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Addressing Knowledge Gaps in the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: a Review of Recent Coronary Artery Calcium Literature

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Abstract

Purpose of Review Coronary artery calcium (CAC) has been proposed as an integrator of information from traditionally measured, non-traditionally measured, and unmeasured risk factors for coronary atherosclerosis. The 2013 American College of Cardiology/American Heart Association Guideline on the Assessment of Cardiovascular Risk identified several knowledge gaps regarding CAC, including radiation risks, cost-effectiveness, and improving discrimination and reclassification of estimated risk over the Pooled Cohort Equations in the ACC/AHA Atherosclerotic Cardiovascular Disease Estimator. In this review, we focus on recent CAC literature addressing these knowledge gaps. We further highlight the potential for CAC to enrich future randomized controlled trials.

Recent Findings The use of CAC allows for personalization of cardiovascular risk despite the presence or absence of traditional risk factors across many demographics. Avenues to reduce radiation exposure associated with CAC scanning include increasing the interval between scans for those with CAC scores of zero and estimating CAC from non-cardiac gated CT scans. While limited studies have suggested cost-effectiveness in cardiac risk assessment with the incorporation of CAC in screening algorithms, several studies have demonstrated the ability of CAC to identify non-traditional risk factors that may be used to expand cardiovascular risk personalization in other high-risk populations.

Summary Literature from the past 2 years further supports CAC as a strong marker to personalize cardiac risk assessment. While multiple potential avenues to reduce radiation are available and cost-effectiveness analyses are encouraging, further studies are necessary to clarify patient selection for CAC scanning given the interplay between CAC and other imaging modalities in risk personalization algorithms.

Keywords Coronary artery calcium · Primary prevention · Cardiovascular disease · Risk assessment · Radiation · Cost-effectiveness

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Abbreviations

CAC	Coronary artery calcium
ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
CCTA	Coronary computed tomography angiography
CVD	Cardiovascular disease
MESA	Multi-ethnic Study of Atherosclerosis
CRP	C-reactive protein
MPI	Myocardial perfusion imaging
ABI	Ankle-brachial index
PCSK9	Proprotein convertase subtilisin/kexin type 9
SPECT	Single photon emission computed tomography
HR	Hazard ratio
OR	Odds ratio

RR   Relative risk
DLR   Diagnostic likelihood ratio
AUC   Area under the curve
ROS   Receiver operating statistics
EFV   Epicardial fat volume
COPD   Chronic obstructive pulmonary disease
ED   Erectile dysfunction
NAFLD   Non-alcoholic fatty liver disease
SLE   Systemic lupus erythematous

Introduction

More US healthcare dollars are spent on cardiovascular disease (CVD) compared to any other disease process, with 1 out of every 6 dollars allocated to CVD [1]. By 2030, total direct medical costs of CVD are expected to triple to $818 billion compared to 2010 values [2]. Despite this influx of healthcare dollars towards its treatment, CVD remains the leading cause of death in the USA [2, 3].

It is therefore imperative to determine which individuals are at risk for developing CVD and to limit progression of atherosclerotic burden via risk identification, lifestyle intervention, and pharmacotherapy if indicated. Recently, the Atherosclerotic Cardiovascular Disease (ASCVD) Estimator from the American College of Cardiology and American Heart Association (ACC/AHA) has been used to identify individuals who are at risk for developing adverse cardiac events or strokes within the next 10 years [4]. Critics of the ASCVD risk estimator point to its (1) reliance on pooled cohorts from the Framingham Original and Offspring Studies, Atherosclerosis Risk in Communities (ARIC), and Cardiovascular Health Study (CHS), which lack ethnic diversity beyond Caucasians and African Americans and are not representative of the 2016 American population, (2) dependency on one-time measurements of limited risk factors such as total cholesterol which lack specificity and have repeat-measurement variability, (3) omission of important risk factors such as genetic influences and lifetime environmental exposures which contribute to total cumulative risk of atherosclerosis development, and (4) potential to overestimate risk by applying a group's average estimate of risk based on limited factors to any one individual with minimal personalization [5–8].

