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Coronary artery calcium scoring for individualized cardiovascular risk estimation in important patient subpopulations after the 2019 AHA/ACC primary prevention guidelines☆

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ABSTRACT

The 2018 and 2019 American Heart Association and American College of Cardiology (AHA/ACC) guidelines for primary prevention of atherosclerotic cardiovascular disease (ASCVD) recommend consideration of so-called "risk-enhancing factors" in borderline to intermediate risk individuals. These include high-risk race/ethnicity (e.g. South Asian origin), chronic kidney disease, a family history of premature ASCVD, the metabolic syndrome, chronic inflammatory disorders (e.g. rheumatoid arthritis [RA], psoriasis, or chronic human immunodeficiency virus [HIV]), and conditions specific to women, among others. Studies suggest, however, that risk may be highly heterogeneous within these subgroups. The AHA/ACC guidelines also recommend consideration of coronary artery calcium (CAC) scoring for further risk assessment in borderline to intermediate risk individuals in whom management is uncertain. Although the combination of risk enhancing factors and CAC burden (together with Pooled Cohort estimates) may lead to more accurate ASCVD risk assessment, few publications have closely examined the interplay between risk enhancing factors and CAC scoring for personalized risk estimation. Our aim is to review the relevant literature in this area. Although further research is clearly needed, CAC assessment seems a highly valuable option to inform individualized ASCVD risk management in these important, often highly heterogeneous patient subgroups.

Contents

Abbreviations: AHA/ACC, American Heart Association/American College of Cardiology; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAC, coronary artery calcium; CARDIA, Coronary Artery Risk Development in Young Adults; CCTA, coronary CT angiography; CHD, coronary heart disease; CHS, Cardiovascular Health Study; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular diseases; DM, diabetes mellitus; ESC, European Society of Cardiology; FHS, Framingham Heart Study; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MESA, Multi Ethnic-Study of Atherosclerosis; MetS, metabolic syndrome; NCP, noncalcified plaques; NRI, net reclassification index; PCE, Pooled Cohort Equations; RA, rheumatoid arthritis.

☆ Statement of conflict of interest: see page XX.

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Risk estimation is the cornerstone of preventive therapy, providing clinicians with the ability to individualize interventions, including the allocation of pharmacotherapies. Initial assessment of atherosclerotic cardiovascular disease (CVD; ASCVD) risk typically involves the use of clinical risk estimators, such as the Pooled Cohort Equations (PCE), which were originally introduced in the 2013 American Heart Association and American College of Cardiology (AHA/ACC) guidelines on the management of blood cholesterol.[1] Nevertheless, current 2018 guidelines on the management of blood cholesterol and 2019 AHA/ACC guidelines of primary prevention of cardiovascular disease acknowledge that there is heterogeneity in risk, particularly across important subgroups. This is especially true among patients with "borderline" and "intermediate" risk estimations, as defined by a 10-year ASCVD risk score of 5 to <20%.

To address this heterogeneity, the 2018 and 2019 AHA/ACC guidelines introduced the concept of "risk-enhancing factors", a group of features which may portend higher ASCVD risk, and the consideration of which can facilitate physician-patient risk discussions, particularly regarding initiation of aggressive lifestyle interventions and pharmacological treatments in asymptomatic individuals.[2] A similar concept of "risk modifiers" had been already included in the European Society of Cardiology (ESC) 2016 prevention guidelines.[3]

The guidelines also formalized the role of coronary artery calcium (CAC) testing as a highly valuable decision aid for patients in whom the decision to treat with statin therapy remains uncertain.[2] Importantly, although a combination of the information provided by the PCE, CAC scoring, and risk-enhancing factors is likely to most effectively individualize risk assessment and subsequent management, the guidelines provided limited guidance regarding the potential interplay between these features. Also, limited guidance was provided regarding the use of CAC in other important patient subpopulations, such as women, patients with diabetes mellitus (DM), or non-South Asian racial/ethnic groups, among others.

A better understanding of the specific role of CAC in these highly relevant subgroups of patients is clearly needed. The aim of this review is this to summarize and discuss the currently available evidence on the potential interplay between CAC scoring and several important patient subpopulations, including those defined by AHA/ACC's risk-enhancing factors (e.g., patients with chronic kidney disease [CKD]) as well as in other clinically relevant patient subgroups.

