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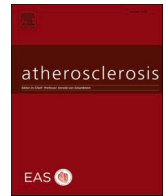
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## Review article

## Utilizing coronary artery calcium to guide statin use

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## ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death worldwide, and accounts for over 30% of annual global fatality. Coronary artery calcium (CAC) screening, a highly distinct marker of coronary atherosclerosis, serves as an important arbitrator of atherosclerotic cardiovascular disease (ASCVD). Particularly in asymptomatic individuals, CAC testing offers a model for initiating or prolonging preventative statin therapies and subsequently up- or down-risking of patients.

Though recent 2018 ACC/AHA Guidelines on Blood Cholesterol recommend CAC as an arbitrator of statin use, it remains uncertain whether these recommendations have been universally followed. Thus, we present a thorough discussion about CAC as an important determinant of ASCVD risk. In this regard we highlight the key points behind coronary artery calcium scoring, as a critical platform for stratifying risk and guiding future preventative treatments.

This review paper supplies a background for the 2018 Cholesterol Guidelines: the rationalization behind CAC as a crucial arbitrator of cardiovascular risk. This paper will first (1) outline the role of CAC in *reclassifying ASCVD risk*. Next, it will (2) discuss studies that illustrate CAC's markedly novel *reduction in the number needed to treat (NNT)* to ameliorate one major cardiac event. Being years removed from 2018 Guidelines provides this paper the lens to (3) elucidate upcoming *value-based advantages, cost effectiveness, and patient adherence* brought by CAC. Last, this paper will also (4) extend the utility of CAC beyond that of the general population, and (5) discuss pertinent limitations brought by CAC score. By summarizing the framework behind recent cholesterol guidelines for ASCVD risk assessment, this review will address the debate of use of CAC for both the clinical setting and preventative therapy applications.

## 1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, and accounts for over 30% of annual global fatality. This paper will discuss at length one approach for adjudicating cardiovascular risk: coronary artery calcium (CAC) screening. A highly distinct marker of coronary atherosclerosis, CAC is widely available and exhaustively studied in the field of cardiovascular medicine [1]. Significantly, coronary calcium serves as an important arbitrator of atherosclerotic cardiovascular disease (ASCVD), and it accounts for both coronary heart disease and stroke.

Particularly in asymptomatic individuals, CAC testing offers a model for initiating or prolonging preventative statin therapies and subsequently up- or down-risking of patients. It enables the risk stratification of atherosclerotic cardiovascular disease. In the setting of statin's overwhelmingly well-established benefits to CVD morbidity and mortality, lipid-modifying therapy marks a paradigm shift for the targeted,

individualized treatment of cardiovascular disease. Uniting coronary artery calcium risk stratification with cholesterol-modifying treatment truly empowers optimal primary prevention of ASCVD.

Traditionally, clinical guidelines for the primary prevention of atherosclerotic cardiovascular disease are predicated upon absolute risk, cardiovascular risk factors, and age. These determinants have long been utilized to estimate an individual's risk for incident ASCVD and subsequently guide the institution of pharmacotherapy—specifically lipid management and antiplatelet therapy [2]. However, as a result of varied clinical recommendations, the use of statin therapy in lipid management remains a challenge to both patients and clinicians. Though guidelines all approve statin treatment for primary prevention in a population at sufficient absolute risk, they do differ in consensus regarding the risk threshold for initiation and intensity of statin use [3]. To that end, coronary artery calcium (CAC) scoring has been mandated by recent guidelines as a method to guide shared clinician-patient decision making and to classify statin use for intermediate-risk patients [3].

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In 2018, the ACC/AHA reformed the Guidelines on Management of Blood Cholesterol to advocate CAC as an appropriate adjudicator of statin use, as illustrated in Fig. 1 [4]. For intermediate-risk individuals with a coronary calcium score of zero and lack of higher risk conditions (i.e. diabetes mellitus, family history of premature CHD, smoking), guidelines suggest withholding statin therapy and reassessing in 5–10 years. With a calcium score of 1–99, guidelines state that statin therapy can be reasonably initiated for individuals  $\geq 55$  years of age. Last, if CAC is either  $\geq 100$  or  $\geq 75$ th percentile, one can initiate statin therapy for any age group [4].