In light of the limitations of the ASCVD risk estimator and to further personalize cardiovascular risk assessment, coronary artery calcium (CAC) scoring has been proposed as a cumulative surrogate for traditionally measured, non-traditionally measured, and unmeasured risk factors for the development of coronary atherosclerosis. The 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk provided a Class IIb recommendation

for the use of CAC in risk profiling when pharmacotherapy indications remain unclear after ASCVD risk estimation and clinician-patient discussion [4]. Specific knowledge gaps outlined in the Guideline focused on cost-effectiveness and radiation related to CAC, with a broader call for research focusing on novel risk markers applicable to different demographic groups that would improve discrimination and reclassification of the ASCVD Pooled Cohort Equations (PCE). Since the publication of the Guideline, multiple studies in 2015–2016 on CAC have focused on these specific areas, providing further evidence for CAC as a potentially useful clinical tool.

In this editorial review, we summarize recently published data addressing the knowledge gaps identified by the 2013 ACC/AHA Working Group in the context of CAC by first briefly reviewing improvements in discrimination and reclassification in cardiovascular risk assessment. We then spend the majority of this review (1) addressing trends regarding radiation and cost-effectiveness and (2) exploring the ability of CAC to identify non-traditional risk factors from a wide-variety of disease states, therefore expanding cardiovascular risk personalization to other high-risk populations. We finally identify future directions for CAC use, including its potential for enriching randomized controlled trials. Key data from representative studies are presented in tables, with trends summarized in the text.

Knowledge Gap 1: Improving Discrimination and Reclassification Across Various Demographic Groups

Our group summarized several CAC trends regarding discrimination and reclassification in an earlier review [9]. Key studies illustrating the ability of CAC to improve risk stratification over the PCE regardless of the presence or absence traditional cardiovascular risk factors will be briefly reviewed here.

Although several studies have identified associations between CAC severity and the number of cardiovascular risk factors [10–12], Joshi et al. evaluated 1391 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) who had low lifetime risks of developing cardiovascular disease based on absence of diabetes, non-smoking status, total cholesterol <200 mg/dL, systolic blood pressure <140 mmHg, and diastolic blood pressure <90 mmHg. At baseline, 34% of participants had detectable CAC despite the absence of these risk factors; over a 10-year follow-up, CAC >100 remained a significant predictor of ASCVD risk (hazard ratio [HR] 5.2), yielding a net reclassification improvement of 34% in an otherwise low-risk population [13••]. MESA participants also exhibited marked CAC heterogeneity stratified by ASCVD risk: 41% of those with ASCVD scores ≥7.5% had no detectable CAC, whereas 57% of individuals with ASCVD risks

between 5 and <7.5% had CAC scores of 0. With relatively low rates of cardiovascular events in those with zero CAC regardless of ASCVD risk, upwards of 50% of the cohort was reclassified into lower-risk groups [14••].

Based on the potential of CAC to correctly re-classify cardiovascular risk irrespective of traditional risk factors, Yeboah et al. compared the discriminatory capacity of CAC to those of other potential risk markers outlined in the 2013 Guideline including high-sensitivity CRP (hsCRP), ankle-brachial indices, and positive family history of ASCVD in 5185 MESA participants. Only CAC improved discrimination over the PCE across all strata of recalibrated ASCVD risk, supporting the superiority of CAC over other novel risk markers [15]. As a corollary to this study, our group focused on negative risk markers in the MESA study, including CAC scores of 0, carotid intima-media thickness <25th percentile, and hsCRP <2 mg/L. A zero CAC score had the strongest predictive capability for both coronary artery disease (diagnostic likelihood ratio [DLR] of 0.41) and cardiovascular disease events (DLR 0.54). Given the clear improvement in risk prediction with the use of CAC, McClelland et al. developed a novel risk estimator incorporating CAC scores with external validation that has been reviewed elsewhere [9, 16].

Knowledge Gap 2: Radiation and Cost-Efficacy

Reduction in Radiation

A 2011 joint statement from the AHA and Council on Cardiovascular Radiology and Intervention suggested that cardiovascular screening algorithms should not exceed 1.0 mSv—a goal repeatedly met by contemporary CAC scanners [17]. One mechanism to further reduce radiation involves lengthening the interval period between computed tomography scans in patients with zero CAC (Table 1). Patients with baseline CAC do not require repeat scans, given rate of CAC progression is unlikely to affect therapy. Prior to 2015, a "warranty" period of 4 years was originally proposed for patients with CAC scores of 0 given low conversions of baseline CAC scores to positive values within this time frame [38]. Alluri extended this warranty to >5 years after evaluating 3112 MESA participants with baseline CAC = 0, of whom 1125 developed CAC over the follow-up period of 2–10 years. Mean time to CAC detection was 6.1 years, with the majority of incident CAC (96%) <100 Agatston units [18].