The 2018 AHA/ACC cholesterol guidelines

According to the guidelines, consideration of risk-enhancing factors is recommended in patients in whom risk management is uncertain after using the PCE. These include high-risk race/ethnicity (e.g. South Asian origin), CKD, a family history of premature ASCVD, the metabolic syndrome, chronic inflammatory disorders (e.g. rheumatoid arthritis [RA], psoriasis, or chronic human immunodeficiency virus [HIV]), and conditions specific to women; among others.

The guidelines also recommend consideration of CAC scoring in patients in whom risk management is uncertain, especially for individuals in the 7.5–20% estimated risk stratum. In such patients, according to the guidelines a CAC score of 0 generally supports deferral of statin therapy unless a patient has diabetes, is a cigarette smoker, or has a very strong family history of premature coronary heart disease (CHD). A CAC score of 1–99 favors initiation of statin therapy, and if CAC is >100 or >75th percentile for age/sex/race, high intensity statin therapy is recommended.

Excluded from this risk assessment algorithm are patients with low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL, as those are generally advised to directly start a high-intensity statin therapy (Class I recommendation). Patients with diabetes and an age of 40–75 years are recommended to start moderate-intensity statin therapy (Class I), with further risk assessment informing consideration of high-intensity statin (Class IIa recommendation).

Potential interplay between CAC scoring and risk-enhancing factors

As discussed above, the 2018 and 2019 AHA/ACC guidelines recommended consideration of risk enhancing factors and CAC as parallel tools, i.e., no hierarchy was specified for the incorporation of this information to decision-making. Also, little guidance was provided regarding the use and interpretation of CAC specifically in the patient subgroups defined by each of those features. Below we discuss some of the potential interplays between CAC and selected risk-enhancing features (Figs 1 and 2).

Race/ethnicity

The AHA/ACC guideline states that race/ethnic features influence the risk of ASCVD and subsequent treatment options (Class IIa recommendation).[2] However, the PCE only takes into account differential ASCVD risk for non-Hispanic Whites and Black individuals.[4] Since the PCE does not adequately estimate the risk of other minority racial/ethnic groups living in the US, such as Latinos or Asians, CAC is proposed as a tool that may prove valuable for improving risk prediction particularly in these groups.[4]

Indeed, multiple population-based cohort studies have demonstrated that CAC predicts ASCVD events well in all ethnicities. The Multi-Ethnic Study of Atherosclerosis (MESA) showed that CAC predicted CVD events beyond traditional risk factors with the same strength in all four US racial/ethnic groups represented in the study.[5] Similarly, data from the CAC Consortium showed that CAC has prognostic value independent of other CVD risk factors for both all-cause and CVD-specific mortality prediction in US Whites, Asians, Hispanics, and Blacks.[4]

The AHA/ACC guidelines define Asian American patients as a highly heterogeneous risk subgroup. Specifically, South Asians (individuals from India, Pakistan, Bangladesh, the Maldives, Nepal, and Sri Lanka) are at increased average ASCVD risk, particularly of coronary heart disease (CHD) events, whereas East Asians (e.g., Chinese [which represented the largest proportion of Asian Americans included in MESA], Japanese and Korean) are at low average CHD risk. As a result, the PCE may underestimate and overestimate ASCVD risk in these groups, respectively. Thus, it is critical to distinguish between South and East Asian individuals when evaluating ASCVD risk, ASCVD risk estimates, and CAC scores.[6]

Based on their increased ASCVD risk as a group, South Asian ethnicity, a growing minority group in the US,[7] is proposed in the guidelines as a risk-enhancing factor. Consequently, many clinician-patient risk discussions may lead to statin therapy initiation in these patients,

