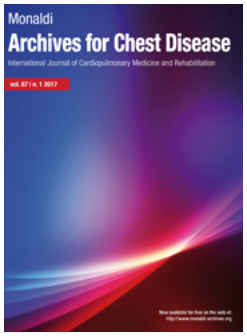

Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2023 [Online ahead of print]

To cite this Article:
Mattesi G, Savo MT, De Amicis M, et al. **Coronary artery calcium score: we know where we are but not where we may be.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2023.2720

Coronary artery calcium score: we know where we are but not where we may be

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Contributions: All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare no conflict of interest.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author upon request.

Abstract

Cardiac computed tomography angiography (CCTA) has emerged as a cost-effective and time-saving technique for excluding coronary artery disease. One valuable tool obtained by CCTA is the coronary artery calcium (CAC) score. The use of CAC scoring has shown promise in risk assessment and stratification of cardiovascular disease. CAC scores can be complemented by plaque analysis to assess vulnerable plaque characteristics and further refine risk assessment. This paper aims to provide a comprehensive understanding of the value of the CAC as a prognostic tool and its implications for patient risk assessment, treatment strategies and outcomes. CAC scoring has demonstrated superior ability in stratifying patients, especially asymptomatic individuals, compared to traditional risk factors and scoring systems. The main evidence suggests that individuals with a CAC score of 0 had a good long-term prognosis, while elevated CAC score is associated with increased cardiovascular risk. Finally, the clinical power of CAC scoring and the develop of new models for risk stratification could be enhanced by machine learning algorithms.

Key words: coronary computed tomography; calcium score; risk stratification; coronary plaque.

Introduction

Coronary artery disease (CAD) is a significant condition characterized by the accumulation of atherosclerotic plaques in the coronary arteries, leading to the narrowing or obstruction of vessels and then a reduced blood flow to the heart muscle [1]. Early detection and risk assessment of CAD are essential for effective management and prevention of adverse cardiac events. CCTA has emerged as a cost-effective and time-saving technique for excluding CAD [2]. Over the last decade, CCTA has witnessed significant technical advancements, validating, and gaining approval in various guidelines and expert consensus documents [3-6]. Its utility now extends beyond the assessment of coronary artery atherosclerosis. One valuable tool in the evaluation of CAD obtained by non-contrast CCTA (NC-CCTA) is CAC score [1]. The CAC score measures the amount of calcium deposits in the coronary arteries, providing information about atherosclerotic plaque burden and serving as a predictor of future cardiovascular events [1]. It plays a crucial role in risk stratification, treatment decision-making, and monitoring of disease progression. With the advent of new advanced techniques, the use of NC-CCTA has diminished. However, NC-CCTA remains relevant for the detection and quantification of CAC, indicating the presence of calcified plaques and serving as a marker of CAD and a surrogate marker of coronary plaque burden [7-9].

This paper aims to provide a comprehensive understanding of the value of the CAC as a prognostic tool and its implications for patient risk assessment, treatment strategies and outcomes.

Performing CT calcium scoring

Calculation and interpretation of coronary calcium score

Calcium scoring of the coronary arteries is typically conducted using a ≥64-slice computed CT system. A spiral non-electrocardiogram (ECG) gated technique is commonly employed, with the patient instructed to take a deep inspiratory breath-hold. The imaging parameters typically include a tube voltage of 120 kV and tube current power ranging from 50 to 200 mAs. The reconstructed images are generated with a slice thickness of 3 mm, a field of view of 250-300 mm, and convolution kernel filtering with b30f [10]. CAC is defined as an area consisting of at least three contiguous voxels in the axial plane along the course of a coronary artery, with an attenuation cut-off of ≥100 HU (corresponding to a minimum lesion area >1 mm^2) in the

3.0 mm reconstruction. Commercial softwares are utilized to perform the CAC scoring, employing the Agatston method that considers the plaque density score. Although ECG-gated acquisition was traditionally required for CAC measurement with the Agatston method, a good correlation has been established between CAC identified on non-gated CT scans and ordinal scores obtained from gated CT scans [5]. The total Agatston score, commonly referred to as the CAC score, is obtained by summing the scores for all the lesions in all coronary arteries (Figure 1). The final score depends on the slice thickness and slice spacing, which can vary depending on the specific protocol used. Patient stratification based on validated CAC score thresholds [5] is as follows: 0 = very low risk; 1-99 = mildly increased risk; 100-299 = moderately increased risk; 300-1000 = moderate to severely increased risk; >1000 = severely increased risk.

Comparison to other advanced cardiac compute tomography tools

While invasive coronary angiography (ICA) remains the gold standard in the diagnosis of coronary artery disease, CCTA has increasingly become a non-invasive alternative for assessing patients at intermediate risk for CAD. CCTA has achieved the temporal and spatial resolution to be able to define the lumen of even distal segments of the coronary artery tree. For this reason, the use of NC-CCTA has become less prevalent with the development of new techniques [9] and recent studies demonstrated the integration of plaque analysis tools and of peri-coronary fat inflammation (pFAI) as valuable additions to cardiovascular risk evaluation, allowing for better stratification of cardiac risk beyond the degree of anatomical coronary artery disease, even in non-significant plaques [11,12]. For example, pFAI showed to have different temporal distributions in patients with acute myocardial infarction type 2 compared to those with myocardial infarction with non-obstructive coronary arteries [13,14]. CCTA therefore has made significant technical advancements and is now validated and approved not only for assessing coronary artery atherosclerosis [3,4,15,16]. On the other hand, CAC offers advantages in terms of cost-effectiveness in its ability to evaluate the overall burden of atherosclerosis and risk stratification [7]. Indeed, the presence and extent of CAC may help to stratify patients at higher risk of adverse outcomes also during hospitalization for non-cardiac diseases, helping to identify patients who may require more intensive management and monitoring [17]. Currently contrasted-enhancement cardiac computed tomography contributes to the evaluation of valve disease severity, particularly in low flow, low gradient aortic stenosis with preserved left ventricular ejection fraction; plays a role in pre-procedural planning of transcatheter aortic valve replacement and in avoiding patient prothesis mismatch. Aortic

valve, annular and root anatomy, size and shape with extent and distribution calcification feasibility of vascular access can be also assessed (Figure 2).

