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EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (K. NASIR, SECTION EDITOR)

Is There a Role of Coronary CTA in Primary Prevention? Current State and Future Directions

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Abstract

Purpose of Review Information on subclinical atherosclerosis burden provides prognostic information on atherosclerotic cardiovascular disease (ASCVD) risk beyond what can be achieved by traditional risk factors alone and may therefore improve allocation of preventive treatment in primary prevention. The purpose of this review is to discuss the potential role and value of assessing subclinical atherosclerosis using coronary artery calcium (CAC) versus computed tomography angiography (CTA) among asymptomatic patients in the context of current primary prevention cholesterol guidelines.

Recent Findings Since 2013, primary prevention cholesterol guidelines have lowered the treatment threshold for initiating statin therapy resulting in high statin eligibility and sensitivity for detecting ASCVD events. Thus, one of the main advantages of assessing subclinical atherosclerosis is to identify those individuals who are at so low ASCVD risk that preventive treatment may safely be withhold. Numerous studies have shown that both CAC and CTA provide highly valuable information on ASCVD risk in the individual patient. However, while extensive data exist regarding the ability of CAC to improve treatment allocation in the context of primary prevention guidelines, such data is sparse for CTA. Furthermore, there is no data to show that CTA improves risk classification and treatment allocation in primary prevention beyond what can be achieved by assessment of CAC.

Summary Although CTA provides important information regarding prognosis in symptomatic patients undergoing clinical CTA, there is no strong evidence to support its use in the primary prevention setting. Thus, the potential value of CTA in primary prevention is not clear and is currently not recommended by guidelines

Keywords Atherosclerosis · Risk prediction · Computed tomography angiography · Coronary artery calcium

Introduction

Assessment of atherosclerotic cardiovascular disease (ASCVD) risk constitutes a key element in daily clinical practice. Although preventable, ASCVD remains a leading global cause of death and disability [1]. In high-income countries with declining ASCVD mortality, the prevalence of ASCVD continues to be high and is in some countries even increasing [1]. For this reason, the burden of disease and economic costs is substantial. Further, most societies are now facing aging populations [2, 3]. It is expected that these demographic changes will increase the overall burden and prevalence of ASCVD even further during the next decades. Prevention of ASCVD therefore represents a tremendous opportunity for societies to ensure a healthy population in the future. Indeed, the most efficient approach to restrict the undue loss of health, life and resources, is to prevent the disease from developing in the first place, that is, by primary prevention initiatives. By preventing a first event, there is no first event to treat and no second one to prevent.

Accurate identification of patients at high and low risk for ASCVD allows for meaningful allocation of preventive therapies to those most likely to derive benefit while safely

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withholding such treatment in patients who are likely not to derive net-benefit. Risk estimation therefore has a central role in all major guidelines on ASCVD prevention [4–8]. This has traditionally been based on risk prediction models relying solely on traditional risk factors. Abundance of evidence, however, have now shown that imaging for subclinical atherosclerosis substantially improves risk prediction beyond what can be achieved by traditional risk factors alone. In particularly, coronary artery calcification (CAC) and computed tomography angiography (CTA) offer highly valuable information on atherosclerosis burden and risk for ASCVD in the individual patient.

The purpose of this review is to summarise the evidence concerning CAC and CTA in asymptomatic patients, that is, in the primary prevention setting. In order to fully understand the potential value and role of CAC and CTA for improving risk prediction and allocation of preventive therapies in contemporary clinical practice, a basic understanding of historical risk prediction is needed as well as an understanding on how the lower treatment thresholds for initiating preventive therapies that have been introduced in recent years in ASCVD prevention guidelines have changed the main purpose of doing imaging to improve treatment allocation. Indeed, the value of imaging (and biomarkers) must be viewed in the context of clinical practice.

Historical Risk Assessment and Treatment Allocation: from Relative to Absolute Risk

A primary goal of the high-risk strategy in the primary prevention of ASCVD is to identify those at highest short-term risk and offer individualised risk-reducing treatment [9]. Based on results from well-characterised cohort studies such as the Framingham Heart Study, risk factors that increase the likelihood of developing ASCVD have been well-known since the 1960's[10]. Early guidelines focused on those risk factors to identify individuals at increased relative risk for ASCVD because of markedly elevated cholesterol or blood pressure levels [11, 12]. However, it became clear that relative risk is not the optimal measure for identifying individuals who benefit from preventive treatment. For example, a relative risk for disease of 5 (=5 times higher risk) may sound high, but if the risk for disease in the reference group is only 0.1%, then risk is still only ≈0.5% in those with high relative risk, and they will have limited benefit from intervention. Thus, instead of focusing on relative risk, current guidelines are based on the principle that intensity of therapy should be proportional to the 10-year absolute risk for ASCVD [4–8]. The rationale for this approach is easy to understand: those at highest absolute risk experience the greatest short-term benefit of treatment, and this approach is most cost effective. As statins were expensive and its documented effect and safety in primary prevention were limited in the early guidelines, a relatively high absolute risk threshold was chosen for only selecting high-risk individuals for treatment (i.e. >20% 10-year risk for cardiovascular disease corresponding to >5% 10-year fatal cardiovascular disease risk used in European guidelines) [13–15]. Thus, at that time, the sensitivity of the high-risk thresholds for treating patients who were destined to develop events was known to be low (i.e. <25% in middle-aged individuals) [16]. Indeed, most events occur among those at intermediate risk, simply because the number of patients in this group far exceed the number of patients in the high risk group—a phenomenon described by Geofrey Rose and widely known as the Rose's prevention paradox [17]. With the low sensitivity of early guidelines, the main rationale of introducing novel predictive biomarkers or imaging modalities was to identify and 'uprisk' patients who really was at high risk despite lower estimated risk based on traditional risk factors (Fig. 1).

