The Implication of Coronary Artery Calcium Testing for Cardiovascular Disease Prevention and Diabetes

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Over the last two decades coronary artery calcium (CAC) scanning has emerged as a quick, safe, and inexpensive method to detect the presence of coronary atherosclerosis. Data from multiple studies has shown that compared to individuals who do not have any coronary calcifications, those with severe calcifications (i.e., CAC score >300) have a 10-fold increase in their risk of coronary heart disease events and cardiovascular disease. Conversely, those that have a CAC of 0 have a very low event rate (~0.1%/year), with data that now extends to 15 years in some studies. Thus, the most notable implication of identifying CAC in individuals who do not have known cardiovascular disease is that it allows targeting of more aggressive therapies to those who have the highest risk of having future events. Such identification of risk is especially important for individuals who are not on any therapies for coronary heart disease, or when intensification of treatment is being considered but has an uncertain role. This review will highlight some of the recent data on CAC testing, while focusing on the implications of those findings on patient management. The evolving role of CAC in patients with diabetes will also be highlighted.

WHAT IS CORONARY ARTERY CALCIUM?

As opposed to risk factors which tell us the risk someone might have of having disease, the detection of calcium in the coronary arteries shows us actual evidence of the disease that we are interested in treating or preventing. Thus, individuals who have coronary artery calcifications do, in fact, have coronary artery disease. However, such disease is often termed as "subclinical" as it is most often detected in asymptomatic individuals and is not associated with any clinical symptoms (Fig. 1).

PROGNOSTIC VALUE OF THE PRESENCE AND ABSENCE OF CORONARY ARTERY CALCIUM

There is substantial evidence to support the fact that among individuals who do not have known cardiovascular disease (CVD), the presence and severity of coronary artery calcium (CAC) provides the strongest measure of future cardiovascular risk. When compared to individuals who do not have any CAC, those with severe calcifications (i.e., CAC score >300) have a

10-fold increase in their risk of coronary heart disease (CHD) and CVD events (Fig. 2) [1].

CAC scoring can independently predict cardiovascular events, and when compared to traditional risk factors, offers im-
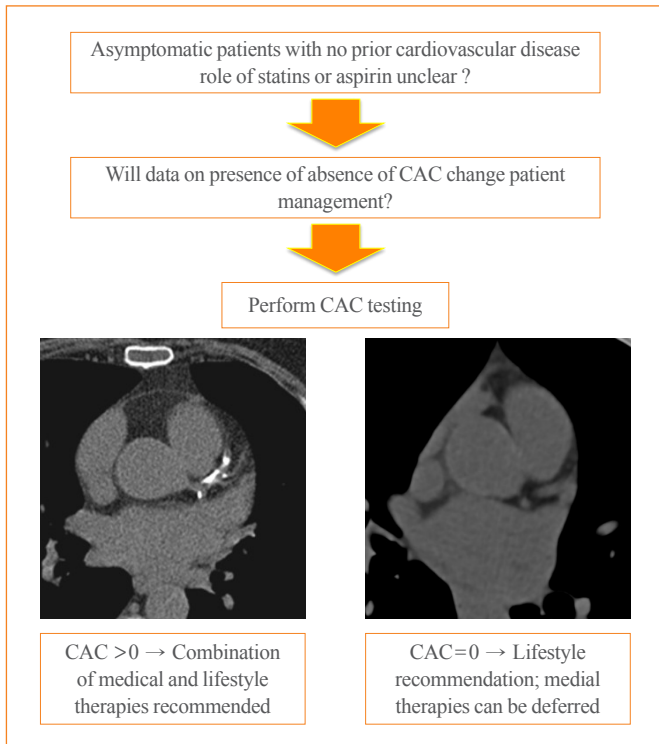
proved discrimination and reclassification [2-5]. Indeed, several large and well-conducted observational studies have demonstrated that when added to standard risk prediction models, CAC has a significantly greater improvement in risk prediction compared with other novel biomarkers or a combined biomarker panel [6-8]. Specifically, among intermediate risk patients, the addition of CAC to the Framingham risk score has been found to have a high net reclassification improvement (66%), with most other novel risk markers—such as carotid intima-media thickness, brachial flow mediated dilation, ankle brachial index, and high-sensitivity C-reactive protein—having a net reclassification improvement index of <10%.