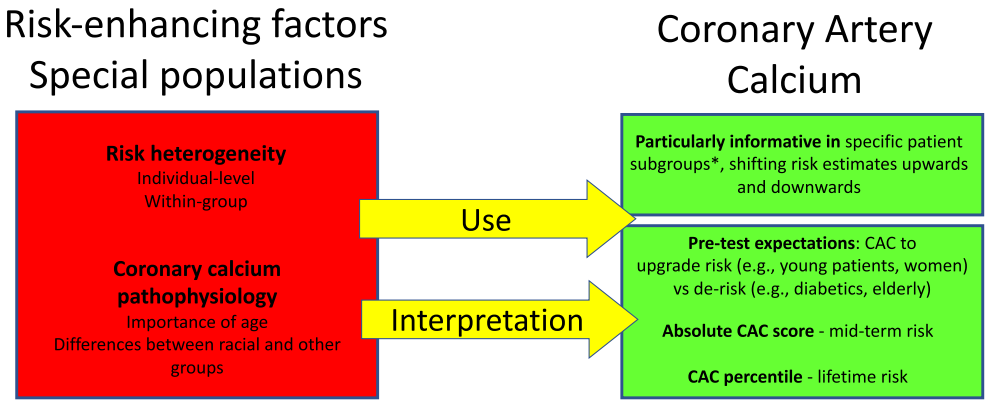

Fig 1. Use and interpretation of CAC.

particularly in those considered at high or intermediate risk using the PCE. Alternatively, CAC scoring may allow for a more personalized assessment, identifying intermediate-risk South Asian patients most likely to get a net benefit from statin therapy, as well as those who could safely refrain or postpone therapy (e.g., patients with a CAC score of zero).[8] However, clinicians should be aware that pre-diabetes and diabetes are highly prevalent in South Asians, particularly in >40 years of age,[9] the presence of which would make a stronger case for statin therapy initiation (see Diabetes mellitus section).

Data also demonstrates the possible benefit of CAC scoring among East Asians across all age groups (20–39 as well as >40 years).[10] Nevertheless, in some East Asian populations, taking sex-differences into consideration may be important, as a publication by Nakao et al. showed that CAC reclassified male Japanese patients more effectively than Japanese women (Net reclassification index [NRI] for women was 0.33 vs 0.71 for men).[11] In Korea, a number of recent research studies have evaluated CAC in large populations of asymptomatic, young Korean adults.[10] This is likely the consequence of local workforce policies and the health checkups required by law for some workers, which may include CAC scoring for subclinical CHD screening purposes. It is important to note, however, that in such studies CAC has typically been used as a surrogate marker of CVD, rather than as a prognostic tool for further ASCVD risk assessment.

Hispanic/Latino individuals represent a very large, growing ethnic group in the US.[12] Studies suggest that Hispanic patients have a lower

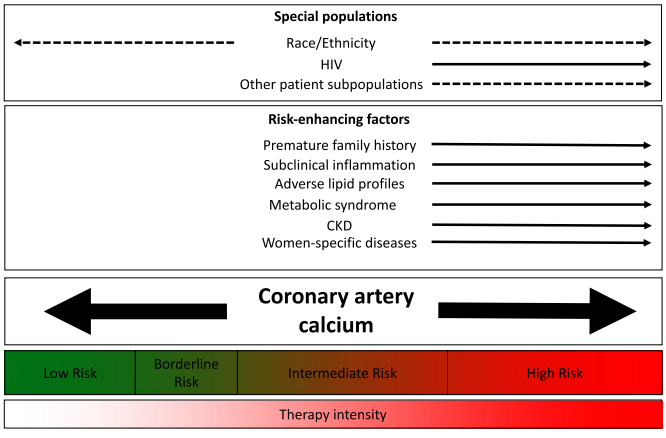

Fig 2. CAC in a personalized risk-based approach for therapy intensity.

CAC burden compared to Asian Americans and Whites.[13] Also, Hispanics living in the United States have a lower CVD mortality than Whites – known as the Hispanic paradox in CVD.[14] Currently there are no CVD risk equations available specifically for Hispanic individuals, and the AHA/ACC guidelines recommend using the PCE designed for non-Hispanic Whites. Nevertheless, specific risk estimation equations for Hispanic men and women are definitely warranted in order to provide a more accurate assessment, and prevent risk overestimation in this group. Moreover, availability of separate equations for different Hispanic subgroups would help better account for risk heterogeneity within this large, growing, heterogeneous group.[15] Until those are available, CAC may be a valuable tool in Hispanics, particularly to identify individuals with zero/very low CAC burden among those with intermediate risk estimations using the current version of the PCE.