Diagnostic accuracy

Early studies evaluated the ability of CAC quantification to predict significant CAD as determined by ICA. Budoff *et al.* examined 1851 patients who underwent ICA for clinical indications. The overall sensitivity of CAC for predicting obstructive disease on ICA was high (95%), but the specificity was low (66%). As the calcium score increased (>20, >80, and >100), the sensitivity decreased (to 90%, 79%, and 76% respectively), and the specificity decreased as well (to 58%, 72%, and 75% respectively) [18]. From 1992 to 2007, a total of 18 studies including 10,355 patients suspected of CAD who underwent CAC testing as well as ICA were conducted. Significant coronary stenosis was defined as >50% stenosis on ICA. Pooled data revealed a high sensitivity of calcium scoring for any degree of CAC (98%), but a low specificity (40%) for predicting significant coronary stenosis. The negative and positive predictive values were 93% and 68%, respectively. It is worth noting that for CAC >100, the sensitivity decreases to 87%, while the specificity increases to 79% [19].

Clinical applications

Role of calcium score in the risk stratification in asymptomatic and symptomatic individuals

Plaque at high risk of rupture and associated with myocardial infarction usually has typical histological characteristics such as inflammation, microcalcification, a thin fibrous cap, and a large lipid-rich necrotic core [12,17]. Each plaque on CCTA should be classified as calcified, non-calcified, or partially calcified. The lipid-rich necrotic core, which is usually not adequately identified by the CAC score, can be detected as low-attenuation non-calcified plaque on CCTA instead [18]. For this reason, the relevance of a CAC score of zero has been extensively debated as it cannot fully exclude CAD in patients with new onset of chest pain symptoms. To ensure non-calcified plaque is also accounted for, the CAC score should be combined with at least a qualitative assessment of total plaque burden [20]. Firstly in 2012, the American Heart Association and American College of Cardiology (AHA/ACC) guidelines deemed CAC scoring evaluation appropriate for patients with a low to intermediate pre-test probability of obstructive CAD [21]. However, in the 2021 AHA/ACC guidelines, the role of CAC scoring was downgraded, suggesting that no tests are necessary in patients with a low pre-test likelihood of CAD, but CAC scoring could be evaluated to assess atherosclerotic cardiovascular disease (ASCVD) burden. According to 2019 ESC Guidelines for the diagnosis

and management of chronic coronary syndromes, in patients with a very low pre-test probability of CAD, performing a CT scan or visually estimating calcium based on prior non-cardiac chest CT can upgrade or downgrade ASCVD risk [16]. A meta-analysis conducted by Sarwar *et al*. [19]. In 29,312 asymptomatic individuals with a CAC score of zero, the average adverse cardiac event rate was 0.47% (range 0 to 4.43%) in 13 studies. Among these, eleven studies had event rates ≤1.01%; the South Bay Heart Watch study reported the highest event rate of 4.43%. The main explanation for this finding was that the use of an unconventional 6-mm slice thickness scanning protocol rather than the standard 3-mm collimation could have reduced the sensitivity and reproducibility in detecting <10 mm2 CAC [19]. A sub-group of the Multi-Ethnic Study of Atherosclerosis (MESA) that had the criteria of the JUPITER trial was studied by Blaha *et al*. [22]. They found that the 5-year number needed to treat to prevent an event of coronary heart disease was 549 for a CAC score of 0, 94 for scores 1-100 and 24 for scores greater than 100. The corresponding 5-year number needed to treat to prevent an event of cardiovascular disease was 124, 54, and 19, respectively [22]. These data were later supported by a prospective follow-up study of 9,715 patients: after an average time of 15 years, patients with an absence of calcium at baseline had a warranty period, with the observed rate of mortality remaining <1% during the entirety of follow-up. Moreover, the risk of all-cause mortality was higher among individuals with a CAC score greater than 0 and low cardiovascular risk compared with those with a CAC score of 0 and high cardiovascular risk [23]. This result has important implications in defining preventive therapy strategies. In appropriately selected low ASCVD risk and asymptomatic patients, a CAC score of zero could potentially be used to emphasize lifestyle therapy, limit costly preventive pharmacotherapy, and refrain from frequent cardiac imaging and testing [24]. On the other hand, fewer studies have investigated the role of a CAC score of zero in symptomatic patients. Sarwar *et al*. [19] examined 7 studies involving a total of 3,924 symptomatic patients, of whom 921 patients (23%) had a CAC score of zero. Overall, a CAC score of zero was found in 23% of symptomatic and 40% of asymptomatic patients. Symptomatic patients with a CAC score of zero had a significantly lower event rate than those with a CAC score greater than zero (1.8% *vs* 8.99%). Mittal *et al*. [24] enrolled 3,914 individuals presenting with stable chest pain or dyspnoea with no prior history of CHD; of these, 1,978 had a CAC score of zero. Kaplan-Meier survival estimated in the group with a CAC score of zero and a calcium score ≥1 was 99.0% and 94.5% at 5 years, and 95.5% and 84.0% at 13 years, respectively. In the group with a CAC score of zero, no one died due to a coronary event. The use of CAC score alone in symptomatic patients is therefore important when quick exclusion of obstructive CAD is required while

certain conditions do not allow for contrast agent injection or pose a considerable risk to the patient (e.g., severe kidney failure, previous anaphylactic reaction to iodine contrast or others).