Valenti's 2015 study longitudinally followed 4864 patients with baseline CAC scores of 0 and found mortality rates <1% during the follow-up period of 15 years. Although CVD events were not assessed, there were very low mortality rates (0.3% events/year) in the first 12 years and slightly increased rates (0.4–0.58%) in the 13th and 14th years of follow-up. The

authors concluded that a longer "warranty" of 15 years may be acceptable for those with no detectable CAC [19•].

In patients who have already undergone CT scans for other indications—including coronary CT angiography (CCTA), non-gated CT assessing lung pathology, or attenuation correction for myocardial perfusion imaging (MPI)—Agatston calcium scoring may be accurately determined from these images without the need for additional, dedicated ECG-gated CT scans (Table 1) [20–25]. Ahmed and colleagues evaluated 100 patients and compared CAC scores from CCTA images via a fully automated algorithm to manually calculate Agatston scores from non-contrasted scans. There was an overall high correlation (Pearson, $r = 0.949$) and intra-class correlation (Pearson, $r = 0.863$) across CAC strata [20]. Similar high correlations (Pearson, $r = 0.94$–0.95) were found in other studies calculating CAC from CCTA [21, 22].

Hughes-Austin and Takx quantified CAC on standard, chest, and thoracic CTs indicated for lung pathology. In the former study, 4544 patients underwent 3-mm ECG-gated CT scans as well as standard 6-mm chest CT scans; although median CAC scores were overall lower in the 6-mm scans, there was a strong correlation in Agatston scores between the two modalities (Spearman, $r = 0.93$) [23]. Lastly, Engers estimated Agatston scores from attenuation CT scans prior to MPI and found agreement coefficients ranging 0.94–0.95 between estimated CAC and actual CAC derived from dedicated ECG-gated scans [25]. Taken together, these studies argue against the need for separate, non-contrasted CTs to determine CAC score if calcification is clearly apparent in a coronary artery distribution.

Another avenue to reduce radiation is improvement in CAC quantification with iterative reconstructive (IR) methodology (Table 1). Hecht initially scanned 102 consecutive patients at standard ECG-gated radiation doses based on weight to evaluate CAC, and again at 50% radiation reduction with IR. Agatston score correlations were excellent ($r = 0.998$) with a weighted kappa for agreement at 0.95, suggesting that lower radiation exposures were acceptable for adequate quantification [26]. Multiple other studies demonstrated the ability of IR as a means to reduce radiation with high levels of agreement (Table 1) [27, 28, 39]. However, given increased noise with lower radiation doses, upwards of 15% of patients may be inappropriately reclassified into lower-risk categories compared to standard-dose Agatston values.

Potential Increase in Radiation

Despite the aforementioned avenues to reduce radiation, several studies have found incremental utility in combining CAC scans with findings from separate scans—CCTA, MPI, and non-coronary findings from CT—to personalize risk stratification at the cost of increased radiation (Table 1) [29–31, 40, 41]. For example, Dedic and colleagues investigated 665

Table 1 Knowledge gap II: representative studies investigating radiation exposure

Topic	Author (population)	Pertinent result
Avenues to decrease radiation		
"Warranty" period	Alluri [18] (MESA)	Mean-time of 6.1 years from baseline CAC = 0 to CAC > 0
	Valenti [19•]	0.3–0.6% mortality rates/y over 15y for those with CAC = 0
Estimated Agatston	Ahmed [20]	High correlation ($R = 0.949$) between CCTA CAC with non-contrast CT CAC
	Schuhbaeck [21]	High correlation ($R = 0.95$) between CCTA CAC with non-contrast CT CAC
	Pavitt [22]	High correlation ($R = 0.95$) between CCTA CAC with non-contrast CT CAC
	Hughes-Austin [23]	High correlation ($R = 0.93$) between 6 mm (standard CT) CT CAC and 3 mm CT CAC
	Takx [24] (NELSON)	Increase in C-statistic from 0.621 to 0.715 with standard chest CT-derived CAC
	Engbers [25]	High correlation ($R = 0.94$–0.95) between attenuation-derived CAC and non-contrast CT CAC
Iterative reconstruction	Hecht [26]	High correlation ($R = 0.99$) between standard dose radiation and low dose+IR
	Willemink [27]	IR lowered CAC scores with Agatston reclassifications in 15% of patients
	Takahashi [28]	High correlation ($R = 0.99$) between standard dose radiation and low dose+adaptive IR
Potential increase in radiation		
CAC+CCTA	Cho [29] (CONFIRM)	CCTA+CAC improved C-statistic by 0.24, NRI 0.62 in those with CAC > 100
	Dedic [30]	CCTA + CAC increased C-statistic from 0.81 to 0.84, NRI 0.19
	Durhan [31]	CCTA+CAC increased detection of significant stenosis in those with CAC = 0
CAC+MPI	Engbers [32]	MPI+CAC increased C-statistic from 0.73 to 0.77
Multi-imaging approach	Mahabadi [33•] (HNR)	LA index, EFV volume, and TAC improved prediction over FRS and CAC (AUC 0.749 to 0.764)
	Brodov [34] (EISNER)	TAC > 100 was a significant predictor of CAC > 0 (OR 1.90)
	Hu [35]	ARC predicts increased prevalence of CAC (87.7% with ARC vs 24.4% without)
	Tanami [36] (CORE)	EFV had no association with CAC (OR: 1.005, $p = 0.126$)
	Possner [37]	Weak correlation ($R = 0.202$) between EFV and CAC