Black individuals represent the largest racial minority group in the US.[12] Multiple studies suggest that Black patients have lower CAC scores than their white counterparts.[13,16] However, studies also revealed that Black patients have higher rates of CHD mortality in spite of lower CAC scores compared to Whites, which may be in part due to social determinants and access to care.[17] Doherty et al. observed that compared to White patients, Black patients had lower CAC scores but also significantly greater age-, sex- and coronary risk-adjusted odds of CHD death, myocardial infarction, angina or revascularization.[18] Nevertheless, multiple cohort studies confirm that CAC also improves ASCVD risk assessment in Black patients, such as data from the Jackson Heart Study or MESA.[19,20] These findings were further established by the Dallas Heart Study that included 46% Black patients, in which CAC improved CHD risk classification.[21] Current guidelines already account for the specific ASCVD risk characteristics of Black men and women by providing separate PCE equations for this racial group. With regards to CAC, MESA researchers have published CAC burden percentile distributions by age, sex and race/ethnicity; and these may be particularly useful when interpreting CAC scores in Black and Hispanic individuals.

Chronic renal disease

The impact of CKD on patients' ASCVD risk is of similar magnitude as DM.[22] As a consequence, current AHA/ACC guidelines consider CKD as a risk-enhancing factor in 40 to 75-year-old adults who are at a 7.5% ASCVD risk or higher and not treated with dialysis or kidney transplantation (Class IIa recommendation). The guidelines also state that, as in the general population, CAC scoring should also be considered in CKD patients if preventive treatment decisions is unclear.

Evidence suggests that traditional risk factors do not adequately predict the CVD risk of CKD patients.[23] For instance, Weiner et al. illustrated that the Framingham Risk calculator markedly underestimated ASCVD events for individuals with CKD.[23] Authors from another study concluded that if CKD patients were classified with a 10-year ASCVD risk of ≥7.5% by the PCE, the observed rate of ASCVD events was actually >15%.[24] If CKD patients were classified with a 10-year risk of <7.5%, the observed rate of events was lower than predicted.[24]

Conversely, an extensive body of evidence supports the utility of CAC scoring on CKD patients. For example, data from MESA revealed that CAC scoring led to the greatest improvement in risk prediction for patients with CKD.[25,26] On the other hand, the Chronic Renal Insufficiency Cohort (CRIC) and other studies have suggested that CAC scoring is better suited for patients with moderate to advanced CKD (Stage 3–5, end-stage renal disease, i.e. glomerular filtration rate < 60), while it is unclear if CAC scoring benefits individuals with mild CKD (stage 1–2).[27,28]

These observations together suggest that, especially for intermediate risk CKD patients, CAC scoring may be a valuable method to re-stratify risk given the decreased precision of the PCE in this subgroup. Nevertheless, it must be noted that a majority of CKD patients, particularly those at advanced CKD stages, will already get high risk estimations using the PCE due to their age and traditional risk factor burden – particularly those with CKD caused by hypertension and/or DM. Also, in many patients with CKD, aggressive management of CVD risk factors, which is the standard management in CKD patients,[29] will already involve the use of statin therapy. Therefore, the group of CKD patients who may ultimately benefit from risk estimation using the PCE and CAC, at least for statin allocation purposes, may be very small.

Family history of premature ASCVD

Family history of premature ASCVD, integrating both genetic predisposing factors as well as shared environmental exposures, is a powerful ASCVD risk factor, with some reports suggesting that a positive family history elevates CHD risk by as much as two-fold.[30] Studies have also shown that family history is associated with the progression of subclinical atherosclerosis. Family history was associated with an OR of 1.55 for developing CAC,[31] and individuals with family history also had greater CAC scores than persons without.[31]

Although these and other epidemiological studies clearly support the AHA/ACC and other guideline recommendations of using a positive family history of ASCVD as a risk-enhancing factor, it is important to note that marked risk heterogeneity exists within this subgroup.[32]