Importantly, the superior predictive capabilities of CAC scoring are due to its ability to correctly reclassify patients to both high and low risk categories. In particular, individuals who do not have any coronary artery calcifications (CAC=0) have an extremely low risk of cardiovascular events of approximately

Fig. 1. Conceptual frameworks of how the presence or absence of coronary artery calcium (CAC) may influence patient management.
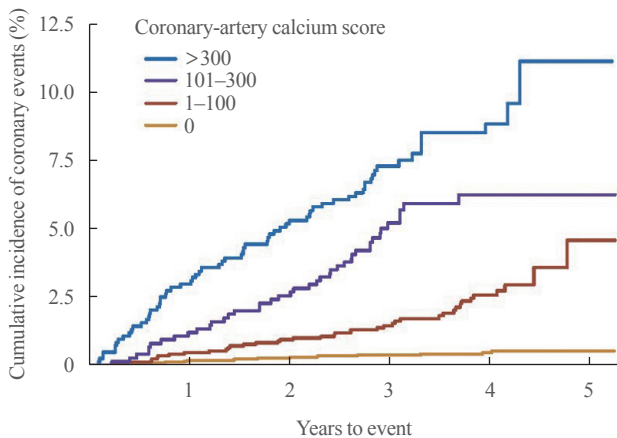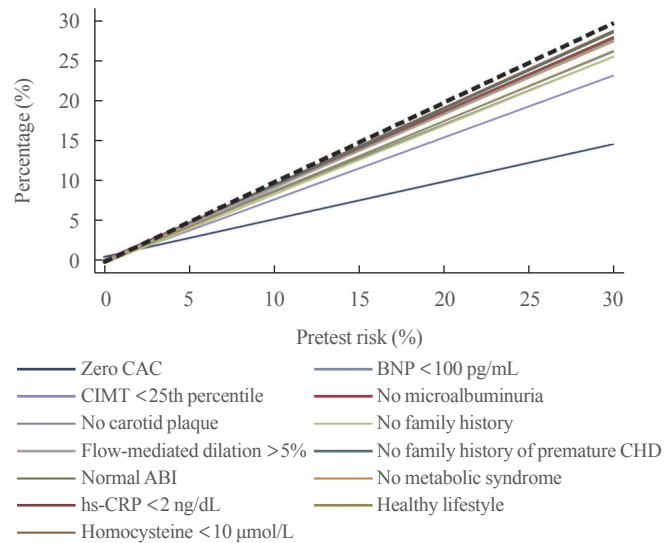

Fig. 2. Unadjusted Kaplan-Meier cumulative-event curves for coronary events among participants with coronary artery calcium scores of 0, 1 to 100, 101 to 300, and more than 300. The figure shows the rates for any coronary event. The differences among all curves are statistically significant ($P<0.001$). Adapted from Detrano et al. [1], with permission from Massachusetts Medical Society.

Fig. 3. Relationship between pretest and posttest cardiovascular disease (CVD) risk after the knowledge of the negative result of each risk marker. The regression lines display the relationship between the pretest predicted 10-year atherosclerotic CVD risk (x axis) and the posttest risk (y axis) after the knowledge of the negative result of each risk marker. A broken back line is displayed as reference (risk shift with no additional testing). Results were obtained by plotting the pretest and posttest risk on the basis of the diagnostic likelihood ratio of each Multi-Ethnic Study of Atherosclerosis (MESA) participant and then applying a linear fit. Adapted from Blaha et al. [10], with permission from Wolters Kluwer Health, Inc. CAC, coronary artery calcium; BNP, brain natriuretic peptide; CIMT, carotid intima-media thickness; CHD, coronary heart disease; ABI, ankle brachial index; hs-CRP, high-sensitivity C-reactive protein.

0.1% per year [9]. The ability of CAC to as a "negative risk marker" has been compared to multiple other risk factors among participants in the Multi-Ethnic Study of Atherosclerosis (MESA) [10]. In this study a CAC of 0 was found to result in the greatest downward shift in cardiovascular risk (Fig. 3).

Much attention has been focused on the utility of CAC scoring to enhance risk prediction for individuals at intermediate risk. However, it is important to note that CAC has significant prognostic value across a wide spectrum of age and risk factor profiles [4,11]. For instance, a prior study by Blankstein et al. [3] examined individuals from MESA with low-density lipoprotein (LDL) cholesterol ≤130 mg/dL, and showed that the presence or absence of CAC was a strong predictor of incident CHD and CVD events, regardless of whether other risk factors were present or absent (Fig. 4). Among individuals traditionally classified as low risk, either based on risk factor burden or calculated risk score, a high CAC score (≥100) is associated with an estimated 10-year all CHD event rate of nearly 10%. In contrast, among individuals traditionally identified as high risk by risk factor

burden or by the Framingham risk score, a CAC score of 0 is associated with a remarkably low 10-year all CHD event rate of roughly 3%. In fact, individuals with no risk factors and an elevated CAC score have nearly three times the event rate of those individuals with multiple risk factors and a CAC score of 0 [4].

WHEN IS CAC TESTING MOST HELPFUL?

While many potential indications exist, in our experience the following groups of patients commonly benefit from statin therapy.

(1) Statin candidates averse to treatment: patients who are advised, by guidelines, to be on statin therapy (atherosclerotic cardiovascular disease [ASCVD] risk score >5% per the pooled cohort equation recommended by the American College of Cardiology/American Heart Association [ACC/AHA]) but who prefer to avoid such therapy.