Clinical use in cardiovascular primary prevention

The 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice acknowledge the value of CAC in risk stratification, stating that CAC scoring can improve risk prediction beyond traditional risk factors [25]. Similarly, the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease emphasizes the importance of CAC in identifying individuals who may benefit from intensified preventive therapies [26]. Several studies have demonstrated the predictive power of CAC in assessing the risk of coronary heart disease (CHD) events. The landmark study by Wilson *et al*. [27] demonstrated that risk factor categories, including CAC, significantly improved the prediction of CHD. The Atherosclerotic Cardiovascular Disease Pooled Cohort risk equations [28] also incorporate CAC as a risk factor. Furthermore, Budoff *et al*. [29] found that even individuals with absent or minimal CAC were still at risk of cardiovascular events. The relationship between CAC and age has been extensively studied. Hoff *et al*. [30] examined the age and gender distributions of CAC detected by electron beam tomography, while Detrano *et al*. [31] investigated the association between CAC and coronary events in different racial or ethnic groups. In a large cohort study, LaMonte *et al*. [32] reported that higher CAC scores were associated with increased risk of coronary heart disease events in both men and women. CAC has also shown value in predicting the progression of coronary artery calcification. Kronmal *et al*. [33] found that traditional risk factors and baseline CAC scores were significant predictors of CAC progression. Moreover, the presence of incidental CAC on non-gated CT thorax was found to correlate with the risk of cardiovascular events and death [34]. In addition to its predictive value, CAC has been shown to improve cardiovascular risk prediction in the elderly [31]. Other studies demonstrated the prognostic value of CAC in suspected coronary artery disease, and highlighted the utility of non-traditional risk markers, including CAC, in atherosclerotic cardiovascular disease risk assessment [35,36]. Comparisons between CAC and other risk markers have also been explored comparing CAC with carotid intima-media thickness in predicting cardiovascular disease incidence [37]. CAC was also evaluated for improving cardiovascular risk assessment in intermediate-risk individuals and in risk stratification [38]. Pergola *et al*. [17] investigated the impact of CAC on in-hospital mortality for SARS-CoV-2 infection, highlighting the potential of CAC as an identifier of at-risk patients.

Recommendations on CAC scoring in treatment decisions

Different guidelines provide varying recommendations regarding the use of CAC score in guiding treatment decisions, specifically in relation to statin therapy or other preventive therapies (Table 1). Notably, Verghese *et al*. [39] conducted a study published in the American Journal of Preventive Cardiology that focuses on the contemporary use of CAC scoring for the allocation of aspirin, specifically considering the 2022 he United States Preventive Services Task Force (USPSTF) guideline recommendations. The American Heart Association and American College of Cardiology (AHA/ACC) in their 2013 guidelines [40] state that CAC scoring may be considered in intermediate-risk patients (10-year risk of 5-20%) to help determine the initiation of statin therapy in those with CAC scores ≥300 Agatston units (AU). However, the guidelines also highlight that the use of CAC scoring is of uncertain value in patients with low (<5%) or high (>20%) 10-year risk estimates. The ESC guidelines, in their 2019 update [4], recognize the potential role of CAC scoring in refining risk stratification. They suggest considering CAC scoring in intermediate-risk individuals (10-year risk of 5-10%) to guide therapeutic decisions, especially when there is uncertainty about treatment initiation. However, the guidelines do not provide specific thresholds for CAC scores or detailed recommendations regarding statin therapy based on CAC scoring. T 2018 USPSTF guidelines [41], does not recommend routine CAC scoring or any other non-traditional risk factors for risk assessment in asymptomatic adults. They state that the current evidence is insufficient to assess the benefits and harms of CAC scoring for guiding preventive medication use in individuals without a history of cardiovascular disease. Also, the SCCT has published guidelines on the use of CAC scoring in clinical practice. In their 2017 guideline [42] they state that CAC scoring provides incremental prognostic information beyond traditional risk factors and may be considered in certain clinical scenarios. They recommend considering CAC scoring in intermediate-risk individuals (10-year risk of 5-20%) when the decision to initiate statin therapy is uncertain. A CAC score of zero may help to reclassify individuals into a lower-risk category, potentially guiding the decision to defer or withhold statin therapy. The SCCT guidelines emphasize that the use of CAC scoring should be integrated into the overall clinical risk assessment and treatment decision-making process, considering individual patient characteristics and preferences.

Comparison to traditional risk scores

For over 40 years, clinical decisions in preventive cardiology have relied on risk assessment equations that utilize office-based measurements of blood lipids, blood pressure, age, smoking history, and the presence or absence of diabetes [43]. The CAC score can modify the predicted

risk obtained from the Framingham Risk Score, especially for patients in the intermediate-risk category [10]. Despite the recognized potential of the CAC score in addition to traditional risk factors, clinical practice guidelines do not currently recommend the use of risk scores that require CAC testing [27,44,45]. Presently, the MESA risk score is the only risk score that incorporates CAC and traditional risk factors to estimate 10-year coronary heart disease (CHD) risk [46]. The MESA risk score is available online ("MESA. MESA 10-year CHD risk with coronary artery calcification. Collaborative Health Studies Coordinating Center". Available at: https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx. Accessed May 23, 2018.) and as a smartphone application, and it can be used to communicate risk and determine risk-based treatment strategies for patients. Among 13 non-traditional negative risk markers, a CAC score of 0 remains the strongest, resulting in the most significant downward shift in estimated cardiovascular disease risk [47].

Limitations and Challenges

Sources of variability in coronary calcium score measurement (non-contrast vs contrast studies)

Sources of variability in CAC score measurement can arise from different factors, particularly when comparing non-contrast and contrast studies [48-50]. Non-contrast studies rely on the measurement of calcium deposits in the coronary arteries using CCT scans [48]. Variability can occur due to factors such as image quality, scanner settings, and patient characteristics [49,50]. Contrast studies, on the other hand, involve the administration of contrast agents to enhance the visualization of the coronary arteries [50]. This introduces additional variables, including the timing and dosage of the contrast agent, which can impact calcium score measurements. Furthermore, differences in image acquisition protocols and interpretation methodologies can contribute to variability in the measurement of coronary calcium scores between non-contrast and contrast studies. Understanding and minimizing these sources of variability are crucial for accurate and consistent assessment of coronary artery calcification [48-50].