Thus, studies suggest that CAC may be informative further stratifying risk also in individuals with a positive family history of ASCVD. Nevertheless, clinicians should be aware that non-negligible CVD risk is still present in patients with family history even if CAC = 0. In a study assessing the significance of family history for CHD in CAC = 0 patients, family history still significantly increased the risk of both CVD and CHD events, even though the absolute event rates were low.[33] Potential contributing factors for this observation are that patients with family history may be associated with a higher burden of non-calcified plaque,[34] which is not as effectively measured by CAC imaging, and a more accelerated development of atherosclerosis.[35]

Metabolic syndrome

According to AHA/ACC, the metabolic syndrome (MetS) occurs if the patient has three or more of the following criteria: 1) waist circumference >40 in. in men and 35 in. in women, 2) elevated triglycerides (150 mg/dL or greater) and reduced high-density lipoprotein cholesterol (HDL-C;<40 mg/dL in men or <50 mg/dL in women), 3) elevated fasting glucose of 100 mg/dL or greater, 4) blood pressure values of systolic 130 mmHg or higher and/or diastolic of 85 mmHg or higher. The MetS is considered a risk-enhancing factor by current AHA/ACC guidelines, accounting for the fact that the PCE do not capture the risk derived from metabolic risk factors such as abdominal obesity, glucose intolerance, or elevated triglycerides; as well as from their interactions, and their interactions with LDL-C levels and other factors included in the equations. This may result in risk underestimation when using traditional risk calculators (such as the PCE) to assess ASCVD risk in patients with MetS.[36]

Importantly, however, not all individuals with MetS are subject to all metabolic risk factors included in the MetS, which results in marked CVD risk heterogeneity among individuals with MetS. This has been demonstrated in studies assessing the prevalence of subclinical calcified coronary atherosclerosis (measured using CAC) in individuals with MetS, showing a graded relationship between the number of metabolic risk factors and CAC score, with CAC scores increasing incrementally with each metabolic risk factor.[37]

Thereby, CAC scoring may be a useful tool to better gauge the risk associated also in patients with MetS. The value of CAC scoring in MetS patients was further established in the MESA cohort, which evaluated the extent incorporating multisite atherosclerosis measures (number of atherosclerotic beds and multisite atherosclerotic score) improved risk discrimination in patients with MetS.[38] Importantly, a CAC score of 0 has been associated with CHD even rates similar to that of individuals without MetS.[39]

Inflammatory disorders

The current guidelines also consider chronic inflammatory disorders, specifically psoriasis, RA and HIV/AIDS, as risk-enhancing conditions. For example, the consideration of HIV as a risk-enhancing factor for initiation or intensification of statin therapy is supported by longitudinal cohort study evidence that shows CVD risk reductions when HIV patients undergo statin therapy. However, it is important to note that currently, it is unclear to what extent chronic inflammatory disorders alter ASCVD risk, and how clinicians should adapt their preventive therapy strategies accordingly. In this context, CAC scoring might help quantify this unknown risk, and guide therapy if management is unclear.

Several studies have evaluated the association between conditions such as psoriasis and subclinical atherosclerosis as measured using CAC. A study in patients with psoriasis showed that individuals with severe psoriasis had higher CAC scores. This study also showed that this association was mainly mediated by a higher prevalence of traditional risk factors for CAD, and not by higher subclinical inflammation as measured using high-sensitivity C-reactive protein (hs-CRP).[40] However, another study showed that psoriasis patients had 2.67 higher odds of developing atherosclerosis, even after adjusting for age, gender, race, body mass index (BMI), smoking, HDL-C and hs-CRP. A study enrolling psoriasis patients older than 10 years of age also demonstrated psoriasis as an independent risk factor for higher CAC scores.[41]

On the other hand, associations with CAC burden are less consistent for patients with HIV. In a cross-sectional study of HIV infected men, coronary arterial plaque was more extensive, independent of CVD risk factors.[42] However, this was especially observed for non-calcified plaques.[42] In general, HIV patients seem to have a higher burden of non-calcified plaque, suggesting a higher prevalence of (non-calcified) atherosclerosis in spite of low CAC scores.[42] This might partially explain the conflicting results regarding CAC scoring among HIV infected individuals; while a meta-analysis found no increased predilection for CAC in HIV-infected patients [OR 0.95 (95% CI: 0.55–1.65), $p = .851$][43] other publications demonstrated an increase prevalence of CAC among HIV infected men.[42,44]