(2) Statin intolerant patients: several studies have suggested that many individuals who previously were deemed as statin in-

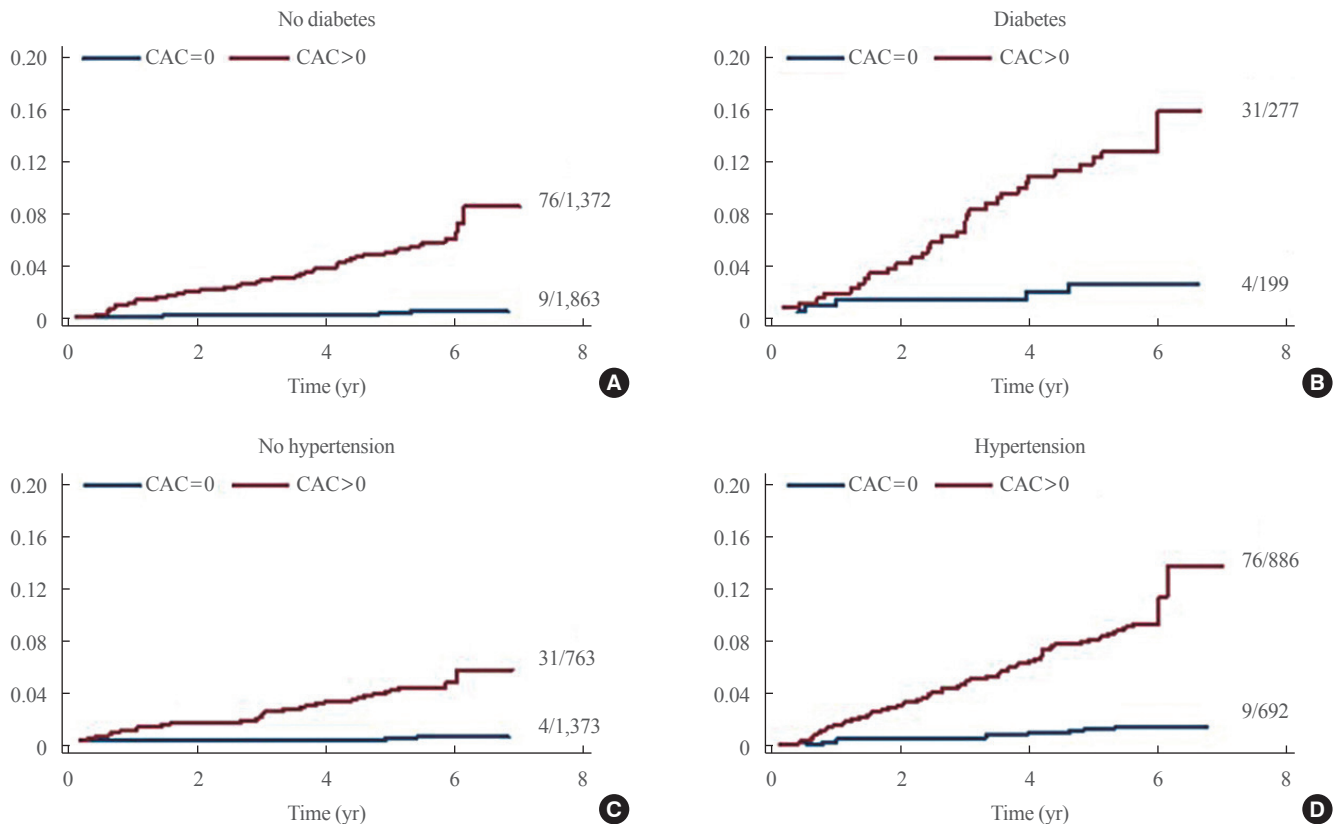**Fig. 4.** Cumulative incidence of coronary heart disease events among Multi-Ethnic Study of Atherosclerosis (MESA) participants with low low-density lipoprotein cholesterol (<130 mg/dL) stratified by the presence or absence of diabetes, hypertension as well as the presence or absence of coronary artery calcium (CAC). (A) No diabetes, (B) diabetes, (C) no hypertension, and (D) hypertension. Adapted from Blankstein et al. [3].

tolerant may be able to tolerate statins when re-challenged. While many such individuals prefer not to be on statins, the identification of coronary plaque may serve as a signal to reconsider a statin, recognizing the greater benefits of such therapies in patients who have higher risk.

(3) Patients with premature family history of CHD: such individuals may benefit from more personalized risk assessment since most traditional risk equations do not include family history of premature CHD. Importantly, even when a strong family history is present, the actual burden of CAC—and thus a person's risk—may be highly variable [12].

USE OF CAC IN LIGHT OF RECENT GUIDELINES?