Current Risk Assessment and Treatment Allocation

The seminal 2013 cholesterol guidelines from the American College of Cardiology and the American Heart Association (ACC/AHA) represented a paradigm shift in the use of statin for primary prevention of ASCVD [18]. The guidelines introduced a new risk calculator (pooled cohort equations (PCE)) and recommended a new risk-dependent threshold above

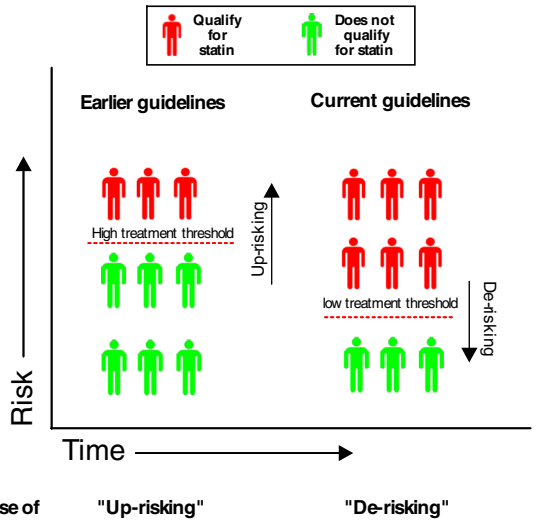

Fig. 1 Lower guideline-defined treatment thresholds have changed the main purpose for doing imaging to improve treatment allocation in primary prevention. Left: In the context of earlier guidelines with high treatment thresholds, the main purpose for doing imaging was to 'uprisk' individuals with extensive subclinical atherosclerosis who did not qualify for statin treatment. Right: Based on growing evidence of safety and efficacy of statin therapy in primary prevention, international cholesterol guidelines have lowered the recommended treatment threshold substantially in recent years. Accordingly, statin eligibility and sensitivity for ASCVD events is now high. The main advantage of doing imaging to improve treatment allocation is therefore to 'de-risk' individuals who are eligible for lifelong statin treatment but are at low risk because of low subclinical atherosclerosis burden.

which primary prevention with statins should be considered [19]. Based on abundance of overwhelming clinical trial evidence showing benefit and safety of statin in the primary prevention setting as well as careful risk-benefit and cost-effectiveness considerations, the threshold for initiating statin therapy was lowered substantially [18]. Specifically, the 2013 ACC/AHA guidelines recommended that it was reasonable to initiate patient-physician discussion on statin therapy when estimated 10-year risk for ASCVD (myocardial infarction and stroke) was ≥7.5%. The new lower evidence-based treatment threshold was estimated to result in an additional ≈13 million (11% of adult US population) statin-eligible patients in the USA alone [20]. Shortly after, the 2014 National Institute for Health and Care Excellence (NICE) cholesterol guidelines in the UK took similar steps and recommended to halve the risk-based threshold for primary prevention with statins based on QRISK risk calculator from 20 to 10% 10-year risk [4]. Since then, cholesterol guidelines from the US Preventive Service Task Force and European Society of Cardiology (ESC) have also expanded the recommendation for statin therapy substantially compared to their earlier recommendations [5, 8, 21]. Thus, current ASCVD prevention guidelines in both the USA and Europe generally have high sensitivity endorsing preventive treatment to the majority of patients who are destined for a future ASCVD event (i.e. ≈70 sensitivity for ACC/AHA and NICE guidelines among those age 40–75 years) [22, 23•, 24•]. Although evidence based, this new approach taken by the guidelines with broadened statin eligibility come at the cost of lower specificity, that is, many more patients who are not destined to develop events are recommended lifelong preventive treatment (i.e. ≈57–60% specificity for ACC/AHA and NICE guidelines) [24•]. As age dominates traditional risk factor-based risk estimation, the sensitivity is even higher (and specificity even lower) in older age groups. For example, in those aged 60–65, 66–70 and 71–75 years of age, the sensitivity ranges from 80 to 100% with specificities being as low as 40 to 0% [22, 24•]. Thus, in the situation of the current liberal statin recommendations and high sensitivities of societal guidelines, there is less room for the traditional 'uprisking' of patients. Instead, identifying those patients who are at low risk despite qualifying for treatment have become a key opportunity for improving treatment allocation in contemporary practice—so-called de-risking (Fig. 1).