In RA patients, evidence suggests that the PCE categorizes up to 60% high risk RA patients (as determined by their CAC burden) into low-risk categories.[45] Studies have also remarked on the high prevalence of CAC among patients with RA older than 45, however, failed to detect CAC in patients younger than 45.[46]

In summary, most studies suggest that the performance of standard risk scores such as the PCE may be suboptimal in individuals with

chronic inflammatory conditions, as they may not adequately identify patients at actual high ASCVD risk. In this setting, CAC may prove useful to further assess risk, although the possibility that patients with CAC = 0 may have a non-negligible burden of non-calcified plaque requires a careful, nuanced interpretation of CAC = 0 scores in these patient subgroups.

CAC for further ASCVD risk stratification in women

Recent epidemiological studies have depicted concerning increasing trends in the incidence of CVD among contemporary US women.[47] Also, women are affected by unique, sex-specific conditions such as pre-eclampsia, which increase their ASCVD risk and are not adequately captured by most ASCVD risk estimators.[48] These, together with mounting evidence on prevailing inequities in the prevention and management of ASCVD in women compared to men have resulted in the notion of women as a special population requiring further ASCVD prevention efforts.[49]

Indeed, much focus of recent current cardiovascular women's health research has been placed on the evaluation of gender-specific risk differences. There is mixed evidence regarding the extent to which traditional risk scores optimally categorize risk in women. In the derivation cohorts used to develop the PCE, in which incident statin use was low during follow-up, the performance of the PCE was similarly good in women and men. More recently, Mora et al. evaluated the accuracy of the PCE in the Women's Health Initiative cohort, which used information on incident events based on both self-report and also claims data, and concluded that the PCE discriminated ASCVD risk well across all ethnic groups.[50] Other studies, conversely, have suggested that risk calculators may sub-optimally categorize risk in women by overestimating ASCVD risk in this group.[2] For instance, a comparative analysis of MESA showed that the PCE and other scores overestimated risk by 46–67% in female MESA participants (participants identified as White 42%, Chinese 12%, African American 26% or Hispanic 20%). This was likely the consequence of high incident use of statins over time particularly in subgroups at higher baseline risk, secular trends in CVD risk factors, and other reasons.[51]

At the same time, concerns about risk underestimation in some young women have also been raised, particularly with less contemporary risk scores.[52] Overall, these observations suggest that the heterogeneity of risk among women may not be fully captured by traditional risk scores, which makes them particularly vulnerable to risk miscalculation.

To ameliorate this, multiple studies have assessed the value of CAC scoring to achieve improved risk stratification in women. In an analysis of MESA data, 32% of women categorized as low risk (<7.5%) were found to have CAC, which was associated with a 6.5 times higher CHD risk.[53] Similarly, data from a meta-analysis combining five population-based cohort studies showed that among women grouped as low 10-year ASCVD risk (<7.5%) using the PCE, CAC was present in one third of participants.[54] Here, CAC was associated with an elevation of 2.92 per 1000 person-years in ASCVD incidence rate. This meta-analysis showed that CAC modestly improved prognostic accuracy of CVD events when added to traditional risk factors.[54]

Thus, there is some evidence that CAC may optimize risk stratification also in women, particularly in those with unclear risk management and concerns for potential risk overestimation/underestimation using clinical scores alone. Importantly, although currently there is scarce data available exploring the sex-specific performance of CAC in different racial/ethnic groups of men and women, in the landmark 2008 MESA analysis, which included 53% female participants, CAC performed well in all four racial/ethnic groups — which is reassuring about its potential prognostic value also in female minority subgroups. It is also important to note, that in young women in whom risk underestimation may be a concern, consideration of AHA/ACC's risk-enhancing factors may be particularly informative, as some, such as chronic inflammatory conditions, are particularly frequent in young adult women.

Women-specific conditions as risk-enhancing factors

The AHA/ACC guidelines also listed a number of additional, women-specific features associated with increased ASCVD risk, as risk-enhancing factors to be considered when assessing ASCVD specifically risk in women. These include premature menopause (i.e., occurring before age 40 years), and history of pregnancy-associated conditions that increase later ASCVD risk (including preeclampsia, gestational DM, preterm delivery, and delivery of small for gestational age infants).