Recent data has evaluated how CAC testing may complement the recent recommendations made by the European Society of Cardiology (ESC) and the AHA/ACC guidelines for use of statin therapy in primary prevention of CVD. Nasir et al. [13] evaluated how the absence of CAC can be used to downward reclassify individuals who are recommended for statin therapy by the AHA/ACC guidelines to a lower risk group who may defer such therapy. They applied the AHA/ACC guidelines to 4,758 participants of the MESA study, of which 50% were recommended by guidelines to be treated with moderate to high intensity statins. Among those individuals recommended for statin therapy, 41% had no CAC (Fig. 5A). Importantly, in the absence of CAC, those individuals who had a baseline 10-year ASCVD risk score between 7.5% to 20% had an observed 10-year risk of 4.6%, which is lower than the 5% threshold used by the guidelines for considering or recommending statins. On the other hand, among individuals who at baseline had an ASCVD risk of >20% and CAC=0, a high risk was observed (11.7%), while those who had a baseline ASCVD risk below <5% had a low event rate irrespective of whether CAC was present or absent (Fig. 5B). Based on these results, the role of CAC testing seems
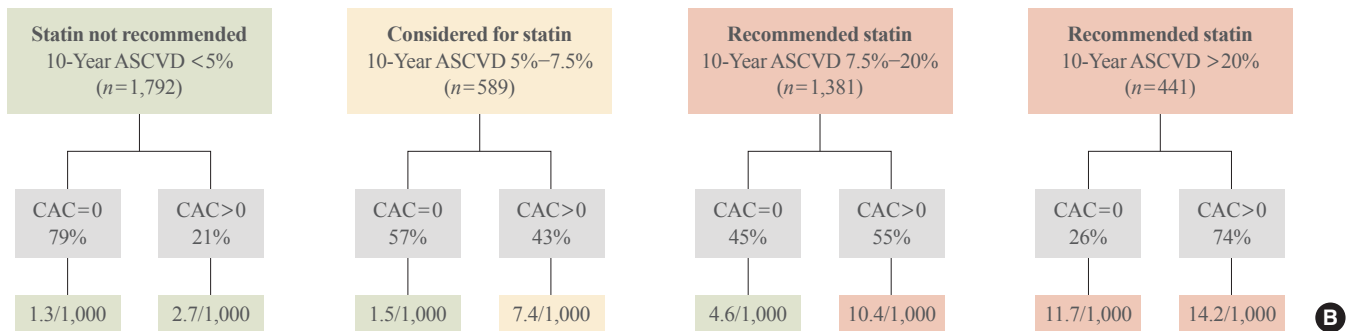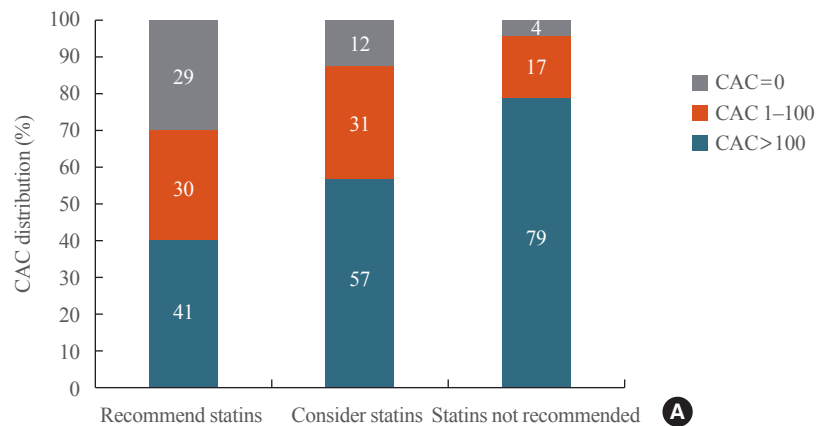
Fig. 5. (A) Coronary artery calcium (CAC) distribution across statin eligibility groups according to the American College of Cardiology/American Heart Association (ACC/AHA) cholesterol management guidelines. (B) Impact of the absence of CAC in reclassifying risk below the threshold for statin consideration suggested by ACC/AHA cholesterol management guidelines across the spectrum of estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk score (nondiabetic patients with low-density lipoprotein cholesterol of 70 to 189 mg/dL). Adapted from Nasir et al. [13].

greatest among individuals who are considered or recommended statins, and have an ASCVD risk of 5% to 20%. In such scenarios, the absence of CAC can be used to identify a low risk group in which statin therapy may be deferred, particularly if such an option is preferred by patients and/or physicians based on evaluating the risk/benefit of treatment in the setting of low risk, while also incorporating patient values and preferences.