CAC coronary artery calcium, *CCTA* coronary computed tomography angiography, *MPI* myocardial perfusion imaging, *NRI* net reclassification index, *IR* iterative reconstruction, *LA* left atrial, *EFV* epicardial fat volume, *TAC* thoracic aorta calcification, *FRS* Framingham Risk Score, *ARC* aortic root calcification, *y* year

patients with at least one traditional cardiovascular risk factor—the inclusion of CCTA results in a model with a CAC score increased the C-statistic from 0.81 to 0.84 with a net reclassification index of 0.19 [30].

Furthermore, the development of an algorithm whereby CCTA is only performed in pre-specified patients undergoing CAC scans was investigated in Durhan's study with 2921 patients. The authors found that in patients who had CAC scores of 0 yet had high pre-test probabilities for CAD, the addition of CCTA helped identify significant atherosclerosis in upwards of 7% of patients with CAC = 0 [31]. Although CONFIRM did not support routine CCTA on top of CAC, these studies suggest potential incremental information from CCTA in carefully selected high-risk patients by traditional risk factor estimation but with zero or very low calcium scores [41].

Similar improvements were found with a combination of CAC and MPI [32, 42–44]. Engbers studied 4897 patients with CAD who underwent both screening modalities. A significant association was found in the frequency of ischemia found on SPECT and increasing CAC scores: only 12% of patients had abnormal SPECT findings with undetectable CAC scores compared to 50% of patients who had CAC scores >1000. When CAC was added to a model with SPECT findings to predict major adverse cardiac events, the C-statistic increased from 0.73 to 0.77 [32].

Using the multi-imaging approach, whereby additional parameters measured from CT scans are used to personalize risk assessment, may help identify which patients would benefit from CAC scans at the expense of increased radiation (Table 1). In a landmark paper by Mahabadi, the authors evaluated the utility of non-coronary CT measurements in 3630

individuals. Epicardial fat volume (EFV), left atrial axial area index (LA index), and thoracic/aortic root calcification (TAC) were independently associated with increased cardiovascular events. In fact, the combination of LA index, EFV, and TAC improved prediction over CAC (*C*-statistic increase to 0.764 from 0.749) [33•].

Similarly, Brodov and Hu both evaluated TAC and aortic root calcifications (ARC), but instead investigated their associations with CAC [34, 35]. In Brodov's study, out of 1648 asymptomatic adults with baseline CAC of 0, 348 adults developed CAC on subsequent scans. A TAC value >100 was found to be an independent predictor (OR 1.90) of conversion from CAC = 0 to CAC >0 [34]. Similarly, in Hu's study, those with ARC were more likely to have CAC [35]. These studies suggest that patients with extensive ARC and TAC but with zero CAC may warrant earlier repeat CAC scans. Conversely, several studies question the relationship between EFV and CAC [45–48]. For example, in 380 patients from the CORE320 MultiCenter Study, there was no significant association between EFV and CAC score [36]. Possner similarly evaluated 275 patients who underwent SPECT-MPI with CT for attenuation correction and found EFV did not significantly predict adverse cardiac events in multivariable analysis once CAC scores were known [37].