Coronary Artery Calcium, Atherosclerosis and Atherosclerotic Events

Assessment of CAC is one of the most thoroughly studied methods for improving ASCVD risk prediction [25]. As atherosclerotic plaques develop, macrophages and smooth muscle cells within or near the necrotic core die resulting in release of free calcium and phosphate that crystallise and form Microcalcification [26]. These microcalcifications eventually confluence into larger sheets of calcium that can be detected by computed tomography as CAC. CAC is therefore a direct marker of coronary atherosclerosis and have been shown to highly correlate with overall atherosclerosis burden [27]. It can be assessed using an inexpensive and reproducible technique without the need for intravenous contrast or other special preparations. The scan can be performed with about 1 mSv radiation, which is similar to a mammogram. CAC can easily be quantified using the Agatston score [28]. Although the Agatston score has limitations that are beyond the scope of this review to discuss, it is by far the most validated and used score for quantifying calcium in the coronary arteries [28].

Based on several large population-based observational cohorts from the USA [29, 30], Germany [31] and the Netherlands [32], CAC has been shown to be a strong predictor of ASCVD events in asymptomatic primary prevention patients. For example, in the Multi-Ethnic Study of Atherosclerosis (MESA)—a prospective multicentre study of 6800 men and women aged 45 to 84 years—CAC predicted ASCVD events beyond traditional risk factors [33]. The predictive ability of CAC was similar across all 4 ethnicities in MESA (white, African-American, Hispanic and Asian) [34]. An important observation was that ≈50% of individuals of mean age ~60 years old have no detectable CAC. This large group has been shown to have very low risk for both coronary and ASCVD events. Concerning major coronary events, for example, Detrano et al. showed that CAC >300 was independently associated with a 7–10 times higher risk (adjusted for traditional risk factors) than those with CAC = 0 [34]. In those with CAC = 0, only 8 persons out of 3409 (0.2%) experienced a major coronary event after a median of 3.8 years of follow-up. Multiple other studies from MESA have shown similar results with longer-term follow-up and in different subpopulations (i.e. in those with elevated C-reactive protein, dyslipidaemia or in those with clinical trial evidence for statin efficacy) [35–37]. Likewise, studies from other cohorts such as Heinz Nixforf Recall study [38]. The Rotterdam study [39], the Framingham Heart study (Framingham offspring and third-generation studies) [40], CARDIA study [41], Jackson Heart Study [42] and the BioImage study [43] have shown very similar results demonstrating (1) that CAC is a very strong predictor of events, (2) that risk increases with increasing CAC scores, (3) that a substantial proportion of individuals have no detectable CAC and (4) that a zero score confers a very low risk of ASCVD events—the so-called power of zero.

CAC for Improving Guideline-Based Treatment Allocation in Primary Prevention

Several analyses have shown that assessment of CAC can improve guideline-based treatment allocation in the primary

prevention setting. Studies on the utility of CAC in the context of the earlier, more-restrictive statin guidelines demonstrated that CAC could reclassify patients from the previous large intermediate 'grey zone' risk group (10 to 20% 10-year ASCVD risk) with—at that time—uncertain treatment indication to both higher (= do treat) and lower (=don't treat) risk groups [44]. However, analyses in the context of current statin liberal guidelines with high statin eligibility such as the 2013/2018 ACC/AHA and 2016 NICE guidelines have shown that the main opportunity by doing CAC scanning is to downgrade ASCVD risk (=do not treat). Especially, CAC = 0 appears to be the strongest negative predictor of ASCVD events when compared to other measures of subclinical cardiovascular disease measures or biomarkers [45, 46]. CAC = 0 allows downward reclassification ('de-risking') of a substantial proportion of patients who are currently considered eligible for primary prevention with statin therapy. In the context of the 2013 ACC/AHA cholesterol treatment guidelines, Nasir et al. used MESA to analyse the potential impact of CAC on statin allocation [47]. The authors showed that in individuals with an estimated 10-year ASCVD risk between 7.5 and 20% using the PCE calculator, a CAC score of zero was associated with 10-year risk that was <5%; below the guideline-recommended threshold for considering treatment. In contrast, individuals with any CAC (CAC >0) had event rates that was above the guideline-recommended risk threshold. Mortensen et al. performed similar analyses using the BioImage study of elderly individuals with a mean age of 69 years (range 55 to 80 years) to assess the potential impact of CAC on 2013 ACC/AHA statin allocation [48]. Due to relatively high age, 86% of BioImage participants was statin eligible at baseline because of an estimated 10-year ASCVD risk ≥7.5%. Accordingly, sensitivity for detecting events was very high at 96% but at the cost of a very low specificity of 15%. Interestingly, in this elderly cohort, CAC = 0 was found in 32% of participants and they had very low event rates for CHD and ASCVD. Down classifying these participants with CAC = 0 from 'statin eligible' to 'statin ineligible' was safe and increased specificity by as much as 22% (from 15 to 37%) and improved overall risk classification. To put it into context, an improved specificity of 22% translates into millions of patients in the USA alone who could safely withhold statin therapy because their risk for ASCVD events is low. In the German Heinz Nixdorf Recall Study (HNRS), Mahabadi evaluated CAC scores according to both 2013 ACC/AHA and 2012 ESC guidelines [49]. Similar to the studies by Nasir and Mortensen performed in US cohorts, participants from the HNRS with CAC = 0 had very low event rates irrespectively of whether they were statin eligible or not. Specifically, participants with CAC = 0 had event rates below the accepted thresholds for initiating treatment by both the ACC/AHA and ESC guidelines. In contrast, participants who had CAC >0 and qualified for guideline-based statin therapy, had risk above the accepted treatment thresholds. Taken together, these US and European studies indicate that in the context of current liberal statin guidelines, the major role of performing imaging to assess subclinical atherosclerosis is to identify and potentially withhold statin therapy in the large group of patients that—despite qualifying for guideline-based statin therapy—are at very low risk because of CAC = 0.