A similar analysis was recently preformed by Mahabadi et al. [14], who applied both AHA/ACC guidelines and the ESC guidelines to participants of the Heinz Nixdorf Recall study. Similar to MESA, this study is a prospective cohort of individuals who did not have any known CVD at baseline. This study found that for both guidelines, and irrespective of statin indication, individuals with higher CAC scores had a higher CHD and

CVD event rate (Fig. 6) [14]. Notably, CAC was absent in 43% of individuals who were met statin indications by the ESC guidelines and 53% of the individuals who met statin indication by the AHA/ACC guidelines.

WHEN IS CAC TESTING NOT HELPFUL?

Individuals who have known CHD, or who are already on aggressive medical therapy to prevent CVD, are unlikely to benefit from CAC testing. Such individuals are unlikely to have any meaningful changes in their management as a result of CAC testing. In addition, patients who are averse to treatment, and who are unlikely to initiate treatment even if CAC is identified, should not undergo CAC testing.
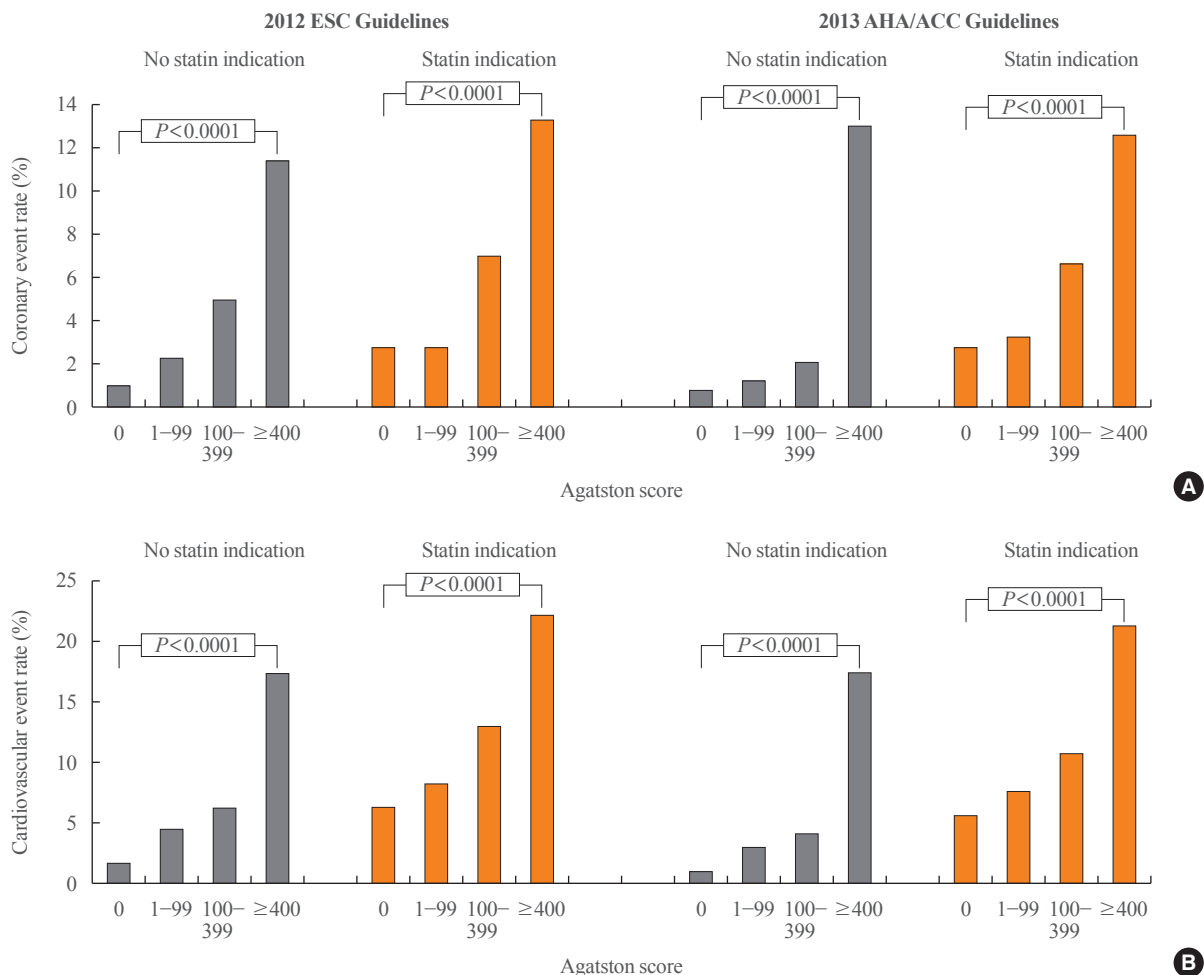
Fig. 6. (A, B) Coronary and cardiovascular event rate for subjects with and without statin indication according to European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines, stratified by coronary artery calcification (CAC) group, showing a distinct increase in event rates for both coronary and cardiovascular events with increasing CAC score, irrespective of statin indication according to ESC and AHA/ACC guidelines. Adapted from Mahabadi et al. [14], with permission from Elsevier.

