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Role of Cardiac CT and Circulating Biomarkers in Coronary Artery Disease: Recent Advances for Expanding Cardiac Imaging Access

EDITORIAL
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Despite recent advances in cardiovascular medicine, medical therapy, and invasive interventions, coronary artery disease (CAD) remains the leading cause of mortality and morbidity worldwide. For the vast majority of patients, the first clinical manifestations of CAD are angina, myocardial infarction (MI), or sudden cardiac death, which require accurate, timely, and quick diagnosis.[1] While catheter coronary angiography remains the gold standard method for the diagnosis of CAD, cardiac computed tomography (CCT) has increasingly become a robust non-invasive imaging technique. Although there are many non-invasive imaging modalities that can help diagnose CAD, only CCT reliably delineates the coronary artery wall and lumen and characterizes the morphological features of plaques.[2] CCT provides important information in asymptomatic patients by identifying the coronary artery calcium (CAC) score for cardiovascular (CV) risk stratification in primary prevention. Moreover, in symptomatic patients, CCT allows for a comprehensive, quantitative, and qualitative assessment of coronary artery plaque burden, detection of high-risk morphological plaque features, evaluation of the hemodynamic significance of coronary artery lesions, and quantification of coronary inflammation by imaging pericoronary adipose tissue.[3]

Coronary Artery Calcium Score for Risk Stratification in Asymptomatic Individuals

The CAC score is a commonly used marker for subclinical CAD and is measured through electrocardiography-gated, non-contrast CCT using the Agatston method. It is particularly valuable in identifying asymptomatic adults who may benefit from more intensive preventative treatment. It is highly recommended for individuals over 40 years of age when there is uncertainty regrading the 10-year risk of atherosclerotic cardiovascular disease (ASCVD) and the initiation of primary prevention drugs.[4] Numerous studies have assessed the CAC score's ability to reclassify patients into high or low-risk groups beyond conventional risk factors, using the net reclassification improvement (NRI). In the Multi-Ethnic Study of Atherosclerosis (MESA), approximately 6800 individuals without any CV disease were followed for atherosclerotic events. This large-scale prospective study demonstrated that individuals with a CAC score of zero were at low risk for CV incidents, even if they possessed several conventional risk factors for CAD. Conversely, individuals without any CV risk factors but with a CAC score of ≥ 100 (Agatston method) exhibited an increased risk for major adverse cardiac events (MACE).[5] In the population-based Heinz Nixdorf Recall study (HNRS), which included 4129 individuals without obvious CAD at baseline, participants were classified into three risk groups (low, intermediate and high) based on CV risk factors according to Adult Treatment Program III guidelines and Framingham risk score (FRS). CCT was performed to obtain a CAC score. Particularly in the intermediate risk group, a significant improvement in future risk prediction of atherosclerotic events was observed through the use of the CAC score.[6] The use of CAC score in intermediate risk group showed similar NRIs in both studies. In a nutshell, both studies revealed that the addition of CAC score information resulted in marked changes in NRI beyond the prognostic information provided by standard conventional risk factors. Reclassification of intermediate risk patients based on the CAC score can help identify those at high or low risk for future atherosclerotic events. Thus, physicians and patients can focus on intensive risk factor management and treatment in those at higher risk. They can also concentrate on lifestyle modifications in lower risk individuals. In 2012, Yeboah et al. used data from the MESA study to compare several new risk factors for improvement in CV risk appraisal

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in intermediate risk patients. They used six CV risk markers for comparison, which included CAC score, carotid intima-media thickness, brachial flow-mediated dilation, ankle-brachial index, C-reactive protein, and family history of CAD. CAC score was found to be the best marker that can be used in addition to FRS.[7]