As statin eligibility, however, is lower with the ESC than the ACC/AHA and NICE guidelines, assessment of CAC for uprisking according to ESC criteria may be useful in selected individuals who do not qualify for ESC recommended statin treatment [8, 24•].

Table 1 summarises current guideline recommendations for CAC and CTA testing in asymptomatic primary prevention patients. While current ACC/AHA and ESC guidelines provide recommendations for CAC assessment, NICE provides no recommendations and USPSTF recommends against it.

Computed Tomography Angiography, Atherosclerosis and Atherosclerotic Events

In contrast to assessment of CAC alone, coronary CTA provides detailed information on non-calcified plaque and lumen stenosis [50, 51•]. Performing a CTA requires administration of i.v. contrast and commonly heart rate-slowing medications. Thus, in patients with iodine allergy or severe kidney dysfunction, CTA is contraindicated. Further, situations such as arrythmias (i.e. atrial fibrillation), sinus tachycardia, obesity, old age (high calcium burden) or difficulty to follow breath hold instructions may result in suboptimal imaging quality. While assessment and interpretation of CAC is done the same way around the world, CTA assessment varies much more by scanner type, imaging technique and with higher inter-reader variability. A CTA normally provides about 6–12 mSv radiation (Fig. 2).

Based on several large cohorts of patients presenting mainly with symptoms suggestive of stable angina, there is an abundance of evidence that the extent and severity of coronary artery disease (CAD) as determined by CTA is a strong predictor of future ASCVD events. CTA, however, does not result in a single, uniform measure of CAD severity [51•]. Instead, CAD severity can be examined in several different ways that all have been shown to provide important information on risk in the individual patient. They include CAD assessment based on (1) lumen stenosis, (2) plaque volumes (i.e. total or low attenuated plaque), (3) the number of coronary segments with atherosclerosis (segment involvement score) and (4) presence of plaque with high-risk features (i.e. positive remodeling, napkin ring sign) [52–58]. These characteristics can be used individually or can be combined and integrated into more advanced CTA risk scores [59, 60]. How the

Table 1 Recommendations for CAC and CTA testing in primary prevention guidelines

Primary prevention guidelines	CAC recommendations	CTA recommendations
2014 NICE	No recommendation	No recommendations in primary prevention
2018 ACC/AHA	In intermediate risk patients (PCE risk 7.5% to <20%) with uncertain decision about statin therapy, CAC assessment should be considered. • If zero CAC, treatment may be withheld or delayed. • CAC >0 favours statin therapy and is indicated if CAC ≥100.	No recommendations in primary prevention
2018 USPSTF	The USPSTF found inadequate evidence to assess whether treatment decisions guided by the ABI, hsCRP level or CAC score, in addition to risk factors in existing CVD risk assessment models, leads to reduced incidence of CVD events or mortality	No recommendations in primary prevention
2019 ESC/EAS	In low- or moderate-risk patients, CAC score assessment may be considered a risk modifier. • CAC >100 indicates higher risk *Although the ESC guideline note that CAC = 0 is associated with very low risk, there is no direct recommendation for using CAC = 0 to withhold statin therapy.*	No recommendations in primary prevention

prognostic performance of all these different CAD measures compare to each other is not well understood. Further, it is likely that they have differential predictive ability for different cardiovascular endpoints; i.e. some may better predict revascularisations while other predicts myocardial infarction. This demonstrates the complexity of integrating all the information derived from CTA into a single risk estimate for the individual patient. The most simple method for quantifying CAD extent that can easily be determined from a CTA analysis is based on the degree of lumen stenosis ranging from 'no CAD' over 'diffuse, non-obstructive CAD' with <50% stenosis to 'obstructive CAD' with luminal stenosis ≥50%; the latter subdivided into 1-, 2- or 3-vessel CAD based on the number of epicardial vessels with stenoses. This relatively simple classification has been shown to provide important information on prognosis regarding both all-cause mortality and ASCVD events [54, 61–63] (Fig. 3). Using the COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicentre (CONFIRM) Registry with 24,775 patients undergoing CTA, for example, Min et al. showed a clear 'dose-response' relationship between all-cause mortality and number of vessels with lumen stenosis (unadjusted hazard ratio of 10.5 for 3-vessel or left main

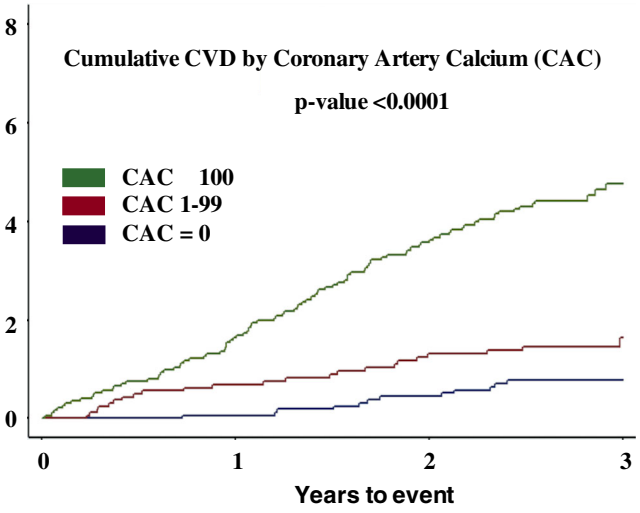

Fig. 2 Cumulative incidence of cardiovascular disease events stratified by CAC in the BioImage cohort of 5805 asymptomatic individuals. CAC provides important information on risk for cardiovascular disease events in asymptomatic individuals (from: Mortensen et al. [48])