Cost-Effectiveness

There are relatively few recent studies investigating the cost-effectiveness associated with CAC. An important distinction to note is cost-efficacy, which pertains to costs under a pre-specified environment such as a randomized controlled trial, differs from cost-effectiveness, which reflects real-world scenarios. Our group directly addressed cost-effectiveness in a 2015 modeling study involving statin-naïve MESA participants with intermediate Adult Treatment Panel (ATP) III FRS ranging 6–20%, and LDL-C levels <160 mg/dL [49••]. We compared three scenarios: (1) a "treat-all" strategy with moderate statin therapy; (2) treatment with moderate statin therapy based on ATP III Guidelines; and (3) further risk-stratifying with CAC prior to treatment (moderate-intensity statins for CAC scores 1–100 and high-intensity statin therapy for CAC scores >100). Stratifying by CAC averted more adverse cardiac events compared to a "treat-all" strategy (5.1 vs 3.9 events per 1000 patients over 5 years) given the ability to selectively treat higher CAC scores with more intensive therapy. Furthermore, only treating those with positive CAC values was the most cost-effective strategy compared to the alternative options when considering adverse reactions to statins and the disutility of statin therapy in truly low-risk populations. The presence of CAC allowed for the identification of an appropriate cohort in which statins would be beneficial, with intensity of therapy linked to degree of CAC.

Demir and Lubbers both investigated the cost-effectiveness of an imaging strategy incorporating CAC compared to functional testing for the diagnosis of CAD. In Demir's study, patients in the functional testing arm underwent exercise tolerance testing and, if positive, coronary angiography. In the imaging pathway, those with low pre-test probability for CAD underwent CAC scanning and, if positive, CCTA. Those with intermediate pre-test probabilities underwent either CCTA or MPI as initial tests. Overall, those in the imaging pathway had lower average costs ($750 +/− $725) compared to those in the functional pathway ($875 +/− $758), with costs in the former group driven down by the low cost of CAC scanning [50]. The CRESCENT trial similarly had an imaging arm, consisting of CAC and subsequent CCTA for CAC scores between 1 and 400, and a functional arm consisting largely of exercise-ECG testing or MPI. In the imaging arm, less downstream testing was ordered with a diagnosis of CAD established earlier, resulting in significantly fewer costs (369€ vs 440€) [51].

Knowledge Gap 3: Disease-Specific Correlations

As previously discussed, there is often discordance between presence of CAC and absence of traditional cardiovascular risk factors, suggesting that other, non-traditional risk factors may directly contribute to the development of subclinical atherosclerosis. CAC scoring can be used to help identify these risk factors that may independently have a causal relationship with atherosclerosis or confound traditional risk factors [52]. The identification of these factors can subsequently help further personalize CVD risk assessment by identifying individuals who may warrant CAC scanning to evaluate risk even in the absence of traditional risk factors (Table 2).

Depression

Depression is often linked with atherosclerosis development given an increased inflammatory state leading to neuroendocrine and autonomic nervous system alterations [53, 54]. Santos used the Clinical Interview Schedule-Revised (CIS-R) score in multivariable regression and found an OR of 1.11 for the development of CAC in those with positive CIS-R scores. Janssen used the Center for Epidemiological Studies Depression Scale (CES-D) in the Study of Women's Health Across the Nation Heart cohort and found those with persistent depressive symptoms defined as at least three separate major depressive episodes were more likely to develop CAC (OR 2.20) compared to those without persistent depression (Table 2) [53, 54]. However, these results were not replicated in older cohorts >80 years of age when assessing the associations of depression (and dementia) with CAC [55]. As such, the association of CAC with depression may be age dependent.

Table 2 Knowledge gap III: representative studies using CAC to identify non-traditional cardiovascular risk factors