Importantly, as with other risk-enhancing features, in most of these conditions cardiovascular risk is likely to be highly heterogeneous, and preventive management has not been clearly defined yet. Consequently, in many young women with any of these conditions, uncertainty may arise regarding initiation of preventive pharmacotherapies, such as statins. In such instances, CAC scoring may be very valuable to further personalize preventive efforts, disentangling women who may benefit from early, aggressive pharmacological preventive interventions from those in whom interventions could be focused on healthy lifestyles. However, more research is warranted to fully characterize the utility of CAC scoring specifically in certain female minority subgroups.

Diabetes mellitus

While DM is not mentioned by the AHA/ACC guidelines as a risk-enhancing factor, it is described as a high ASCVD risk condition, with most patients with DM being considered to qualify for statin therapy for ASCVD prevention purposes.

Importantly, a major update of the current guidelines is the proposition of CAC scoring as a tool for “de-risking” individuals from the general population and, as a result, withholding or delaying statin therapy, based on the very favorable prognosis of a CAC score of zero – the so-called “power of zero”.[8] However, according to the guidelines, this approach is not recommended for patients with DM. Nevertheless, this statement is currently a matter of controversy.

Historically, DM was considered a CHD risk equivalent. However, a recent large meta-analysis of studies with a mean follow up of 13 years demonstrated that DM individuals were at a lower risk of developing total CHD events compared to patients without DM with established CHD.[55] The authors concluded that primary prevention strategies in the DM population should be based on DM patients' absolute risk, rather than follow a “treat all” approach.[55] Other experts have supported this viewpoint, arguing that just because affected by the same DM, not all DM individuals are subject to similar risk.[56] For instance, studies have shown that DM patients <60 years with CAC = 0 have a low, near-term risk of <5 deaths/1000persons,[57] a rate similar to individuals without DM. Some publications suggest a “warranty period” for a CAC score of 0; Valenti et al. shows that CAC = 0 de-risks patients up to 5 years while Malik et al. extends this period for up to 10 years.[58,59]

More studies have also remarked on the ability of CAC to help guide the allocation of other pharmacological preventive therapies in DM patients. For example, in the current 2019 ADA guidelines, aspirin is recommended as a primary prevention strategy for patients with DM with increased CVD risk.[60] Nevertheless, concerns regarding hemorrhagic risk with aspirin have recently been raised.[61] In such scenario, CAC may be a highly valuable tool informing number needed to treat, number needed to harm and net benefit estimations.[62]

In all, pharmacological preventive management of patients with DM is currently a matter of intense scientific debate. In this context, CAC has the potential to be a valuable risk assessment tool that may guide a more individualized allocation of preventive pharmacotherapies, by identifying both patients most likely to benefit from lifelong pharmacological therapies such as statins, aspirin, other lipid-lowering agents, and novel anti-DM drugs, as well as young and otherwise healthy diabetics where less aggressive and/or less expensive therapies could be used (e.g., individuals with a CAC score of zero).

Age

While most published research has evaluated the prognostic value of CAC scoring in cohorts of mostly middle-aged individuals, studies also suggest that CAC may be highly valuable as well for risk stratification in individuals at the extremes of the age distribution. The Walter Reed Cohort Study analyzed the value of CAC for the prediction of ASCVD events in young (mean 43.8 years), low risk individuals.[63] Overall, CAC improved risk prediction irrespective of age. A CAC score >0 was associated with an elevated risk of ASCVD events even among young individuals without any traditional CVD risk factors. The Coronary Artery Risk Development in Young Adults (CARDIA) prospective cohort study similarly concluded that approximately 10% of the 3043 CARDIA participants aged 32 to 46 years (mean age 40 years) had any CAC (CAC > 0) and that those individuals had a 3-fold increase in ASCVD outcomes compared to those with CAC = 0.[64] Miedema et al. also recently concluded that a CAC score >100 elevated risk of CVD mortality 3-fold and the risk of CHD mortality 5-fold compared to individuals with CAC = 0 in adults 30 to 49 years of age.[65] Compared with the CARDIA study, Miedema et al. found a higher prevalence of any CAC (34.4% vs 10%) with 7.2% having a CAC score of >100, likely owing to the presence of clinical indications for CAC scoring in the CAC Consortium. Overall, this evidence together with the non-negligible prevalence of CAC >0 in some subgroups of young adults such as some US cohorts[65] supports the use of CAC scoring also in young adults. As discussed above, further studies are needed to better understand the value of CAC specifically in subgroups of young adult men and women of different races/ethnicities.