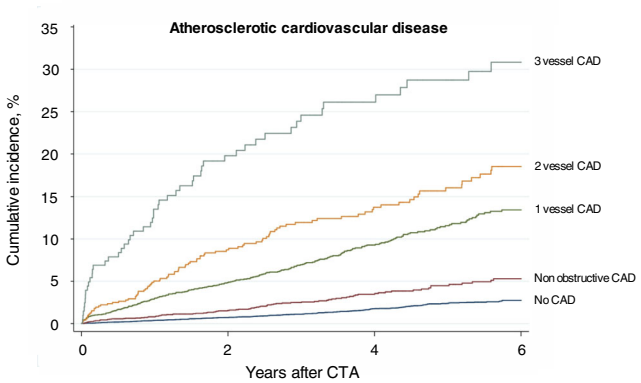

Fig. 3 Cumulative incidence of atherosclerotic cardiovascular disease events stratified by CTA-derived CAD severity in the Western Denmark Heart Registry of 20,241 symptomatic patients. The relatively simple classification of CTA-derived CAD severity based on number of vessels with stenoses (>50% stenosis by CTA) provides important information on risk for atherosclerotic cardiovascular disease events (from: Mortensen et al. [64••])

stenosis vs. no CAD). Similarly, Nielsen et al. showed a stepwise increase in risk for myocardial infarction, coronary revascularisations and death in the Western Denmark Heart Registry (WDHR). Thus, current evidence clearly demonstrate that CTA provides important and graded information for risk assessment with patients having extensive, multivessel CAD being at a substantially higher risk for ASCVD than patients with no atherosclerotic plaque or stenosis.

CTA for Improving Guideline-Based Treatment Allocation in Primary Prevention

To date, only few smaller studies have assessed the prognostic value of CTA-derived CAD severity information in asymptomatic individuals in the context of current statin liberal primary prevention guidelines [65, 66]. Although they indicate that the segment involvement score is independently associated with cardiovascular events in both those who qualify and those who do not qualify for guideline-based statin treatment, it is unknown whether this will result in reclassification of patients across the guideline-defined treatment thresholds, that is, whether the information will change clinical decision making. Using the Western Denmark Heart Registry of symptomatic patients, Mortensen et al. estimated the number needed to treat to prevent one ASCVD event by treating to ACC/AHA and ESC LDL-cholesterol targets in patients with varying degree of CAD severity [64••]. The authors showed that the NNT in 6 years to prevent one event ranged from 110 in those with no CAD (primary prevention LDL goals) to only 9 in those with 3-vessel obstructive CAD (secondary prevention LDL goals) when treating according to the ACC/AHA guidelines. With the ESC guidelines, the corresponding numbers were 233 to 8. Although this analysis showed CAD severity is a major determinant of benefit from statin treatment, it did not specifically assess whether CTA could improve treatment allocation in the primary prevention setting. Thus, currently, the evidence is limited that CTA improves treatment allocation in asymptomatic individuals in the context of primary prevention guidelines.

CAC Versus CTA for Prognosis

CAC- and CTA-derived CAD severity both assess the extent of CAD and are, therefore, highly correlated. Generally, the higher the CAC burden, the greater is the extent of CAD as assessed by CTA. Some important differences between CAC and CTA are, however, evident. This includes the visualisation of non-calcified plaque and stenoses by CTA which may provide incremental predictive value. Indeed, CTA has been shown to improve risk prediction models beyond what can be achieved by CAC alone. Data from the Prospective Multicentre Imaging Study for Evaluation of Chest Pain (PROMISE) that included symptomatic patients, for example, have shown that overall predictive performance of risk models are improved by including CTA-derived CAD severity information to a model including CAC as evident by higher c-statistics [67]. Results from CONFIRM similarly have shown that the c-statistics are improved beyond CAC by including CTA measures. For example, Al-Mallah et al. showed that among symptomatic patients, the predictive performance of a model predicting myocardial infarction and all-cause death was improved by addition of different CTA measures on top of a clinical model containing CAC (c-statistics 0.82 vs. 0.79) [68]. Cho et al. also showed improved c-statistics by addition of CTA measures to a clinical model containing CAC among asymptomatic patients from the CONFIRM registry (0.74 vs. 0.71) [69]. However, importantly, the improvement in net reclassification was negligible, meaning that CTA information would not result in improved treatment allocation beyond what was achieved by CAC. Regarding all-cause mortality, CTA does not seem to provide additional predictive information beyond CAC [70].

Future Directions for CTA in Primary Prevention

Although CTA provides important information regarding prognosis in symptomatic patients undergoing clinical CTA, there is no strong evidence to support its use in the primary prevention setting, that is, among asymptomatic patients. In particular, its potential value in changing clinical management beyond what can be achieved by assessment of CAC is unknown and requires further investigation. Improvements in overall c-statistics of risk prediction models by addition of CTA (or other biomarker) measures is of little value for understanding if they improve risk classification of patients across guideline-defined treatment thresholds.