This image was published in 2018 by the American College of Cardiology and American Heart Association Task Force on Clinical Practice Guidelines. The figure elucidates the primary prevention guidelines for assessing ASCVD risk. Notably, the blood cholesterol guidelines discuss CAC as an arbitrator of statin use. CAC = 0 suggests withholding statin therapy, while CAC = 1–99 favors statin for individuals over 55 years. Lastly, CAC of over 100 requires initiation of statin therapy [4].

These recent guidelines recommend CAC as a definitive advancement, rather than a supplement to traditional risk factors. However, the 2018 ACC/AHA recommendations provide only minimal justification for CAC reliance. Hence, a thorough discussion about CAC as an important model for stratifying ASCVD risk is absolutely vital. The true value of CAC recommendations remains under-appreciated in clinical practice, and thus this paper will reaffirm the rationale. In this regard the current manuscript will highlight key points behind coronary artery calcium scoring, as a critical platform for stratifying risk and guiding future preventative treatments.

In summary, this review paper will for the first time supply a detailed background for the 2018 Cholesterol Guidelines: the rationalization behind CAC as a crucial arbitrator of cardiovascular risk. This paper will first (1) outline the role of CAC in reclassifying ASCVD risk. Next, it will (2) discuss studies that illustrate CAC's markedly novel reduction in the number needed to treat (NNT) to ameliorate one major cardiac event.

Being years removed from 2018 Guidelines finally provides this paper the lens to (3) elucidate upcoming value-based advantages, cost effectiveness, and patient adherence brought by CAC. Last, this paper will also (4) extend the utility of CAC beyond that of the general population, and (5) discuss pertinent limitations brought by CAC score. By summarizing the framework behind recent cholesterol guidelines for ASCVD risk assessment, this review will address the debate of use of CAC for both the clinical setting and preventative therapy applications.

## 2. Background

### 2.1. The benefits of lipid-lowering therapy

First, a review of the many benefits of lipid therapy is essential to fully understand the clinical utilization and rationale of CAC in blood cholesterol management. Extensive evidence supports the mortality and morbidity improvements of lipid pharmacotherapy such as statin treatment, and even indicates statin's advantages for alternate high-risk CVD syndromes. The PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial, for instance, demonstrated that in patients with acute coronary syndromes, aggressive lipid-lowering via atorvastatin 80 mg/day safeguarded against major CVD events significantly more than did moderate lipid-lowering via pravastatin 40 mg/day [5]. Event rates were 26.3% (537/2063) in the standard dose pravastatin group versus 22.4% (464/2099) in the high-dose atorvastatin group ( $p = 0.005$ ). This yielded a significant 16% relative risk reduction, favoring high-dose atorvastatin 80 mg (CI, 5%–26%) [5]. These findings overwhelmingly support high-dose statin therapy and lowering LDL-C (low density lipoprotein cholesterol) concentrations below current target levels, to improve defense against future CV events [5].

An extensive list of trials similarly evidences the immense benefit of statin therapy. The Treating to New Targets (TNT) Study indicated that a primary event occurred in 10.9% of patients receiving 10 mg