Several guidelines or expert consensus documents have recommended the use of the CAC score to make a decision on commencing statin treatment for primary prevention between the healthcare provider and the patient. The expert consensus document of the Society of Cardiovascular Computed Tomography in 2017 supports the use of the CAC score in asymptomatic individuals aged between 40 and 75 with a 5%–20% ASCVD risk, as well as in the less than 5% ASCVD risk group with a family history of early-onset CAD. The 2019 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on Primary Prevention of Cardiovascular Disease assigned a IIa recommendation for the utilization of the CAC score for ASCVD risk appraisal in asymptomatic individuals with intermediate ASCVD risk. Furthermore, the 2019 European Society of Cardiology guidelines on the management of dyslipidemias assigned a IIa recommendation for the CAC score in asymptomatic individuals.[8-10]

For many asymptomatic patients, seeing their CAC score picture is worth a thousand words when making serious lifestyle changes or agreeing to start statin therapy (Figure 1). Currently, the radiation dose for obtaining a CAC score is between 0.7 and 1.0 mSv, which is slightly higher than a mammogram. Not yet, but in the future, the CAC score can become the mammogram of the heart.[11]

Cardiac Computed Tomography (CT) for the Appraisal of Symptomatic Individuals

Retrosternal chest pain is often a sign of CAD and is one of the most common diagnostic challenges encountered in our daily clinical practice. Based on presenting symptoms, a detailed history, physical examination, electrocardiographic (ECG) changes, and cardiac enzyme levels, patients can be categorized into low, intermediate, and high pre-test probability groups for CAD. After acute coronary syndrome has been ruled out, physicians have a variety of diagnostic imaging modalities to choose from in order to determine the presence of CAD and quantify its extent in these patients. CCT is an excellent non-invasive imaging technique that reliably delineates the anatomic extent of CAD. The analysis of ECG-gated CCT images allows for accurate assessment of both the presence and degree of coronary arterial obstruction. In addition to diagnosis, CCT helps in treatment management. Recently published 5-year follow-up data from the Scottish Computed Tomography of the Heart (SCOT-HEART) trial demonstrated a significant reduction in the incidence of Myocardial Infarction (MI) among patients randomized to CCT compared with standard care.[12] CCT has perfect sensitivity and negative predictive value, and helps physicians avoid unnecessary invasive diagnostic coronary angiography. However, the specificity of CCT is lower than its sensitivity and negative predictive value. In addition to obtaining anatomical information from CCT, after 20 years of employing CCT for assessing the anatomical severity of luminal narrowing secondary to CAD, a new modality for obtaining functional information from CCT has been developed to enhance its specificity by evaluating lesion-specific ischemia (Figure 2). This modality uses computational fluid dynamics to measure the fractional flow reserve (FFR) value from CCT. For the computed tomography-derived FFR (CT-FFR or FFR_{CT}) value of the lesion, additional image acquisition and radiation exposure, or the use of any pharmacologic stress drug during CCT, are not necessary.[2] Although functional assessment of coronary artery lesions can be carried out by stress CT perfusion, it requires additional image acquisition and radiation exposure or pharmacologic stress drug.[13]

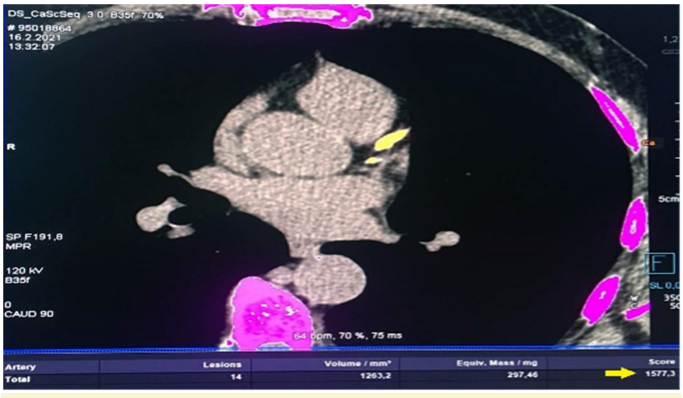

Figure 1. Asymptomatic 64-year-old hypertensive patient with 11% (intermediate) 10-year ASCVD risk. LDL is 150 mg/dL. Total CAC score is 1577 Agatston Units (yellow arrow). The patient agreed to start statin therapy after seeing their CAC score picture. This image is from my Cardiac CT archive; the video was submitted to view the full part of the CAC score.