Category	Author (study population)	Pertinent result
Neurologic		
Depression	Santos [53] (ELSA-Brazil)	OR for CAC: 1.11 for 1-SD increase in CIS-R
Depression	Janssen [54] (Women's Health)	OR for CAC: 2.20 with >3 depressive episodes as determined by CES-D
Cognition	Kuller [55] (CV Health-Cognition)	Dementia rate: 102/1000 PY vs 31/1000 PY for CAC > 400 vs CAC = 0
Environmental		
Pollution	Kaufman [56] (MESA-Air)	CAC progression: 4.1 units/y per 5 μg $PM_{2.5}/m^3$ increase in particulate matter
Pollution	Dorans [57] (Framingham)	CAC progression: −0.8 units/y ($p > 0.05$) per $PM_{2.5}/m^3$ particulate matter change
Psychosocial	Juonala [58] (Young Finns)	OR for CAC: 0.83 for 1-SD increase in favorable psychosocial score
Neighborhood	Wing [59] (MESA)	CAC progression: −19.99 units for 1-SD increase in food density stores
Rheumatologic		
Psoriasis	Hjuler [60]	CAC > 0 distribution: 29.8% in psoriasis patients vs 15.2% in control patients
Lupus	Kiani [61] (MESA)	Prevalence ratio for CAC: 2.8 in those with lupus
Gastroenterologic		
NAFLD	Al Rifai [62] (MESA)	OR for CAC: 1.37 in those with NAFLD
Diet	Miedema [63] (CARDIA)	OR for CAC: 0.74 in highest tertile of fruits/vegetable consumption
Diet	Miller [64] (MESA)	Progression ratio for CAC: 0.72–0.74 for >1 cup of tea consumption
Endocrine		
Metabolic syndrome	Kim [65]	HR for CAC progression: 1.32 in those with metabolic syndrome
Testosterone	Basaria [66] (TEAAM)	CAC progression: 41.4 units/y (placebo) vs 31.4 units/y (testosterone) ($p > 0.05$)
Renal		
Lab values	Roy [67] (Multicenter AIDS)	OR for CAC: 1.30 per 10 ml/min/1.73 m^2 decrease in GFR <90 ml/min/1.73 m^2
Lab values	Kim [68] (CRONOS-ADM)	CAC severity: 241.3 units (−albuminuria) vs 429.1 units (+albuminuria)
Cardiovascular		
A. fib	Chaikriangkrai [69]	HR for CAC: 1.60 in those with atrial fibrillation
A. fib	Uehara [70]	OR for CAC: 2.03 in those with CHADS2 score >2
LV dysfunction	Maragiannis [71]	OR for CAC: 13.82 in those with diastolic dysfunction
ED	Feldman [72] (MESA)	OR for CAC > 100: 1.43 in those with erectile dysfunction
Oncologic		
	Whitlock [73] (MESA)	RR for CAC: 1.41–1.54 in those with cancer based on gender
Infectious disease		
HIV	Bahrami [74] (Multicenter AIDS)	CAC prevalence: 52.5% (HIV+ men) vs 52.7% (HIV− men)
HIV	Chow [75] (Hawaii Aging)	RR for CAC: 1.20 in those with HIV

OR odds ratio, *CAC* coronary artery calcium, *NAFLD* non-alcoholic fatty liver disease, *HR* hazard ratio, *RR* relative risk, *ED* erectile dysfunction, *A. fib* atrial fibrillation, *PY* person-years, *SD* standard deviation, *CIS-R* Clinical Interview Schedule-Revised, *CES-D* Center for Epidemiological Studies Depression Scale, *y* year

Environmental Risk Factors

A recent MESA-Air Pollution study investigated 6795 participants and found a CAC increase of 4.1 Agatston units per year for every 5 μg $PM_{2.5}/m^3$ increase in air particulate matter [56]. However, no such association was found in a study of 3399 Framingham Offspring and Third-Generation Cohort participants (Table 2) [57].

Further studies are therefore needed to define the relationship between air quality and coronary atherosclerosis.

Prior data have suggested that environmental psychosocial factors including stress and life events may herald atherosclerotic development. Juonala investigated the relationship between psychosocial factors in childhood and subsequent development of adulthood CAC in 311 participants from the Cardiovascular Risk in Young Finns Study. All participants

were graded in binary fashion with respect to six psychosocial domains including socioeconomic factors and family structure. These binary terms were then aggregated into a composite score. The authors found an inverse relationship between increasing composite scores (more favorable) and presence of CAC (0.85 probability for CAC for each standard deviation change in composite score) [58].

When assessing neighborhood characteristics and the association with atherosclerosis in MESA participants followed for over a 12-year period, an inverse association was found between increases in neighborhood healthy food store density and decreases in CAC (−20 decrease in Agatston units for every 1 standard-deviation increase in healthy food store density) [59]. No other significant associations were found between CAC and other neighborhood features such as recreational center density and walking environment.

Rheumatologic Risk Factors

Cross-tabulation studies suggest a higher prevalence of CAC in patients with rheumatologic diseases: upwards of 30% of psoriasis patients, 45% of atopic dermatitis patients, and 58% of lupus patients have CAC compared to 15–20% CAC rates in propensity-matched control groups (Table 2) [60]. Interestingly, when comparing lupus patients with CAC to controls with CAC, there was no significant difference in median Agatston scores, suggesting lupus is likely one of many initial risk factors leading to the same clinical endpoint of atherosclerosis [61]. However, despite the increased prevalence of atherosclerosis in rheumatologic diseases, the 2013 ASCVD risk estimator only accurately classifies ~40% of patients with rheumatoid arthritis to high-risk groups despite the presence of CAC. CAC may therefore be particularly valuable for improving risk assessment in these patients.