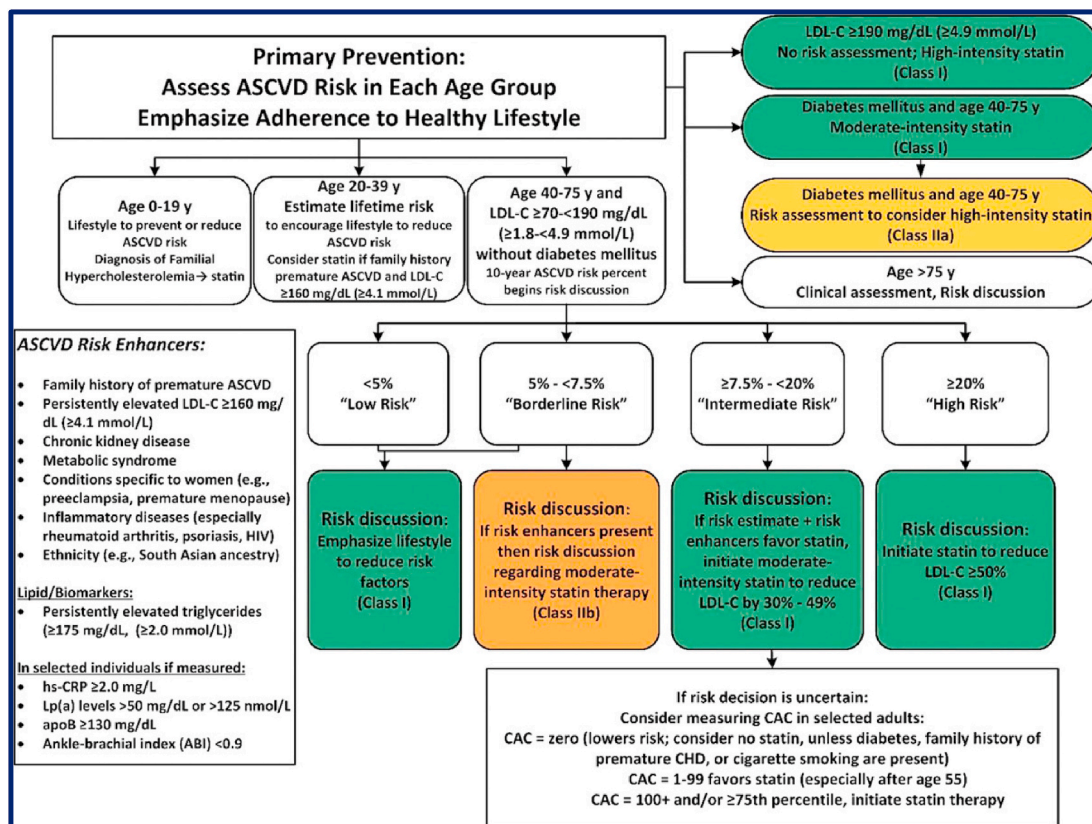


Fig. 1. ACC/AHA guidelines recommend CAC to determine statin therapy.

atorvastatin, compared to only 8.7% in those receiving 80 mg atorvastatin [6]. This represents a 22% relative reduction in risk (hazard ratio, 0.78; 95% confidence interval, 0.69 to 0.89;  $p < 0.001$ ) [6]. Again, intensive lipid-lowering therapy yielded overwhelming advantage; 80 mg of atorvastatin in those with stable CHD contributed significant benefit beyond 10 mg of daily atorvastatin treatment [6]. Likewise, the JUPITER Trial (Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP) illustrated the power of aggressive lipid-lowering therapy in primary CVD prevention. The JUPITER Trial demonstrated that rosuvastatin reduced LDL-C by 50% and hsCRP (high sensitivity C-reactive protein) by 37% [7]. With a 44% reduction in cumulative incidence of myocardial infarction (MI), stroke, revascularization, and CV death, rosuvastatin significantly decreased the outcome of major cardiovascular events in healthy, non-hyperlipidemia patients [7].

Significant reductions in all-cause mortality, major adverse cardiovascular events (MACE), and revascularization procedures underline the immense benefits of long-term statin therapy for primary prevention (Fig. 2) [8]. In addition to precluding myocardial infarction, stroke, and death, statin treatment minimizes more invasive angioplasties, stents, and bypass surgeries. Importantly, these statin-based improvements in patient health are significant regardless of cardiovascular risk: even for individuals with less than 1% yearly risk of a MACE [8].

This image was published in 2013 by the American College of Cardiology and American Heart Association Task Force on Clinical Practice Guidelines. The figure elucidates the summary of statin initiation recommendations for the treatment of blood cholesterol to reduce ASCVD risk. Statin therapy is recommended for patients at increased ASCVD risk who will experience a net benefit with regard to risk decrease and any adverse effects [9].