Influence of medications on the score "the calcium paradox"

The relationship between statin therapy and cardiac calcium scores has been the subject of several studies, with some findings suggesting that treating patients with atherosclerosis using statins can actually increase the calcium score, despite the fact that elevated scores are often the reason for initiating statin treatment. A study by Lee *et al*. [51] investigated potential

mediators between statins and CAC. However, a study by Puri *et al*. [52] shed light on the implications of this increase in calcium scores. The study reviewed eight separate studies that utilized intravascular ultrasound (IVUS) to evaluate the size and composition of atherosclerotic plaques in patients undergoing statin therapy. The researchers made two important observations. First, high-dose statin therapy tended to shrink plaques. Second, as the plaques were shrinking, their composition underwent changes. Specifically, the volume of lipid deposits within the plaques decreased, while the volume of fibrotic cells and calcium increased. This transformation from unstable "soft" plaques to more stable "hard" plaques may reduce the risk of sudden rupture and subsequent cardiovascular events. It is believed that these changes contribute to the significant reduction in cardiovascular risk observed in patients with coronary artery disease receiving statin therapy. Thus, the available evidence suggests that statin therapy not only reduces cholesterol levels but also modifies existing plaques, making them less prone to rupture. As a part of this process, the plaques may become more calcified, leading to an increase in the CAC score. Therefore, an elevated calcium score following statin therapy should be seen as an indication of treatment success rather than a cause for alarm. In the recent PARADIGM study, Park *et al*. [53] investigated the impact of statins on coronary plaque progression in mild stenosis lesions. This study aimed to evaluate the effects of statin therapy on plaque features associated with a high risk of adverse cardiovascular events. The results indicated that statins had a significant impact on slowing the progression of coronary plaque in mild stenosis lesions, particularly when high-risk plaque features were present. These findings highlight the importance of tailoring statin therapy based on individual plaque characteristics to effectively manage and prevent cardiovascular disease [54].

Potential limitations and challenges in clinical implementation

The clinical implementation of CAC scoring for assessing coronary artery disease can face certain limitations and challenges. Factors such as motion artifacts, calcification in non-coronary arteries, or blooming effects can affect the accuracy of calcium scoring (Figure 3). Another challenge is the variability in calcium score thresholds used to define the presence or severity of disease, as different guidelines or institutions may have different cut-off values. Additionally, the radiation exposure associated with CCTA scans used for calcium scoring raises concerns, especially for repeat testing and younger populations. Cost can also be a barrier, as calcium scoring may not be universally reimbursed, limiting its accessibility. Furthermore, integrating calcium scoring into clinical workflows and electronic health records may require adjustments to optimize efficiency and ensure proper data interpretation.

Addressing these limitations and challenges through ongoing research, standardization of protocols, education, and appropriate utilization can enhance the clinical implementation of calcium scoring and its potential benefits [54].

Future directions and research

Emerging technologies and techniques for coronary calcium scoring

Emerging technologies and techniques in CAC scoring hold promise for advancing the field. One notable approach is the application of deep learning and convolutional neural networks, as demonstrated in studies by Wolterink *et al*. [55], Mu *et al*. [56], and Wang *et al*. [57]. These methods have shown the potential for automated and accurate CAC scoring in cardiac CCTA images, eliminating the need for additional non-contrast CT imaging and providing efficient risk assessment [55-57]. Continued advancements in deep learning algorithms and image analysis techniques are expected to further enhance the performance and efficiency of coronary calcium scoring.

Potential for integrating coronary calcium score with other biomarkers

Integrating CAC scores with other biomarkers has the potential to improve risk assessment and enhance the predictive value of CAC scoring. Machine learning models, as demonstrated by Han *et al*. [58] and Ren *et al*. [59], have shown the benefits of incorporating clinical variables alongside CAC scores in predicting outcomes such as all-cause mortality and obstructive coronary heart disease [58,59]. The combination of CAC scores with additional biomarkers, such as blood biomarkers, genetic markers, or imaging features, may provide a more comprehensive assessment of cardiovascular risk and aid in personalized risk stratification. Further research is needed to explore the integration of coronary calcium scores with other biomarkers and develop comprehensive risk prediction models [58,59]. In summary, future directions in coronary calcium scoring research involve exploring emerging technologies and techniques, such as deep learning algorithms, to improve the accuracy and efficiency of CAC scoring in CCTA images. Additionally, there is a growing interest in integrating CAC scores with other biomarkers to enhance risk assessment and predictive value [56-59]. These advancements have the potential to refine risk stratification strategies and improve the management of cardiovascular disease [57-59]. Further studies and collaborations are needed to validate and optimize these approaches for clinical application.

Conclusions

Summary of key findings and implications

The use of CAC scoring has shown promise in risk assessment and stratification of cardiovascular disease. The CRESCENT trial demonstrated the effectiveness and safety of a tiered cardiac CT protocol utilizing CAC score determination and selective performance of CT angiography [60]. This approach resulted in significant cost savings and reduced the need for additional diagnostic testing. Individuals with a CAC score of 0 had a good long-term prognosis, while elevated CAC scores were associated with increased cardiovascular risk. CAC scoring has demonstrated superior ability in stratifying patients, especially asymptomatic individuals, compared to traditional risk factors and scoring systems. Furthermore, CAC scoring in patients with diabetes mellitus has shown adequate correlation with outcomes. Evaluating CAC scores can be complemented by plaque analysis to assess vulnerable plaque characteristics and further refine risk assessment (Figure 4). The use of machine learning algorithms has confirmed the value of CAC scoring in assessing cardiovascular risk and presents opportunities to develop new algorithms and models for improved risk stratification.