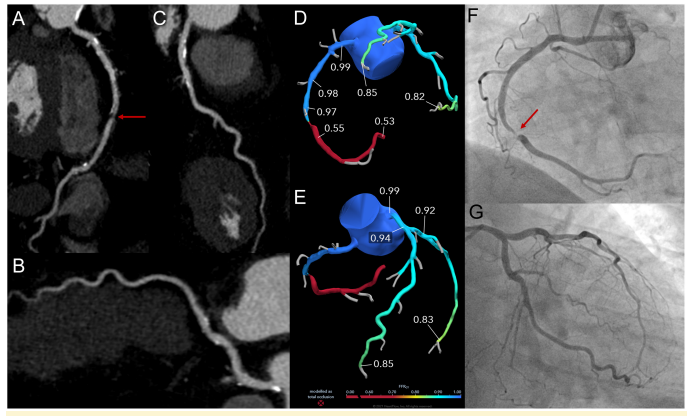

Figure 2. A 60-year-old man with dyslipidaemia and a family history of CAD presented with exertional chest pain, and CCT was performed. (A) Evidence of severe luminal narrowing in the right coronary artery (RCA) (red arrow), and (B) mild stenosis in the left main (LM), (C) circumflex (Cx), and (D) proximal left anterior descending (LAD). FFR_{CT} demonstrated (E) a remarkable FFR_{CT} value at the level of RCA stenosis, (F) while showing normal values in LAD and Cx; (G) invasive coronary angiography confirmed critical stenosis in RCA (red arrow) and (H) mild stenoses in LM, Cx, and LAD. This image was provided by Professor Gianluca Pontone and was also used in my review article as referenced in reference 2.

We know that most acute MIs occur as a result of occlusion in coronary arteries due to the rupture of non-obstructive plaques. CCT provides important information about the morphology and composition of coronary artery plaques that have the tendency to rupture. This includes high-risk plaque features such as the napkin-ring sign, positive remodeling, spotty calcification, and low CT-attenuation plaque. These high-risk plaque features have been found to be independent predictors of MACEs and plaque rupture. Coronary artery inflammation plays a prominent role in the pathophysiology of atherosclerosis and plaque rupture. Recently, a new CCT-based imaging biomarker for assessing coronary artery inflammation by analyzing conventional CCT, known as the pericoronary fat attenuation index (FAI), has advanced our understanding of the pathophysiology of plaque rupture.[3] FAI can help distinguish stable plaques from vulnerable plaques. In 2017, Antonopoulos et al. demonstrated that, ΔFAI had excellent diagnostic value for discriminating between these plaques.[14] In another study published in 2018, known as the Computed Tomography Coronary Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry (CRISP-CT) study, Oikonomou et al. showed that a pericoronary FAI level ≥−70.1 Hounsfield unit was a robust predictor of increased cardiac and all-cause mortality, independent of traditional risk factors.[15] Dai et al. demonstrated a decrease in FAI in a follow-up CCT in patients who started statin treatment after an initial CCT.[16] In summary, FAI serves as a strong, convenient, and clinically applicable procedure for stratifying CV risk in daily clinical practice (Figure 3).