Gastroenterological Risk Factors

In a retrospective study of 4731 adults without CVD over 3.9 years, Sinn and colleagues found the presence of non-alcoholic fatty liver disease (NAFLD) was an independent predictor of CAC development and progression [76]. In 3976 participants from the MESA, NAFLD was significantly associated with inflammation as measured by hsCRP >2 (OR 1.47) and presence of CAC >0 (OR 1.37) [62]. Similar associations were found in the Consortium for Preclinical Assessment of Cardioprotective Therapies Study, Framingham Heart Study, and Kangbuk Samsung Health Study (Table 2) [77, 93]. However, in an older population with a mean age of 68 years largely consisting of white adults, Jacobs found no association between hepatic steatosis and either development or progression of CAC. In fact, in the study's 5-year follow-up, the prevalence of NAFLD decreased while mean CAC increased [78].

With regards to dietary intake, a CARDIA analysis found that baseline consumption of fruits and vegetables was associated with lower odds of CAC in a graded response [63]. We recently reported a similar protective association in tea drinkers in MESA [64]. Harmful associations of dietary intake with CAC were found with choline and betaine, egg consumption, sugar-sweetened carbonated beverages, increased dietary glycemic index, and calcium supplementation.[79–80, 94–95].

Endocrine Risk Factors

Our group previously reviewed the association between diabetes and CAC [81]. Here, we review other endocrine risk factors contributing to atherosclerosis. Kim followed 2426 persons who had baseline and follow-up CAC scans, of whom 825 were diagnosed with metabolic syndrome (Table 2). At baseline scan, individuals with metabolic syndrome had higher CAC scores. The presence of metabolic syndrome was further independently associated with CAC progression (HR 1.32) [65].

In the Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) randomized controlled trial, 308 men with low testosterone levels were enrolled, of whom 156 received 7.5 g of 1% testosterone in the interventional arm and 152 men were allocated to the control arm with placebo. There was no significant change in CAC progression between the two arms: the interventional arm had an increase in CAC by 31.4 Agatston units per year compared to 41.4 Agatston units/year in the placebo arm [66].

Renal Risk Factors

Patients with end-stage renal disease have unique risks with atherosclerosis development due to uremia-induced inflammation, abnormal processing of calcium and phosphate, and mineral deposition in medial layers of arteries rather than intimal layers, thereby altering underlying plaque stability [67, 68, 82, 83]. Whereas decreased glomerular filtration rates, presence of microalbuminuria, and increased density of plaques (Agatston score divided by plaque volume) are significantly associated with CAC in patients with advanced renal failure (Table 2) [67, 68, 84], patients with end-stage renal disease may be more prone towards developing non-calcified plaques.

Moody used a combined imaging approach with CAC and MPI. While abnormal perfusion (HR 5.32) and mild-moderate CAC (HR 3.55) were associated with a composite outcome of death and myocardial infarction in univariate analysis, only abnormal perfusion retained a significant association in multivariable analysis [82]. Likewise, Winther found superiority in a CCTA/SPECT combination compared to CACS/SPECT in diagnosing obstructive

CAD in patients with end-stage renal disease, suggesting standard CAC screening in renal dysfunction may not appropriately capture true atherosclerotic risk [83].

Cardiovascular/Vascular Risk Factors

Patients manifesting with arrhythmias or heart failure often undergo a workup for the presence of obstructive CAD. Chaikriangkrai identified 860 patients with no known history of CAD, of whom 430 were diagnosed with atrial fibrillation. The authors found in multivariable analysis that atrial fibrillation was significantly associated with CAC (HR 1.60) [69]. More importantly, 19% of the atrial fibrillation group qualified for anticoagulation when including findings of CAC as evidence of vascular disease in the CHADS2-Vasc score. Furthermore, those with CHADS2 scores of ≥2 are 2.03 times as likely to have calcified plaque present on imaging (Table 2) [70]. These studies suggest (1) a potential use for CAC scanning in reducing stroke risk in a relatively high-risk population and (2) those with higher CHADS2 scores may be considered for additional testing to evaluate for atherosclerosis, which may have implications on downstream treatment.