Table 1. Recommended Interventions to Prevent Cardiovascular Disease Based on CAC Score

CAC=0	CAC >0
Lifestyle changes	Lifestyle changes
Guideline directed care of all modifiable risk factors	Guideline directed care of all modifiable risk factors
Statin therapy may be deferred if patient preference to avoid, and 10-year risk of ASCVD is <20%	Moderate to severe intensity statin therapy, especially if CAC ≥100 Consider aspirin therapy if CAC ≥ 100

CAC, coronary artery calcium; ASCVD, atherosclerotic cardiovascular disease.
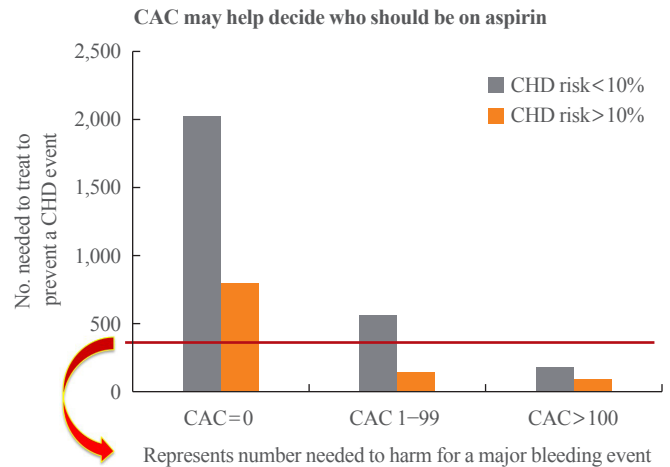

Fig. 7. Estimated risk/benefit of aspirin in primary prevention by coronary artery calcium (CAC) score in Multi-Ethnic Study of Atherosclerosis (MESA) participants. Coronary heart disease (CHD) risk was calculated using the Framingham Risk Score. The red line represents the estimated 5-year number needed to harm based on a 0.23% increase in major bleeding over 5 years. The 5-year number needed to treat estimations is based on an 18% relative reduction in coronary heart disease events. Adapted from Miedema et al. [16], with permission from Wolters Kluwer Health, Inc.

WHAT ARE THE LIMITATIONS OF CAC TESTING?

CAC scanning is associated with a low level of radiation, estimated at 1 to 2 mSV, which is equivalent to the dose of a mammogram [15]. CAC scanning cannot be used to follow treatment response, as CAC does not regress, and may even progress with statin therapy. When CAC testing is performed, incidental findings (e.g., lung nodules) may be found, and these can result in additional downstream costs when further investigations are required.

WHAT SHOULD BE DONE WHEN CAC IS ELEVATED?

Table 1 lists some of the recommended interventions to consider for individuals who are found to have elevated CAC. In addition to initiation of statin therapy, individuals with CAC >100 are also likely to benefit from aspirin therapy (Fig. 7) [16]. Information on CAC burden, when combined with other clinical risk factors, may also inform how aggressive to treat individuals with pre-hypertension or hypertension [17].

WHAT PREDICTS THE DEVELOPMENT OF CAC LATER IN LIFE?

The Coronary Artery Risk Development in Young Adults (CARDIA) study examined the association of various risk factors in young adults with incident CAC 15 to 25 years later. This study found that the levels of modifiable risk factors in young adults predicted incident CAC in middle age. Similarly, longer duration of overall obesity (e.g., body mass index ≥30) or abdominal obesity was associated with greater CAC progression

later in life [18]. While these findings support the fact that the development of atherosclerosis if often preceded by a constellation of unfavorable risk factors, there is no model which reliably predicts the development or absence of CAC and it has been established that even among individuals who do not have any traditional risk factors, the presence of CAC signified elevated risk of both CHD and CVD events [4,19].

A recent important finding from the CARDIA study is that the presence of any CAC in early adult life (i.e., CAC >0), even after accounting for other risk factors, indicates a higher risk of having a future CHD or CVD event during the next decade [20]. Since the presence of CAC in young adults aged 32 to 46 was relatively rare (~10%), widescreen unselected CAC testing in those less than 45 is not recommended. However, future studies are needed to identify which young individuals are most likely to benefit from CAC screening. However, the fact that CAC prevalence significantly increases in the third to fifth decade of life suggests that this is a particularly important time period to implement preventive measures [21].

DOES CAC TESTING IMPROVE OUTCOMES?