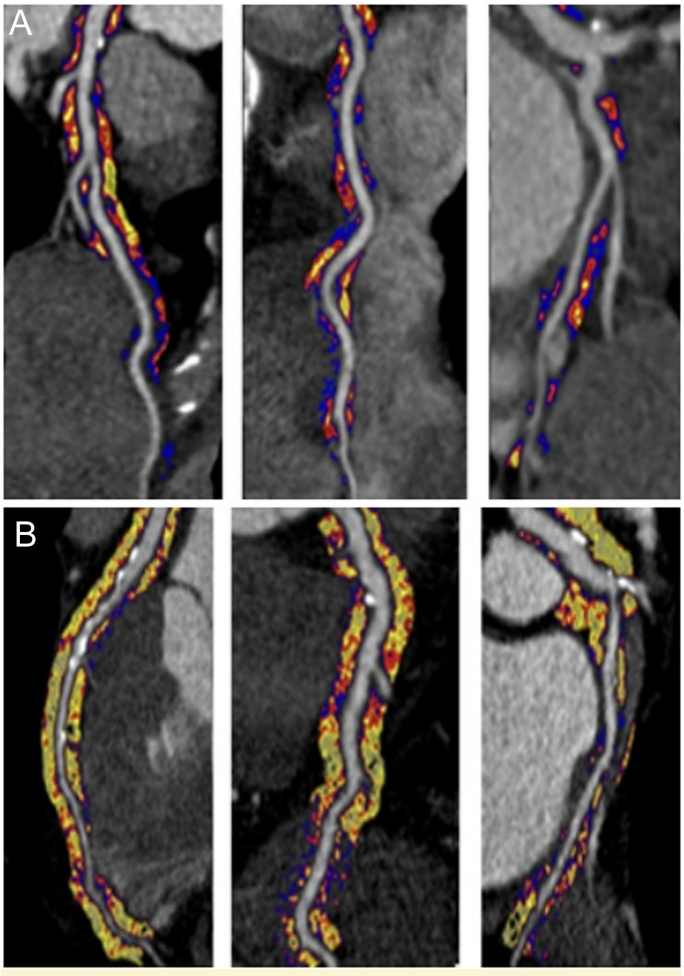

Figure 3. Fat Attenuation Index (FAI) around the three main coronary arteries. (A) Image shows high coronary inflammation in a patient with minor plaque disease. The eight-year risk for a cardiac event by FAI is 31.2% (CaRi-Heart Risk). (B) The image shows low coronary inflammation. The calculated eight-year risk for a cardiac event by FAI is 9.8% (CaRi- Heart Risk). The images are courtesy of Caristo Diagnostic Ltd., Oxford, UK.

Circulating Biomarkers in Coronary Artery Disease

Circulating biomarkers are substances that can be measured in the blood and provide information about the presence, severity, or prognosis of a disease. In the context of CAD, several biomarkers from different physiopathological mechanisms have been identified to predict atherosclerotic incidents. The addition of biomarkers to risk assessment may contribute to enhancing risk stratification in primary and secondary prevention. Some frequently used biomarkers in studies include high-sensitive troponin, B-type natriuretic peptide, heart-type fatty acid-binding protein, 25-hydroxyvitamin D, lipocalin-2, adiponectin, adipocyte fatty acid-binding protein, fibroblast growth factor 19 and 21, retinol-binding protein 4, and sclerostin. Many of these biomarkers have shown promise in improving the risk prediction of CAD.[17]

In this issue of the Archives of Turkish Society of Cardiology, an article entitled 'Relationship Between Sclerostin Levels and Coronary Artery Calcification and Plaque Composition" has been published. The investigators found higher serum sclerostin levels in patients with calcified and mixed coronary plaques and a positive correlation between sclerostin and CAC. They concluded that increased serum sclerostin concentration is a biomarker of coronary atherosclerotic plaque burden and has value in predicting one-year MACE. Sclerostin is best known for its role in controlling bone formation but is also produced in other tissues such as the heart, aorta, coronary, and peripheral arteries. As the authors pointed out in the discussion section, there are inconsistent results on the role of sclerostin in CAD in different studies. Particularly, this discrepancy is prominent between animal and human studies. There are a number of possible explanations for this discrepancy, with reverse causality being one of them. High sclerostin levels in patients with CAD could be a response to the underlying disease rather than a cause.[18]

Conclusion

When it comes to diagnosis, risk stratification, or management of CAD, we have multiple options, including imaging techniques and circulating biomarkers. CCT is a unique imaging modality that has emerged for assessing chest discomfort due to possible underlying CAD and evaluating CV risk. CCT provides us with anatomical and functional information about coronary artery plaque. It can serve as a gatekeeper for the catheter laboratory in patients with suspected CAD, similar to how mammography is used for asymptomatic individuals. On the other hand, Sclerostin, a circulating biomarker, can contribute to risk stratification and

prognosis in CAD. However, more studies are needed to determine its clinical utility.

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