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EDITORIAL COMMENT

Premature coronary artery disease primary prevention – Searching for the Holy Grail

Prevenção primária da doença coronária prematura - Em busca do Santo Graal

Jorge Alcaravela[a,b,c,d]

[a] *Clínica Médica Jorge Alcaravela, Abrantes, Portugal*
[b] *Serviço de Cardiologia, Centro Hospitalar Médio Tejo, Abrantes, Portugal*
[c] *Abranclínica, Cardiologia, Portugal*
[d] *Centro de Cardiologia de Intervenção, Hospital da Luz-Lisboa, Luz-Saúde, Portugal*

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The impact of premature coronary artery disease (CAD) is enormous as it has social, economic, and health implications. In recent decades, atherosclerotic cardiovascular disease (ASCVD) events have been declining in older adults, with improved outcomes, but these gains have not extended to younger adults, especially in women with acute myocardial infarction (MI).[1] Another issue in younger CAD patients is the lack of consistent data about real risk factor prevalence, therapeutic prescription and compliance, genetic disorders, drug abuse, special disease prevalence associated with CAD and the real incidence of cardiovascular death, especially in out-off hospital cardiac arrest. This makes it difficult to interpret the results of observational registries.[2]

Although CAD primarily affects patients over the age of 45, labeled premature <55 years for men or <65 years for women, it can also affect those <45 years and is associated with poor long-term prognosis. In this condition, the causes are multifold: CAD, drug abuse-related MI, hypercoagulable conditions, and non-atheromatous CAD. There is a significant overlap between each category. Hypertension, smoking, diabetes, dyslipidemia, obesity, inactivity, unbalanced diet, binge drinking alcohol and related substances, and chronic inflammation are all risk factors, and when associated, make the implementation of a prevention strategy difficult.

In this issue of the *Journal*, Juan-Salvadores et al.[3] compare three groups of patients undergoing coronary angiography: very young patients (≤35 years) with CAD (definition – stenosis ≥75% on angiography or a positive invasive ischemia test or a diagnosis of myocardial infarction with no obstructive coronary atherosclerosis); subjects aged ≤35 years without CAD (control A); and young patients (≥36–40 years) with CAD (control B). In a single-center, retrospective, nested case–control study, with 299 patients referred for the first time for coronary angiography due to clinical suspicion of MI or stable angina, 107 patients were aged ≤35 years and 190 patients were aged 36–40 years. The control group A consisted of 54 patients, and they were followed for five years.

The aim of this study was to evaluate major adverse cardiac events (MACE) in very young CAD patients and explore the risk-adjusted association of various risk factors. These CAD patients were mainly male (80%) and smokers (85%), with a 30% family history of CAD. CAD patients <35 years reported 22% use of cocaine, 24% cannabis, and 16% alcohol. Although 60% had left descending artery disease and 40% one-vessel occlusion, the mean left ventricular ejection fraction was 55%.

E-mail address: jorgealcaravela@gmail.com

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During follow-up, despite initial prescription of aspirin (99%), P2Y12 inhibitors (90%) and statins (87%) in CAD <35 years patients, 21% had a recurrent MACE, and 6% died.

Key study findings were as follows: (1) only smoking and having a family history of CAD revealed a risk of premature CAD; (2) patients ≤35 years showed unfavorable long-term prognosis; (3) illicit drug and alcohol use were associated with premature CAD; (4) subjects ≤35 years with a history of diabetes, dyslipidemia, and depression have a higher risk of MACE at long-term follow-up. In sum, this study helped shed light on factors associated with CAD events and poor prognosis in very young patients and opportunities for enhanced prevention.

Preventing CAD in young, healthy adults remains challenging due to the limitations in risk calculators and the insufficient observational data for this age group. In young adults aged <40 years, lipid-lowering and blood pressure-lowering drug treatments are not usually considered, except for patients with familiar hypercholesterolemia or specific blood pressure disorders. A healthy lifestyle that is maintained throughout life is more relevant for the very young.[4] Interestingly, in the YOUNG-MI registry, most adults <50 years would not have been guideline-eligible for statin therapy prior to their event.[5] Nonetheless, it is crucial to estimate the 10-year cardiovascular disease (CVD) risk (SCORE2) in >40 years population. In those aged <40, the evaluation of conventional risk factors and CVD risk modifiers such as imaging, genetics, psychosocial factors, and ethnicity, may improve risk estimation. Nevertheless, the adult population needs education to promote the intensification of lifestyle measures and track improvements in risk factors.[4]