Some have proposed a large prospective randomized controlled

Table 2. Mechanisms by Which Coronary Artery Calcium Testing May Improve Cardiovascular Outcomes

How does coronary artery calcium testing improve outcomes?
√ Improvement in risk factor profile
√ Intensification of preventive therapies
√ Better adherence to preventive therapies
√ Dietary modifications
√ Increased exercise

trial (RCT) showing the impact of CAC testing on patient outcomes. Such a study is unlikely to occur in the current era where statins are increasingly being used for prevention. The challenges with a CAC RCT trial are also inherent in the fact that it would be unethical to randomized patients that have severe amount of CAC into an arm of no therapy. It is also noteworthy, that such trial data is also not available for any risk scores, which have been proposed for evaluating patients with suspected CAD.

Nevertheless, there are a few insights that that were highlighted by prior studies. In the St. Francis Heart study, 1,005 asymptomatic, apparently healthy men and women age 50 to 70 years with CAC scores ≥80th percentile for age and gender were randomized to atorvastatin 20 mg daily in addition to vitamins C and E in a double-blind placebo-controlled trial [22]. After a mean follow-up of 4.3 years, treatment with atorvastatin reduced LDL cholesterol levels by nearly 40% and showed a trend towards reduction in atherosclerotic CVD events (6.9% vs. 9.9% in atorvastatin vs. placebo arms respectively, $P=0.08$). The effect of atorvastatin on CVD event reduction was stronger in the subgroup of patients with CAC >400 (8.7% vs. 15%, $P=0.046$). This study, while small when compared to contemporary trials, and clearly underpowered, provides an important signal that patients with increased CAC are most likely to benefit from cholesterol lowering therapies.

When evaluating the impact of CAC testing on patient outcomes it is important to consider the various mechanisms by which CAC testing may improve outcomes, including both pharmacological and non-pharmacological interventions (Table 2). A recent meta-analysis by our group assessed the odds of initiation or continuation of pharmacological and lifestyle cardiovascular preventive therapies in patients with non-zero versus zero CAC score detected on cardiac computed tomography [23]. In this meta-analysis of six studies [24-29] involving 11,256 participants in a mean follow-up of 1.6 to 6 years, we found that identifying calcified coronary plaque, significantly

increased the likelihood of initiation of aspirin and blood pressure lowering medications, initiation and continuation of lipid lowering medications, as well as intensification of exercise and dietary changes. These findings remained significant after adjustment for baseline patient characteristics and cardiovascular risk factors in individual studies.

To date, several RCTs have investigated the effect of CAC scan versus no scan on preventive pharmacotherapies in asymptomatic individuals [24,30-32]. O'Malley et al. [30] did not find the impact of CAC scan on change in 10-year Framingham risk score over 1 year among group of patients to whom CAC scan information was provided versus withheld. However, participants in this trial were asymptomatic active duty United States Army personnel, with very low cardiovascular risk at baseline (0 CAC score in 85.3% of patients), in whom an additional risk-reduction would be hard to achieve. Similarly, a small RCT of 56 postmenopausal women without known CAD did not show an independent benefit of CAC scanning on cardiovascular risk factor control that included systolic blood pressure and lipid profile (CAC <10 in 73.1% of 26 women who underwent CAC scan) [32]. It must be emphasized that the low risk populations in these studies are not fully representative of the population in which CAC scan is intended. Indeed, consistent evidence supports the concept that individuals who are at intermediate risk by traditional risk scores have the greatest potential for risk reclassification and modification of primary prevention therapies. By comparison, Rozanski et al. [24], in Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) trial, performed a large, well-designed RCT of 2,137 middle-aged subjects with cardiovascular risk factors in whom a large proportion of the patients with CAC testing had a non-zero CAC score ($n=680/1,311$, 52%). In this study CAC scanning was associated with superior CAD risk factor control compared to usual care alone.

Whelton et al. [33] conducted an updated meta-analysis of the four available RCTs and found a non-significant trend towards reduction in blood pressure, lipid levels, and smoking cessation among individuals who had a CAC scan compared to those who were managed by standard care. However, the EISNER trial [24] showed that within the CAC scan group, there was significant increase in aspirin, statin and blood pressure lowering medications in individuals with non-zero CAC. Therefore, abnormal CAC score, and not just merely the CAC scan itself, likely accounts for behavioral changes following CAC scan. A RCT by Mols et al. [34] further supports this view. They found that in stable chest pain patients with hyperlipidemia and no ob-

structive CAD who have CAC >70 on calcium scan, visualization of CAC, and brief recommendations about risk modification led to a favorable influence on plasma total cholesterol concentration and adherence to statin therapy.

WHAT ARE THE IMPLICATION OF CAC TESTING BEYOND CHD?

Recent studies have shown that increased CAC is associated with higher rate of cerebrovascular accidents [35,36], heart failure [37,38], and atrial fibrillation [39]. In addition, compared to individuals who have no CAC, those with increased CAC are more likely to have other non-cardiac conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, and hip fractures [40].