Recommendations for clinical practice

Based on the evidence presented, incorporating CAC scoring into clinical practice can provide valuable insights for risk assessment and management of cardiovascular disease. Based on our review of the literature we suggest the following recommendations:

1. Consider the use of CAC scoring as an additional risk factor in the evaluation of patients, particularly in asymptomatic individuals, to enhance risk stratification.
2. Utilize a tiered cardiac CT protocol that includes CAC scoring and selective CT angiography in patients with intermediate risk or high CHD pre-test probability, as demonstrated in the CRESCENT trial, to optimize diagnostic evaluation and reduce costs.
3. Recognize the prognostic value of a CAC score of 0, which indicates a good long-term prognosis and may warrant a longer interval before further testing.
4. Perform plaque analysis in conjunction with CAC scoring to assess vulnerable plaque characteristics and identify patients at elevated ASCVD risk.
5. Embrace the potential of machine learning algorithms to further enhance the clinical power of CAC scoring and develop new models for risk stratification.

Implementing these recommendations can lead to more accurate risk assessment, targeted interventions, and improved management of cardiovascular disease.

References

1. Lloyd-Jones D, Adams RJ, Brown TM et al. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 2010;121:948-54. Erratum in: Circulation 2010;121:e259.
2. Agatston, AS, Janowitz, WR. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336-45.
3. Vahanian A, Beyersdorf F, Praz F, Milojevic M, et al. [2021 ESC/EACTS Guidelines for the management of valvular heart disease].[Article in Italian]. G Ital Cardiol (Rome) 2022;23:e1-e75.
4. Authors/Task Force Members, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 2019;290:140-205. Erratum in: Atherosclerosis 2020;294:80-2.
5. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-32.
6. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation 2006;114:1761-91
7. Criqui MH, Denenberg JO, Ix JH, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA 2014;311:271-8. Erratum in: JAMA 2015;313:1374.
8. Rumberger JA, Kaufman L. A Rosetta stone for coronary calcium risk stratification: agatston, volume, and mass scores in 11,490 individuals. AJR Am J Roentgenol 2003;181:743-8.
9. Cury RC, Leipsic J, Abbara S, et al. CAD-RADS™ 2.0 - 2022 coronary artery disease-reporting and data system: An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR), and the North America Society of Cardiovascular Imaging (NASCI). J Cardiovasc Comput Tomogr 2022;16:536-57.
10. Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210-5. Erratum in: JAMA 2004;291:563.
11. Rodriguez-Granillo GA, Carrascosa P, Bruining N, et al. Defining the non-vulnerable and vulnerable patients with computed tomography coronary angiography: evaluation of atherosclerotic plaque burden and composition. Eur Heart J Cardiovasc Imaging 2016;17:481-91.
12. Pergola V, Cabrelle G, Mattesi G et al. Added value of CCTA-derived features to predict MACEs in stable patients undergoing coronary computed tomography. Diagnostics (Basel) 2022;12:1446.
13. Pergola V, Previtero M, Cecere A, et al. Clinical value and time course of pericoronary fat inflammation in patients with angiographically nonobstructive coronaries: a preliminary report. J Clin Med 2021;10:1786.

14. Baritussio A, Vacirca F, Ocagli H, et al. Assessment of coronary inflammation by pericoronary fat attenuation index in clinically suspected myocarditis with infarct-like presentation. J Clin Med 2021;10:4200.
15. Writing Committee Members, Gulati M, Levy PD, et al. AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2021;78:e187-285.
16. Knuuti J, Wijns W, Saraste A et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-77. Erratum in: Eur Heart J 2020;41:4242.
17. Pergola V, Cabrelle G, Previtero M, et al. Impact of the "atherosclerotic pabulum" on in-hospital mortality for SARS-CoV-2 infection. Is calcium score able to identify at-risk patients? Clin Cardiol 2022;45:629-40.
18. Budoff MJ, Diamond GA, Raggi P, et al. Continuous probabilistic prediction of angiographically significant coronary artery disease using electron beam tomography. Circulation 2002;105:1791-6.
19. Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and prognostic value of absence of coronary artery calcification. JACC Cardiovasc Imaging 2009;2:675-88. Erratum in: JACC Cardiovasc Imaging 2010;3:1089.
20. Winther S, Schmidt SE, Mayrhofer T, et al. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. J Am Coll Cardiol 2020;76:2421-32.
21. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44-e164.
22. Blaha MJ, Budoff MJ, De Filippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. Lancet 2011;378:684-92.
23. Valenti V, Ó Hartaigh B, Heo R, et al A 15-year warranty period for asymptomatic individuals without coronary artery calcium: a prospective follow-up of 9,715 individuals. JACC Cardiovasc Imaging 2015;8:900-9.
24. Mittal TK, Pottle A, Nicol E, et al. Prevalence of obstructive coronary artery disease and prognosis in patients with stable symptoms and a zero-coronary calcium score. Eur Heart J Cardiovasc Imaging 2017;18:922-29.
25. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227-37. Erratum in: Eur Heart J 2022;43:4468.
26. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American

College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:1376-14. Erratum in: J Am Coll Cardiol 2019;74:1428-9. Erratum in: J Am Coll Cardiol 2020;75:840.
27. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.
28. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA 2014;311:1406-15.
29. Budoff MJ, McClelland RL, Nasir K, et al. Cardiovascular events with absent or minimal coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J 2009;158:554-61.
30. Hoff JA, Chomka EV, Krainik AJ, et al. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol 2001;87:1335-9.
31. Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. Circulation 2005;112:572-7.
32. LaMonte MJ, FitzGerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol 2005;162:421-9.
33. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;115:2722-30.
34. Wetscherek MTA, McNaughton E, Majcher V, et al. Incidental coronary artery calcification on non-gated CT thorax correlates with risk of cardiovascular events and death. Eur Radiol 2023;33:4723-33.
35. Rijlaarsdam-Hermsen D, Lo-Kioeng-Shioe MS, Kuijpers D, et al. Prognostic value of the coronary artery calcium score in suspected coronary artery disease: a study of 644 symptomatic patients. Neth Heart J 2020;28:44-50.
36. Yeboah J, Young R, McClelland RL, et al. Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. J Am Coll Cardiol 2016;67:139-47.
37. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 2008;168:1333-9. Erratum in: Arch Intern Med 2008;168:1782.
38. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA 2012;308:788-95.
39. Verghese D, Manubolu S, Budoff MJ. Contemporary use of coronary artery calcium for the allocation of aspirin in light of the 2022 USPSTF guideline recommendations. Am J Prev Cardiol 2022;12:100427.
40. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2935-59. Erratum in: J Am Coll Cardiol 2014;63:3026.

41. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Risk assessment for cardiovascular disease with nontraditional risk factors: us preventive services task force recommendation statement. JAMA 2018;320:272-80.
42. Hecht HS, Cronin P, Blaha MJ, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. J Cardiovasc Comput Tomogr 2017;11:74-84.
43. Sundström J, Sullivan L, D'Agostino RB, et al. Plasma homocysteine, hypertension incidence, and blood pressure tracking: the Framingham Heart Study. Hypertension 2003;42:1100-5.
44. Authors/Task Force Members, Piepoli MF, Hoes AW, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur J Prev Cardiol 2016;23:NP1-NP96.
45. Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society Guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2016;32:1263-82.
46. McClelland RL, Jorgensen NW, Budoff M, et al. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (multi-ethnic study of atherosclerosis) with validation in the HNR (Heinz Nixdorf recall) Study and the DHS (Dallas Heart study). J Am Coll Cardiol 2015;66:1643-53.
47. Blaha MJ, Cainzos-Achirica M, Greenland P, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the multi-ethnic study of atherosclerosis (MESA). Circulation 2016;133:849-58.
48. Yu J, Qian L, Sun W, et al. Automated total and vessel-specific coronary artery calcium (CAC) quantification on chest CT: direct comparison with CAC scoring on non-contrast cardiac CT. BMC Med Imaging 2022;22:177.
49. Ota K, Nakanishi R, Hashimoto H, et al. Association between coronary artery calcium score on non-contrast chest computed tomography and all-cause mortality among patients with congestive heart failure. Heart Vessels 2022;37:262-72.
50. Yang G, Chen Y, Ning X et al. Automatic coronary calcium scoring using noncontrast and contrast CT images. Med Phys 2016;43:2174.
51. Lee D, Joo HJ, Jung HW, Lim DS. Investigating potential mediator between statin and coronary artery calcification. PLoS One 2018;13:e0203702.
52. Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. J Am Coll Cardiol 2015;65:1273-82.
53. Park HB, Arsanjani R, Sung JM, et al. Impact of statins based on high-risk plaque features on coronary plaque progression in mild stenosis lesions: results from the PARADIGM study. Eur Heart J Cardiovasc Imaging 2023:jead110. Online ahead of print.

54. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007;49:1860-70.
55. Zreik M, Lessmann N, van Hamersvelt RW, et al. Deep learning analysis of the myocardium in coronary CT angiography for identification of patients with functionally significant coronary artery stenosis. Med Image Anal 2018;44:72-85.
56. Mu D, Bai J, Chen W, et al. Calcium scoring at coronary CT angiography using deep learning. Radiology 2022;302:309-16.
57. Wang W, Wang H, Chen Q, et al. Coronary artery calcium score quantification using a deep-learning algorithm. Clin Radiol 2020;75:237.e11-237.e16.
58. Han D, Kolli KK, Gransar H, et al. Machine learning based risk prediction model for asymptomatic individuals who underwent coronary artery calcium score: Comparison with traditional risk prediction approaches. J Cardiovasc Comput Tomogr 2020;14:168-76.
59. Ren Y, Li Y, Pan W, et al. Predictive value of CAC score combined with clinical features for obstructive coronary heart disease on coronary computed tomography angiography: a machine learning method. BMC Cardiovasc Disord 2022;22:569.
60. Lubbers M, Dedic A, Coenen A, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. Eur Heart J 2016;37:1232-43.

Table 1. Summary of recommendations on coronary artery calciulm scoring in treatment decisions: a comparison of guidelines.

Guidelines	**Recommendation**
AHA/ACC 2013 [40]	CAC scoring may be considered in intermediate-risk patients (10-year risk of 5-20%) to determine the initiation of statin therapy in those with CAC scores ≥300 Agatston units (AU). However, the use of CAC scoring is of uncertain value in patients with low (<5%) or high (>20%) 10-year risk estimates.
ESC 2019 [4]	Considering CAC scoring in intermediate-risk individuals (10-year risk of 5-10%) to guide therapeutic decisions, especially when there is uncertainty about treatment initiation. However, the guidelines do not provide specific thresholds for CAC scores or detailed recommendations regarding statin therapy based on CAC scoring.
USPSTF 2018 [41]	Routine CAC scoring or any other non-traditional risk factors are not recommended for risk assessment in asymptomatic adults. The current evidence is insufficient to assess the benefits and harms of CAC scoring for guiding preventive medication use in individuals without a history of cardiovascular disease.
SCCT 2017 [42]	CAC scoring provides incremental prognostic information beyond traditional risk factors and may be considered in certain clinical scenarios. Consider CAC scoring in intermediate-risk individuals (10-year risk of 5-20%) when the decision to initiate statin therapy is uncertain. A CAC score of zero may help to reclassify individuals into a lower-risk category, potentially guiding the decision to defer or withhold statin therapy. The use of CAC scoring should be integrated into the overall clinical risk assessment and treatment decision-making process, considering individual patient characteristics and preferences.