The most prevalent risk factor in young CAD patients is cigarette smoking, as seen in this study and like other registries. CVD risk in smokers <50 years is five-fold higher than in non-smokers. Linked to inflammation, thrombus formation, vasospasm, plaque rupture or erosion, smoking is associated with acute cardiovascular disease, and the duration of exposure is not so relevant as seen in lung cancer. Cessation and not a reduction are associated with a rapid decline in CVD risk, reducing to half in the first year.[6]

Non-invasive CAD imaging with coronary artery calcium (CAC) and coronary CT angiography (CCTA) are the cornerstones of the presence of atherosclerosis in younger adults and associated with poor cardiovascular prognosis. (1) Studies have shown that the presence of CAC (>0) ranged from 10% to 34% in young adults and carried a significantly increased risk for future cardiovascular and all-cause mortality.[7] (2) In the CONFIRM registry, an artificial intelligence model incorporating clinical features, in addition to CAC, can accurately estimate the pre-test likelihood of obstructive CAD on CCTA.[8] (3) Mushtaq et al. linked the burden of non-obstructive coronary lesions (a CT Leaman score >5) on CCTA with the same prognosis as with obstructive coronary disease.[9] In this context, the 2024 guidelines for the management of chronic coronary syndrome (CCS) empower CAD imaging: (1) CAC – in individuals with a low (>5%–15%) pre-test likelihood of obstructive CAD, CAC should be used to reclassify subjects and to identify more individuals with very low (≤5%) CAC-weighted clinical likelihood (IIa); (2) CCTA – in individuals with suspected CCS and low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA is recommended to diagnose obstructive CAD and to estimate the risk of MACE(IA).[10] As we all know, a picture is worth more than a thousand words – this is likely to be the case.

And probably the most important demonstration of atherosclerosis by CCTA is the increased implementation of preventive lifestyle modifications and pharmacotherapies, where statins and aspirin are crucial. High-dose statins are recommended in the 2021 ESC Guidelines when CAD, even with non-obstructive coronary lesions, is present. Ezetimibe and PSCK9 inhibitors may also be considered.[4] Concerning aspirin, trials show a benefit in MACE, especially in younger patients, despite an increased bleeding risk observed more in gastrointestinal than in intracranial forms. There is an underuse of proton pump inhibitor, as seen in ASCEND trial, with just 13% at randomization and 25% at the end of the study.[11] Guidelines recommend aspirin use in significant coronary lesions and higher-risk patients at SCORE2.[4,10]

In the future, the key is to start earlier and earlier in controlling risk factors, according to ESC guidelines, identifying special conditions associated with premature CAD, educating the general population, and adopting healthier lifestyles.

Searching for new data, there are two promising studies to guide the cardiology community: (1) PRECAD (Primary Prevention of Subclinical Atherosclerosis in Young Adults) trial is recruiting participants, age 20–39 years, to achieve LDL-C <70 mg/dl and maintain strict control of blood pressure and glucose to reduce MACE[12]; (2) SCOT-HEART 2 (Computed Tomography Coronary Angiography for the Prevention of Myocardial Infarction; (NCT03920176) trial enrolling 6000 individuals at risk for CVD and determine whether a risk score-guided versus a CCTA-guided approach reduces MACE.

Looking to the future, where accurate preventive measures, optimal risk stratification, multi-modality imaging, polygenic risk scores, inflammatory markers, adequate therapeutic options, and AI models, there will be an improvement in clinical outcomes in the younger population. Until then, Cardiology faces a lack of consistent preventive policies, a NO cigarette smoking strategy, an erratic distribution of general medicine, difficult access to CCTA and other exams, an anti-aspirin culture in primary prevention, and an unequal primary PCI capacity distribution.

For now, a team-based, patient-centered, and locally focused approach seems the best option in defeating CAD in the young population.

According to this study, smokers and/or those with a family history of CAD deserve special attention, where statins and aspirin make a difference.

Coronary artery calcium and CCTA will help to change this FADO (destiny).

There is hope in AI models to study, measure, and quantify the most important factors in this population: LUCK.

Conflicts of interest

The author has no conflicts of interest to declare.

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