Other areas regarding the potential consequences of using CTA among asymptomatic patients also need to be studied. For example, as CTA provides information on lumen stenosis, it may result in an increase in unnecessary procedures such as catheterisation and revascularisations. Even for assessing CAC, increased downstream testing have been a concern, and the National Lipid Association 2020 Scientific statement on the use of CAC to guide preventive therapies specifically stated that downstream testing should be avoided: 'in adults with predominantly left main calcification, multi-vessel coronary involvement, or a high CAC score, stress testing or invasive coronary angiography, in the absence of clinically relevant symptoms, is not recommended (COR III—harm)' [71]. Thus, future studies should demonstrate that CTA in the primary prevention setting does not result in increased downstream testing that counteract the potential benefits of doing CTA.

Conclusion

Assessment of subclinical atherosclerosis using CAC and CTA provides highly valuable information on risk in the individual patient. In the context of current more liberal primary prevention cholesterol guidelines worldwide with higher statin eligibility and sensitivities for allocating treatment to those destined for ASCVD events, one of the major reasons for assessing subclinical atherosclerosis is to down-grade risk, that is, identifying those individuals with very low risk that preventive therapies can safely be withhold. While numerous analyses have demonstrated that CAC provides meaningful reclassification across guideline-defined treatment targets mainly due to 'down-risking' of patients without CAC, such evidence is missing for CTA-derived CAD severity measures. Further, whether CTA provides information that would change treatment allocation beyond what is achieved by CAC is unknown. Thus, the potential incremental value of CTA in primary prevention is currently not clear, and its use is therefore not recommended by guidelines. Future studies are needed to assess whether performing CTA instead of CAC will improve risk prediction, reclassification and clinical management (without increases in downstream testing) in the context of guideline-based treatment allocation. Especially, there may be specific subgroups of asymptomatic patients where CTA could be of particular value such as in younger individuals with familial hypercholesterolemia or strong family history of premature ASCVD. With the continued advances in CT technology (i.e. decreased radiation doses, less need for heart rate control etc.), the role of CTA in primary prevention may change in the future.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Dr. Mortensen has nothing to disclose. Dr. Blaha reports grants from NIH, FDA, AHA and Aetna Foundation; grants and personal fees from Amgen Foundation and Novo Nordisk; and personal fees from Sanofi, Regeneron, Novartis, Bayer, 89Bio, Akcea, Kaleido, Inozyme and Kowa, outside the submitted work.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. J Am Coll Cardiol. 2019;74:2529–32.
2. Fuster V. Changing demographics: a new approach to global health care due to the aging population. J Am Coll Cardiol. 2017;69: 3002–5.
3. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet. Elsevier. 2017;389: 1323–35.
4. National Institute for Health and Care Excellence (NICE) clinical guideline CG181: lipid modification - cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. National Clinical Guideline Centre. 2014. http://www.nice.org.ukGuidancecg. Accessed 31 May 2021.
5. Preventive Services Task Force US, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. JAMA American Medical Association. 2016;316:1997–2007.
6. Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. Elsevier. 2016;32:1263–82.
7. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73:3168–209.
8. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019;37:2999.
9. Lloyd-Jones DM. Cardiovascular risk prediction: basic concepts, current status, and future directions. Circulation. American Heart Association, Inc. 2010;121:1768–77.
10. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J. Factors of risk in the development of coronary heart disease–six year follow-up experience. The Framingham Study. Ann Intern Med. 1961;55:33–50.
11. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The Expert Panel. Arch Intern Med. 1988;148:36–69.
12. The 1980 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med. 1980;140:1280–5.
13. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143–421.
14. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003;24(17):1601–10. https://doi.org/10.1016/s0195-668x(03)00347-6.
15. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987–1003.
16. Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the