Data from three US cohorts (the Framingham Heart Study [FHS], MESA and the Cardiovascular Health Study [CHS]) showed that CAC better discriminated incident ASCVD than age in older individuals (>60 years).[66] Importantly, in this age group, 31% of the study population had CAC = 0. Several other studies have also depicted the prognostic value of CAC specifically in elderly individuals, with a CAC score of zero marking an excellent prognosis also in these individuals.[67–70] These data support the notion that CAC scoring can be particularly useful to "de-risk" older adults, avoiding or at least delaying statin therapy in those with CAC = 0.[66] This is consistent with the recommendations included in current AHA/ACC guidelines.

Role of CAC vs. coronary computed tomographic angiography (CCTA)

In addition to CAC scoring, which is already widely supported by primary prevention guidelines around the world, it has also been proposed that CCTA may offer a future alternative method for further risk stratification primary preventive care.

CCTA is able to detect nonobstructive calcified, noncalcified plaques (NCP) and plaques with positive remodeling, all of which may mediate the development of vulnerable plaques and are associated with the risk of myocardial infarction.[71] NCP are especially relevant for young patients; a study showed that in individuals under 55 from families with early onset of CHD, 75–80% of plaque was noncalcified.[34] Further, CCTA may be a valuable tool stratifying risk in patients with extreme family history, as estimates suggest that around 60% of CHD in individuals under 65 is associated with familial CHD.[34] Since CAC does not effectively picture noncalcified plaque, CCTA may be considered for selected cases, such as individuals with extremely high risk due to existing CHD family history.

So far, the major trial on CCTA was the SCOT-HEART trial, however, it was conducted in symptomatic (i.e., not primary prevention) patients. In the future, the SCOT-HEART 2 trial, which is currently ongoing, will evaluate a CHD screening strategy using CCTA in asymptomatic individuals and provide valuable insights on the utility of CCTA in primary prevention settings.

Until those results become available, multiple other barriers will have to be overcome in order for CCTA to become more established in primary preventive care. Radiation dose with typical CCTA is 3–5× higher than a CAC score. Another major limit to precise imaging is tachycardia and motion artifacts during imaging, often requiring heart rate reducing therapy.[72] Currently, CCTA is still quite expensive. For now, CCTA plays a more important role in secondary rather than primary prevention.

Conclusion

Given the complexity of the factors that devise each patient's individual ASCVD risk, in many settings the PCE alone will not be sufficient to guide accurate, personalized risk management. To inform these clinical scenarios, the AHA/ACC 2018 and 2019 prevention guidelines have identified a number of "risk-enhancing factors", i.e., patient subgroups at increased average ASCVD risk in whom shifting risk estimations upwards is considered as a reasonable management approach. More research is needed to better understand the ASCVD risk implications of some of these features.

Epidemiological studies suggest that ASCVD risk is actually highly heterogeneous in some of these groups (e.g., individuals with chronic inflammatory conditions), as well as in other special patient populations, such as women, or patients with DM. In all of those instances, CAC is endorsed in the AHA/ACC 2018 and 2019 guidelines as a key tool for further ASCVD risk assessment in individuals in whom primary preventive management is unclear, including tailored allocation of statins, low-dose aspirin, and other preventive pharmacotherapies.

More research is needed to better quantify the risk heterogeneity of these groups in order to tailor the use of CAC. Further studies are also needed to characterize how CAC can specifically inform therapy allocation in each of these subgroups. One challenge may be finding untreated individuals for long-term follow-up to determine value of CAC for risk prediction in non-European ancestry individuals. Finally, research is also needed comparing the efficacy, effectiveness, safety and net benefit of personalized, CAC-guided management approaches as compared to "treat-all" strategies.

Statement of conflict of interest

All authors report no crossing conflict of interest relevant to the context of this manuscript.

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