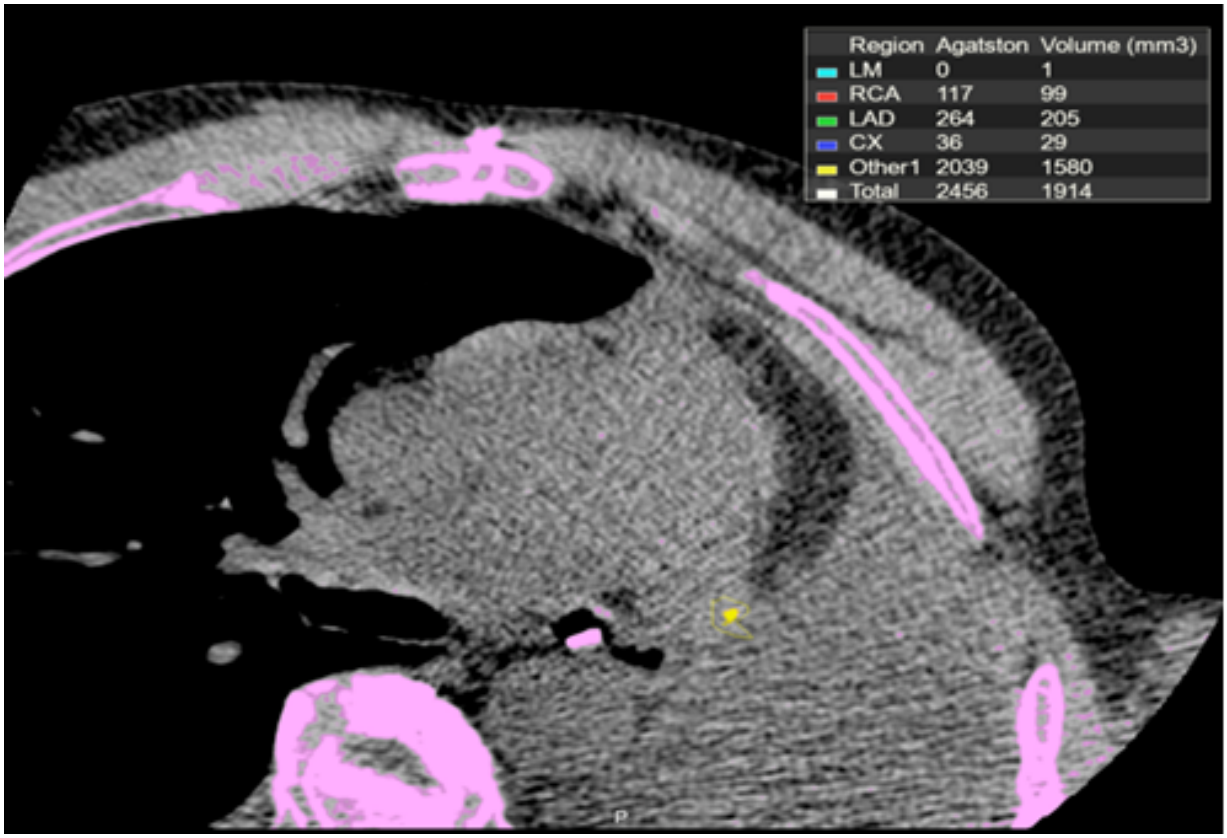

Figure 1. Example of coronary artery calcium scoring from a noncontrast CT. Agatston number is evaluated for each coronary artery. Final Agatston score, commonly referred to as the CAC score, is obtained by summing the scores for all the lesions in all coronary arteries.

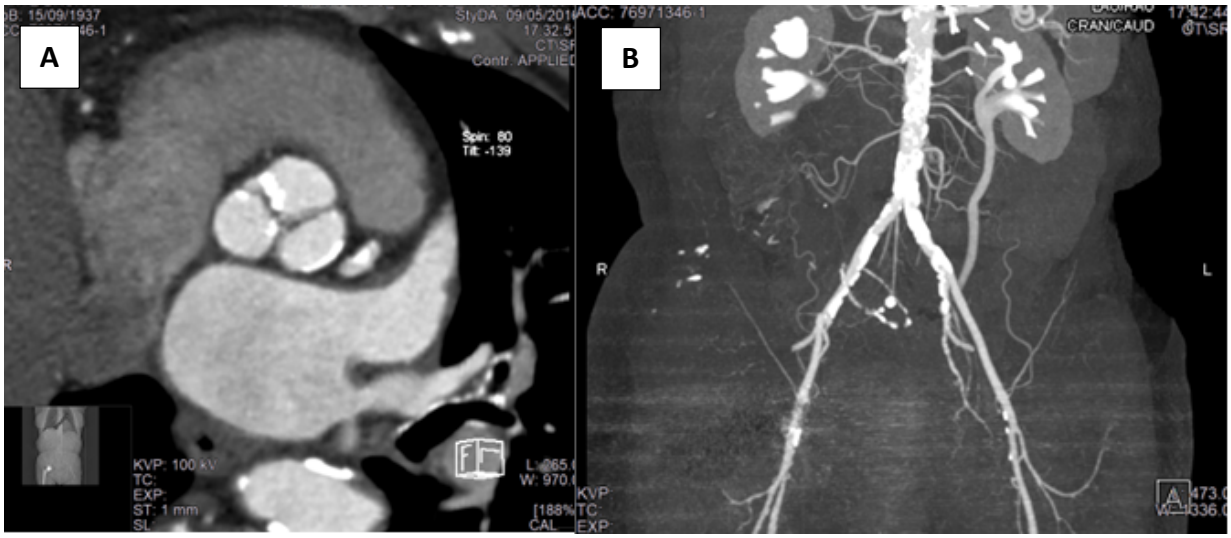

Figure 2. Aortic valvular calcification. A) In the planning before transcatheter aortic valve replacement, CCTA has a role in defining the valvular aortic calcification, its morphology, the new valve size and the landing zone. B) Aortic vessels calcification assessment before TAVI is essential to plain procedure and select the best percutaneous road.