National Cholesterol Education Panel III guidelines perform? J Am Coll Cardiol. 2003;41:1475–9.
17. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985;14:32–8.
18. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889–934. https://doi.org/10.1016/j.jacc.2013.11.002.
19. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 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. 2013, 2014:2935–59.
20. Pencina MJ, Navar-Boggan AM, D'Agostino RB, Williams K, Neely B, Sniderman AD, et al. Application of new cholesterol guidelines to a population-based sample. N Engl J Med. 2014;370:1422–31.
21. Mortensen MB, Nordestgaard BG. 2019 vs. 2016 ESC/EAS statin guidelines for primary prevention of atherosclerotic cardiovascular disease. Eur Heart J. 2020;316:1997.
22. Navar-Boggan AM, Peterson ED, D'Agostino RB, Pencina MJ, Sniderman AD. Using age- and sex-specific risk thresholds to guide statin therapy: one size may not fit all. J Am Coll Cardiol. 2015;65:1633–9.
23.• Mortensen MB, Nordestgaard BG. Comparison of five major guidelines for statin use in primary prevention in a contemporary general population. Ann Intern Med. American College of Physicians; 2018;168:85–92. **This paper demonstrates high statin eligibility by guidelines.**
24.• Mortensen MB, Nordestgaard BG. Statin use in primary prevention of atherosclerotic cardiovascular disease according to 5 major guidelines for sensitivity, specificity, and number needed to treat. JAMA Cardiol. American Medical Association; 2019;4:1131–8. **This paper demonstrates that sensitivity for detecting ASCVD events is high with current primary prevention guidelines.**
25. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. J Am Coll Cardiol. 2018;72:434–47.
26. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res. 2014;114:1852–66.
27. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation. 1995;92:2157–62.
28. Blaha MJ, Budoff MJ, Tota-Maharaj R, Dardari ZA, Wong ND, Kronmal RA, et al. Improving the CAC score by addition of regional measures of calcium distribution: Multi-Ethnic Study of Atherosclerosis. JACC Cardiovasc Imaging. 2016;9(12):1407–16. https://doi.org/10.1016/j.jcmg.2016.03.001.
29. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol. 2002;156:871–81.
30. Muntendam P, McCall C, Sanz J, Falk E, Fuster V. High-risk plaque initiative. The BioImage Study: novel approaches to risk assessment in the primary prevention of atherosclerotic cardiovascular disease–study design and objectives. Am Heart J. 2010;160:49–57.e1.
31. Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. Risk Factors, Evaluation of Coronary Calcium and Lifestyle. Am Heart J. 2002;144:212–8.
32. Oei H-HS, Vliegenthart R, Hak AE, Iglesias del Sol A, Hofman A, Oudkerk M, et al. The association between coronary calcification assessed by electron beam computed tomography and measures of extracoronary atherosclerosis: the Rotterdam Coronary Calcification Study. J Am Coll Cardiol. 2002;39:1745–51.
33. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2006;113:30–7.
34. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008;358:1336–45.
35. Blaha MJ, Budoff MJ, DeFilippis AP, Blankstein R, Rivera JJ, Agatston A, 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.
36. Martin SS, Blaha MJ, Blankstein R, Agatston A, Rivera JJ, Virani SS, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the Multi-Ethnic Study of Atherosclerosis. Circulation. 2014;129:77–86.
37. Mortensen MB, Falk E, Li D, Nasir K, Blaha MJ, Sandfort V, et al. Statin Trials, cardiovascular events, and coronary artery calcification: implications for a trial-based approach to statin therapy in MESA. JACC Cardiovasc Imaging. 2018;11(2 Pt 1):221–30. https://doi.org/10.1016/j.jcmg.2017.01.029.
38. Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol. 2010;56:1397–406.
39. Vliegenthart R, Oudkerk M, Hofman A, Oei H-HS, van Dijck W, van Rooij FJA, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. Circulation. Lippincott Williams & Wilkins. 2005;112:572–7.
40. Ferencik M, Pencina KM, Liu T, Ghemigian K, Baltrusaitis K, Massaro JM, et al. Coronary artery calcium distribution is an independent predictor of incident major coronary heart disease events: results from the Framingham Heart Study. Circ Cardiovasc Imaging. Lippincott Williams & Wilkins Hagerstown, MD. 2017;10:1749.
41. Okwuosa TM, Greenland P, Ning H, Liu K, Lloyd-Jones DM. Yield of screening for coronary artery calcium in early middle-age adults based on the 10-year Framingham Risk Score: the CARDIA study. JACC Cardiovasc Imaging. 2012;5:923–30.
42. Shah RV, Spahillari A, Mwasongwe S, Carr JJ, Terry JG, Mentz RJ, et al. Subclinical atherosclerosis, statin eligibility, and outcomes in African American individuals: the Jackson Heart Study. JAMA Cardiol. 2017;2(6):644–52. https://doi.org/10.1001/jamacardio.2017.0944.
43. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. J Am Coll Cardiol. 2015;65:1065–74.
44. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA. 2010;303:1610–6.
45. Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, 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. American Heart Association, Inc. 2016;133:849–58.

