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Editorial

Coronary computed tomography angiography in asymptomatic patients: Still a taboo or precision medicine?

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In this issue of the journal, Pérez de Isla and colleagues [1] report on 259 asymptomatic patients with genetically diagnosed familial hypercholesterolemia (FH) submitted to coronary computed tomography angiography (CCTA). They performed a quantitative assessment of coronary plaque burden and composition in all patients and followed them for an average of 3.9 years after the initial scan. The results should be considered in the context of the current cardiovascular risk assessment approaches. Despite advances in the diagnostic work-up and both pharmacologic and invasive treatment of coronary artery disease (CAD), acute coronary syndromes (ACS), sudden death and progressive heart failure are still the leading causes of morbidity and mortality in the Western world [2]. Cardiac computed tomography angiography (CCTA) is a unique diagnostic tool that provides non-invasive visualization of moving coronary arteries with isotropic submillimeter spatial and high temporal resolution. In contrast to all other non-invasive diagnostic techniques, CCTA provides not only an opportunity to diagnose obstructive CAD but also a direct assessment of the atherosclerotic plaque burden and plaque composition that can be differentiated into calcified and non-calcified or low-attenuation non-obstructive plaques. Low attenuation plaques, along with other high-risk features, such as spotty calcification, positive remodeling, or the napkin-ring sign [3], have the potential to improve patients' risk stratification independent of stenosis severity [4]. In a recent publication, low-attenuation plaque burden was associated with a 5-fold higher risk for subsequent ACS, clearly surpassing the prognostic value of stenosis severity [5].

Although the prognostic implications of plaque burden and composition by CCTA is widely recognized in patients with symptomatic CAD [6], the role of CCTA for risk stratification of asymptomatic individuals at high risk for atherosclerotic disease remains controversial. In this regard, a sub-analysis of 1226 patients from the multi-center CONFIRM registry previously showed that CCTA findings do not exhibit incremental value over traditional risk factors or calcium scoring. Therefore, current guidelines do not recommend the use of CCTA in asymptomatic individuals. However, a recent metanalysis of studies involving 5012 asymptomatic patients with diabetes mellitus demonstrated the ability of CCTA plaque burden to predict future cardiac events [7]. Thus, it is conceivable that even asymptomatic individuals at high risk for atherosclerotic disease due to diabetes mellitus, FH or family history of premature CAD may benefit from individual risk stratification by CCTA and subsequent tailored pharmacologic therapies.

In the study by Pérez de Isla and colleagues [1], subclinical coronary atherosclerosis visualized by CCTA was highly prevalent in asymptomatic patients with definite FH. Multivariable regression analysis demonstrated that plaque burden was predictive of future outcomes (5 ACS and 10 revascularization procedures), independent of conventional risk factors, coronary artery calcium, laboratory markers and lipid lowering medications. Hence, this is the first study to highlight the role of non-calcified atherosclerotic plaque burden as a predictor of subsequent cardiac events in asymptomatic individuals with FH. However, the study included a relatively small number of patients and the number of cardiac events, especially ACS, was low. In addition, no control group was included, whereas selection biases need to be considered since the population is at very high risk for cardiac events and most such individuals already receive potent lipid-lowering medications by clinical indication.

The role of lipid-lowering therapies such as statins, ezetimibe and anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies for the prevention of cardiovascular events is firmly established, and these treatment options are endorsed by current clinical guidelines for primary and secondary prevention in individuals at risk, including those with FH and in patients with atherosclerotic

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Fig. 1. Role of coronary computed tomography angiography in risk stratification of coronary artery disease: high-risk plaque features (left side) and plaque stabilizing pharmacotherapies targeting lipid accumulation and inflammation (right side).

Low attenuation, non-obstructive plaque in the mid LAD (top), (SOMATOM Force CT scanner, Donation of the Hector Foundation, GRN Hospital Weinheim)

cardiovascular disease [8]. New drugs, such as bempedoic acid, a small molecule that inhibits cholesterol synthesis [9], or inclisiran, a new *anti*-PCSK9 operating as a synthetic small interfering ribonucleic acid (siRNA), are currently being evaluated as additional weapons to be added to our armamentarium [10]. Beyond LDL lowering drugs, anti-inflammatory drugs such as colchicine [11,12], and purified omega 3 fatty acids [13] may add plaque-stabilizing effects, by modifying low-attenuation plaque components, as shown by recent CCTA studies [14,15]. CCTA features suggestive of high-risk individuals for future ACS and sudden death, along with targeted pharmacologic options for plaque stabilization, are summarized in Fig. 1.

Since almost 50% of patients who experience a sudden cardiac event do not have warning symptoms such as angina or dyspnea [16], CCTA may help identify asymptomatic individuals at high risk for future events and improve cardiac outcomes in this context, as currently being investigated in the randomized SCOT Heart 2 study (ClinicalTrials.gov Identifier: NCT03920176). The randomized SCOT Heart 1 study already demonstrated that the use of CCTA is associated with significantly lower rates of cardiac death and nonfatal infarctions compared to standard care in symptomatic patients [17]. Modern CT scanners enable CCTA acquisitions with a radiation exposure of <1mSv [18], and the small risk inherent to this low radiation dose should be weighed against the potential benefit of therapeutic interventions that reduce the risk of cardiovascular events.

The study by Pérez de Isla et al. [1] provides preliminary evidence that CCTA can improve risk stratification in high-risk asymptomatic individuals with FH. Whether CCTA can help us identify the asymptomatic individuals, who are at high risk to develop future coronary events is a fascinating hypothesis, now being tested in ongoing randomized studies, such as the SCOT Heart 2 trial. If successful, these studies might lay the ground for preemptive tailored pharmacologic interventions in high-risk asymptomatic individuals, creating a whole new perspective in the management of CAD. Our health care system will also need to consider adapting reimbursement structures, providing incentives for prevention strategies based on CCTA over more costly and often less effective invasive procedures in this context.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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