The association between CAC and left ventricular diastolic dysfunction was assessed by Maragiannis; 52 out of 114 patients in this study had diastolic dysfunction noted on echocardiogram and all patients underwent myocardial perfusion imaging with no evidence of ischemia. In multivariable analysis, diastolic dysfunction was an independent variable (OR 13.82) for predicting CAC >0 [71]. The authors suggested that patients with diastolic dysfunction but with no known CV history and no inducible ischemia noted on MPI should probably undergo further evaluation for atherosclerosis as a possible etiology of left ventricular dysfunction.

Other, extra-cardiac vascular diseases were also associated with CAC. A study of 1862 men from the MESA—of whom 839 had symptoms of erectile dysfunction (ED)—found that those with ED were more likely to have CAC >100 (36.4% of ED patients compared to 17.2% controls). In multivariable analysis, CAC >100 was significantly associated with ED (OR 1.43) [72].

Oncologic Risk Factors

Whitlock investigated 3122 MESA participants free from baseline CVD and cancer. Over a 10-year follow-up, 135 participants developed cancer, with an average of 4.2–4.8 year gap between diagnosis and repeat CAC scan based on sex. After adjusting for traditional cardiovascular risk factors, those with cancer had 29–32% increased risk of developing new CAC (relative risk [RR] = 1.41–1.54) compared to control patients without cancer. When isolating participants with baseline CAC, there was no difference in the progression of CAC regardless of cancer status [73].

To expand CAD screening in women, several studies have investigated the association between breast artery calcification (BAC) on mammography and presence of CAC. CAC associations have been noted with BAC score, number of BAC vessels, maximum BAC length, and maximum BAC density [85–87]. Taken together, these data suggest the potential for large-scale CVD personalized risk assessment in asymptomatic women by using cancer screening (mammography) as a gateway for downstream CAC scanning.

Infectious Disease (HIV) Risk Factors

Patients with HIV are at increased risk for cardiovascular events due to the presence of traditional cardiovascular risk factors and a chronic inflammatory state, even in those patients who are virologically suppressed [74, 75, 88]. A study of 923 HIV-positive men in the Multicenter AIDS Cohort Study found significantly higher levels of circulating inflammatory markers compared to control patients without HIV. However, there was no significant difference in CAC presence or severity when comparing the HIV-infected and HIV-uninfected groups [74]. Different markers of HIV status including viral load, CD4 count, and length of HIV infection also did not correlate to the presence or severity of CAC [75].

A subsequent analysis in the Multicenter AIDS Cohort Study found that HIV-infected men with baseline CAC scores of zero were more likely to have non-calcified coronary plaque (prevalence ratio 1.31) when taking into account traditional cardiovascular risk factors [88]. Therefore, despite an underlying inflammatory condition, CAC scans may be an insufficient assessment of the true burden of coronary atherosclerosis given a propensity for non-calcified plaque formation in certain high-risk subgroups. CAC scanning if used should thus be interpreted more cautiously in this population.

Conclusions: Remaining Knowledge Gaps

Literature from the past 2 years further supports CAC as a strong risk marker with an ability to re-classify risk in a variety of populations. Depending on the population, CAC may help downgrade risk ("de-risk") such that pharmacotherapy may be avoided or it may help identify high-risk populations that may warrant more aggressive risk personalization and downstream therapy [89, 90]. While multiple potential avenues to reduce radiation are available and cost-effectiveness analyses are encouraging, further studies are still necessary to clarify optimal patient selection for CAC scanning considering the interplay between CAC and other imaging modalities in risk personalization algorithms.

With respect to remaining knowledge gaps, the debate for and against randomized controlled trials evaluating outcomes directly tied to CAC has been discussed elsewhere [91]. Aside

from testing CAC itself in a randomized trial, it may also be an untapped tool to enrich future randomized controlled trials exploring the comparative effectiveness of lipid-lowering therapies, or cost-efficacy and cost-effectiveness of different treatment options [92]. As an example, PCSK9 inhibitors have yet to receive FDA approval for primary prevention in high-risk individuals who are intolerant to statin therapy. The annual treatment costs with PCSK9 inhibitors based on 2015 data exceed $14,000 and identifying individuals as "high-risk" using only ASCVD risk estimation from the PCE may not be cost-effective. As outlined in this review, there is marked heterogeneity in atherosclerotic burden across ASCVD risk groups; therefore, exploring the cost-effectiveness of PCSK9 inhibitors in statin-intolerant patients with CAC scores >100 or >400 in a randomized controlled trial could help ensure the enrollment of a more uniformly high-risk population that may benefit the most from intervention.

Compliance with Ethical Standards

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