46. Mortensen MB, Fuster V, Muntendam P, Mehran R, Baber U, Sartori S, et al. Negative risk markers for cardiovascular events in the elderly. J Am Coll Cardiol. 2019;74:1–11.
47. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2015;66:1657–68.
48. Mortensen MB, Fuster V, Muntendam P, Mehran R, Baber U, Sartori S, et al. A simple disease-guided approach to personalize ACC/AHA-recommended statin allocation in elderly people: the BioImage Study. J Am Coll Cardiol. 2016;68:881–91.
49. Mahabadi AA, Möhlenkamp S, Lehmann N, Kälsch H, Dykun I, Pundt N, et al. CAC score improves coronary and CV risk assessment above statin indication by ESC and AHA/ACC primary prevention guidelines. JACC Cardiovasc Imaging. 2017;10:143–53.
50. Thomas DM, Divakaran S, Villines TC, Nasir K, Shah NR, Slim AM, et al. Management of coronary artery calcium and coronary CTA findings. Curr Cardiovasc Imaging Rep. Springer US. 2015;8:18–4.
51.• Shaw LJ, Blankstein R, Bax JJ, Ferencik M, Bittencourt MS, Min JK, et al. Society of Cardiovascular Computed Tomography/North American Society of Cardiovascular Imaging - expert consensus document on coronary CT imaging of atherosclerotic plaque. Cardiovasc Comput Tomogr. 2021;15(2):93–109. https://doi.org/10.1016/j.jcct.2020.11.002. **This expert consensus provide important information regarding assessment of subclinical atherosclerosis using computed tomography.**
52. Hadamitzky M, Achenbach S, Al-Mallah M, Berman D, Budoff M, Cademartiri F, et al. Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry). J Am Coll Cardiol. 2013;62:468–76.
53. Hadamitzky M, Täubert S, Deseive S, Byrne RA, Martinoff S, Schömig A, et al. Prognostic value of coronary computed tomography angiography during 5 years of follow-up in patients with suspected coronary artery disease. Eur Heart J. 2013;34:3277–85.
54. Bittencourt MS, Hulten E, Ghoshhajra B, O'Leary D, Christman MP, Montana P, et al. Prognostic value of nonobstructive and obstructive coronary artery disease detected by coronary computed tomography angiography to identify cardiovascular events. Circ Cardiovasc Imaging. 2014;7:282–91.
55. Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, et al. Plaque Characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol. 2015;66:337–46.
56. Nadjiri J, Hausleiter J, Jähnichen C, Will A, Hendrich E, Martinoff S, et al. Incremental prognostic value of quantitative plaque assessment in coronary CT angiography during 5 years of follow up. J Cardiovasc Comput Tomogr. 2016;10:97–104.
57. Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE Trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation. American Heart Association, Inc. 2017;135:2320–32.
58. Ayoub C, Erthal F, Abdelsalam MA, Murad MH, Wang Z, Erwin PJ, et al. Prognostic value of segment involvement score compared to other measures of coronary atherosclerosis by computed tomography: A systematic review and meta-analysis. J Cardiovasc Comput Tomogr. 2017;11:258–67.
59. Motwani M, Dey D, Berman DS, Germano G, Achenbach S, Al-Mallah MH, et al. Machine learning for prediction of all-cause mortality in patients with suspected coronary artery disease: a 5-year multicentre prospective registry analysis. Eur Heart J. 2017;38:500–7.
60. van Rosendael AR, Maliakal G, Kolli KK, Beecy A, Al'Aref SJ, Dwivedi A, et al. Maximization of the usage of coronary CTA derived plaque information using a machine learning based algorithm to improve risk stratification; insights from the CONFIRM registry. J Cardiovasc Comput Tomogr. 2018;12:204–9.
61. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol. 2011;58:849–60.
62. Nielsen LH, Bøtker HE, Sørensen HT, Schmidt M, Pedersen L, Sand NP, et al. Prognostic assessment of stable coronary artery disease as determined by coronary computed tomography angiography: a Danish multicentre cohort study. Eur Heart J. 2017;38(6):413–21. https://doi.org/10.1093/eurheartj/ehw548.
63. Mortensen MB, Steffensen FH, Bøtker HE, Jensen JM, Rønnow Sand NP, Kragholm KH, et al. Heterogenous distribution of risk for cardiovascular disease events in patients with stable ischemic heart disease. JACC Cardiovasc Imaging. 2021;14(2):442–50. https://doi.org/10.1016/j.jcmg.2020.08.039.
64.•• Mortensen MB, Steffensen FH, Bøtker HE, Jensen JM, Rønnow Sand NP, Kragholm KH, et al. CAD severity on cardiac CTA identifies patients with most benefit of treating LDL-cholesterol to ACC/AHA and ESC/EAS targets. JACC Cardiovasc Imaging. 2020;13:1961–72 **This paper demonstrates the ability of CTA to identify patients most likely to benefit from treating LDL cholesterol to guideline targets.**
65. Muniyappa R, Noureldin RA, Abd-Elmoniem KZ, Khouli El RH, Matta JR, Hamimi A, et al. Personalized statin therapy and coronary atherosclerotic plaque burden in asymptomatic low/intermediate-risk individuals. Cardiorenal Med. 2018;8:140–50.
66. Seo J, Choi SI, Kim YK. Subclinical coronary atherosclerosis: implication of coronary computed tomography angiography findings among statin candidates according to the 2013 ACC/AHA Cholesterol Management Guidelines. Korean J Radiol. 2019;20:1156–66.
67. Budoff MJ, Mayrhofer T, Ferencik M, Bittner D, Lee KL, Lu MT, et al. Prognostic value of coronary artery calcium in the PROMISE Study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation. 2017;136:1993–2005.
68. Al-Mallah MH, Qureshi W, Lin FY, Achenbach S, Berman DS, Budoff MJ, et al. Does coronary CT angiography improve risk stratification over coronary calcium scoring in symptomatic patients with suspected coronary artery disease? Results from the prospective multicenter international CONFIRM registry. Eur Heart J Cardiovasc Imaging. 2014;15:267–74.
69. Cho I, Chang H-J, Sung JM, Pencina MJ, Lin FY, Dunning AM, et al. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). Circulation. Lippincott Williams & Wilkins Hagerstown, MD. 2012;126:304–13.
70. Cho I, Al'Aref SJ, Berger A, Hartaigh BÓ, Gransar H, Valenti V, et al. Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study. Eur Heart J. 2018;39:934–41.
71. Orringer C, Blaha M, Blankstein R, Budoff M, et al. The National Lipid Association Scientific Statement on the coronary artery calcium score to guidele preventive strategies for ASCVD risk reduction. J Clin Lipidol. 2020;s1933-2874(20):30342.