1.452).[12]

Building on this research, Santos et al. explored the prognostic impact of the *TCF21* rs12190287 gene variant among patients with a history of acute coronary syndrome.[11] They included all 1713 CAD patients of the GENEMACOR study and followed them for a mean of 5.0±4.3 years. The study found that the dominant genetic model (heterozygous GC plus homozygous CC) was an independent risk factor for the occurrence of major adverse cardiovascular events (MACE) (hazard ratio 1.41; $p=0.033$). Similarly, patients with the C allele showed worse survival (22.5% vs. 44.3%) at 15 years of follow-up.[11]

An important limitation of this study is that it did not account for the significant impact that the management of traditional risk factors and antithrombotic therapy may have had on the occurrence of MACE during follow-up. Nevertheless, the findings are in line with previous studies. TCF21 has been shown to promote de-differentiation, proliferation, and migration of smooth muscle cells into the developing atherosclerotic lesion, where they contribute to the protective fibrous cap.[13] The *TCF21* rs12190287 G>C variant is associated with reduced TCF21 expression, thereby increasing plaque vulnerability and potentially the rate of MACE.[14]

In conclusion, the study by Santos et al. is pioneering in Portugal, providing insights into our genetic background and its relation to CAD and recurrent MACE. Further research is needed to confirm the association between the *TCF21* rs12190287 G>C variant and prognosis in patients with CAD, to establish causality, and then to determine how to manage CAD patients at higher genetic risk.

Conflicts of interest

The authors have no conflicts of interest to declare.

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