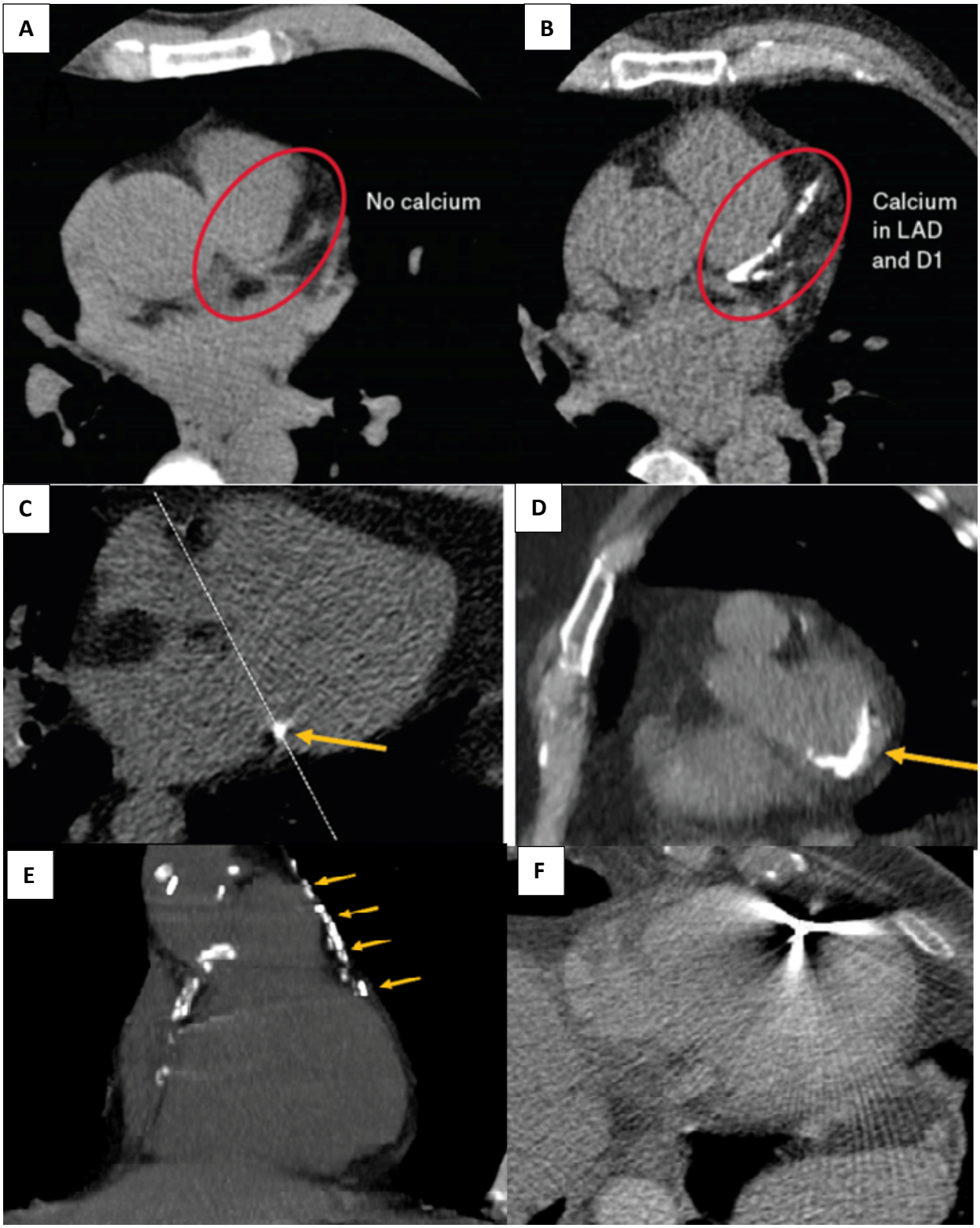

Figure 3. A,B) Distribution of coronary calcium on cardiac CT in two different patients: no detectable coronary calcium (A), coronary calcium in epicardial coronary arteries (B), including the left anterior descending and diagonal artery. C,D) distribution of calcium in the mitral valve. E) Evidence of coronary artery calcium, the yellow arrows indicate pericardium cardiac calcium. F) the presence of electrode impedes coronary calcium assessment.

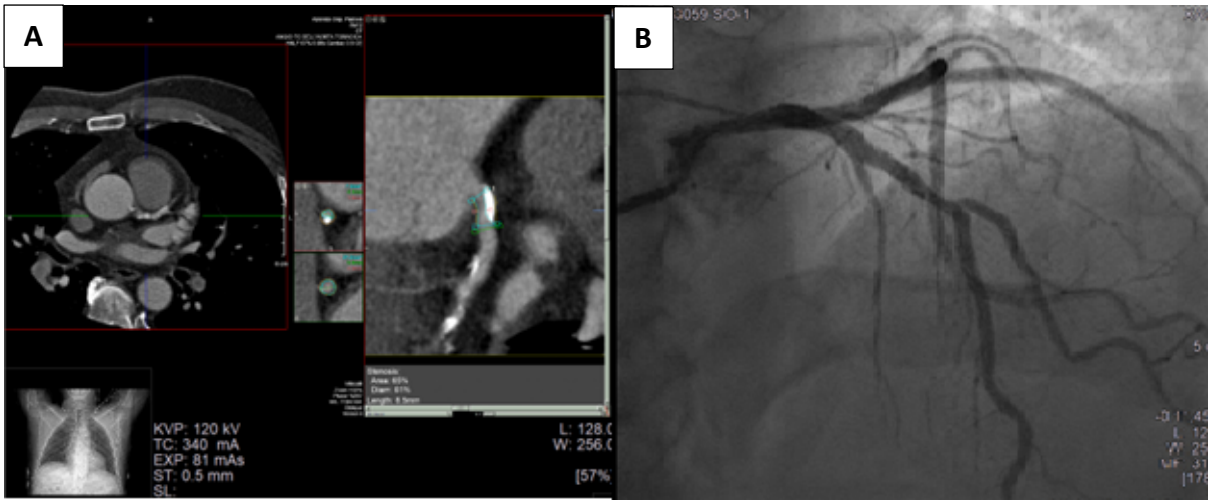

Figure 4. Coronary artery disease evaluation. A) CCTA reconstruction, in particular a moderate left main artery stenosis. B) The same patient underwent invasive coronary angiography which confirms moderate left main artery stenosis.