THE ROLE OF CAC IN INDIVIDUALS WHO HAVE DIABETES

For more than a decade, the presence of diabetes has been considered a CHD risk equivalent. However, several recent studies have shown that the CVD risk of patients with diabetes is markedly variable. A recent large, contemporary cohort showed that diabetes alone did not confer the same level of CHD risk as individuals with prior CHD. Compared to individuals without diabetes or CHD, the risk doubled among those with diabetes alone, but tripled among those with prior CHD alone. Importantly CHD event rates were very low among individuals with diabetes who were less than 40 years of age [41]. While these results suggest a potential role for further risk stratification among those with diabetes [42], prior trials using nuclear myocardial perfusion imaging [43] or coronary CT angiography [44] have not shown any improvement in patient outcomes associated with screening. In part these negative results were due to the fact that event rates in these studies were lower than predicted, and medical therapy was highly prevalent, regardless of whether screening was performed or not. Accordingly, while there may remain an unproven role for screening very high risk individuals with diabetes using functional testing, in younger and lower risk individuals the role of screening may ultimately be to identify which individuals—despite their diabetes—have a sufficiently low long-term risk that they can defer treatment with statins.

Supporting the potential role of CAC screening in diabetes or metabolic syndrome, Malik et al. [45] evaluated the association of CAC with CHD events in 6,603 people aged 45 to 84 years
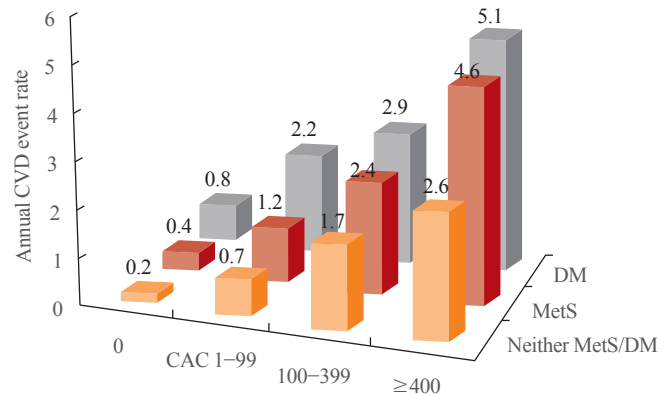

Fig. 8. Annualized unadjusted cardiovascular disease (CVD) event rates in Multi-Ethnic Study of Atherosclerosis (MESA) stratified by coronary artery calcification (CAC) and the presence of diabetes mellitus (DM), metabolic syndrome (MetS), or neither. Adapted from Malik et al. [45], with permission from American Diabetes Association.

without clinical CVD in the MESA and risk factor-adjusted hazard ratios for CHD for CAC 1 to 99 to ≥400 versus 0 in subjects with neither metabolic syndrome nor diabetes ranged from 2.6 to 9.5; in those with metabolic syndrome ranged from 3.9 to 11.9; and in those with diabetes ranged from 2.9 to 6.2 (all $P<0.05$). Patients with metabolic syndrome or diabetes and a CAC score of 0 had a projected annual CHD event rate of 0.4% and 0.8%, respectively, whereas those with CAC score of >400 had annual CHD event rate of 4.6% and 5.1%, respectively. Diabetes mellitus has traditionally been considered as a CHD risk equivalent. However, 45% of patients with metabolic syndrome and 38% patients with diabetes in this study had a CAC score of 0 with annual CHD event rate similar to those without these conditions (Fig. 8).

These findings imply that CAC testing in these patients could help with risk-reclassification of a significant proportion of patients with diabetes or metabolic syndrome. Nevertheless, the use of routine CAC screening in individuals with diabetes remains uncertain, and a trial assessing the impact of CAC testing in this population has not been conducted. Such a trial would have to be based on the fact that the greatest utility of CAC testing is to identify those individuals who are being considered for statin therapy, in whom there is a strong patient preference to avoid statins (if the CAC score is 0), but a willingness to initiate therapy if coronary atherosclerosis is detected.

FUTURE ROLE OF CAC BEYOND STATINS

In the future, additional preventive therapies beyond statins may

be considered for selected individuals who do not have known CVD. Realizing such therapies are likely to be more expensive and may be associated with more adverse effects, it is plausible that the allocation of newer therapies may be improved by using CAC testing in order to identify those with the highest risk, who therefore stand to have the greatest reduction in events. Realizing this potential role, future drug development trials may benefit from using CAC testing as a way to better enrich the population tested.

CONCLUSIONS

CAC testing is now well recognized as a simple, reproducible, and inexpensive test to assess for the presence or absence of coronary atherosclerosis. Most individuals who have a CAC=0 have a very low risk of future cardiovascular events over the next 10 to 15 years and can elect to defer statin therapy and instead focus on lifestyle intervention. On the other hand, for those who are being considered for statin therapy, the presence of CAC—irrespective of whether other risk factors are present or absent, and regardless of age—can be used to provide a more precise risk assessment, and consequently provide a more compelling case for using pharmacotherapy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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