## 2.2. Coronary artery calcium testing

Next, this paper will review the basics of coronary artery calcium testing to reinforce an understanding of CAC screening for blood cholesterol management.

CAC testing is a noninvasive, direct measure of coronary artery atherosclerotic plaque burden. Measured via non-contrast cardiac computed tomography (CT), CAC is a robust indicator of future CHD, stroke, and ASCVD events in addition to non-CVD events [1]. Utilizing gantry rotation, multidetector CT scanners reconstruct hundreds of uniquely angled snapshots into a complete image. With high detector counts and increased gantry speed, even nongated studies can provide quantitative coronary artery calcium via Agatston scoring. Requiring only 10–15 min of total room time at 1mSv of radiation, nongated CT screening is comparable to gated CT and does not call for contrast agents [1].

CAC screening by CT enhances the accuracy of risk scores for predicting ASCVD outcome and offers a means to optimize patient selection for statin treatment [10,11]. Importantly, CAC is predictor independent of traditional ASCVD risk estimates, which are strongly skewed toward chronological rather than arterial age [3]. Notably, Detrano et al.'s landmark paper determined that CAC functions as more than a strong predictor of incident CHD. In a multi-ethnic cohort, coronary artery calcium actually provides predictive value beyond that of standard coronary risk factors [12]. Meanwhile, CAC screening also bypasses an isolated risk assessment (Fig. 3). In place, calcium scoring captures direct atherosclerosis measurement and integrates a lifetime of risk exposure. It facilitates risk upgrading in younger patients when extensive CAC presents, and promotes de-risking of older individuals with lack of calcium [3].

Studies which fail to incorporate CAC, a well-established predictor of atherosclerosis, rely solely upon inclusion criteria such as hypertension, elevated CRP, or multiple risk factors. These clinical trials therefore have a higher likelihood of incorporating individuals without ASCVD, who would likely not benefit from statin use [13]. Studies which lack CAC testing are therefore underpowered to demonstrate improvement in patients on statin intervention [13]. Because these clinical trials cannot accurately predict presence of ASCVD without supplementary CAC testing, they decrease the overall efficacy of the participants in the study.

By offering an invaluable tool to refine predicted ASCVD and mortality risk, the presence or absence of CAC is vital for adjudicating

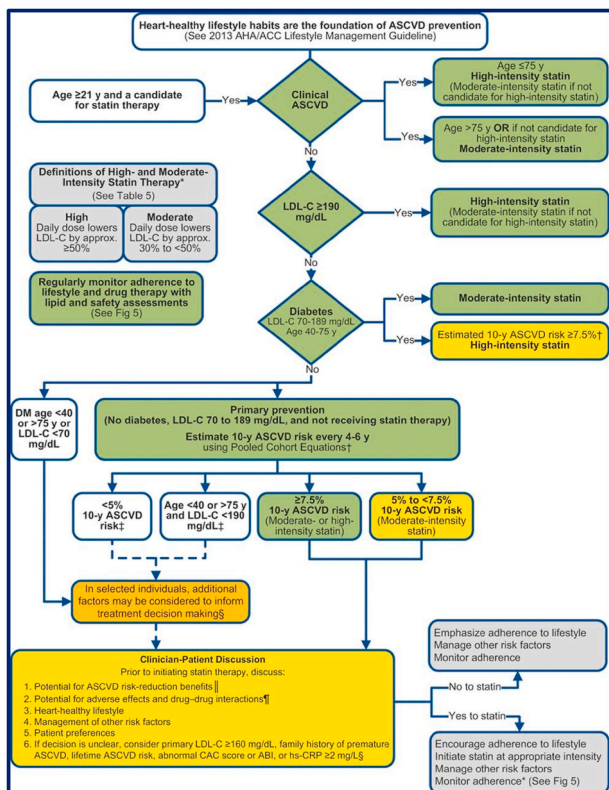


Fig. 2. ACC/AHA statin initiation guidelines to reduce ASCVD risk.

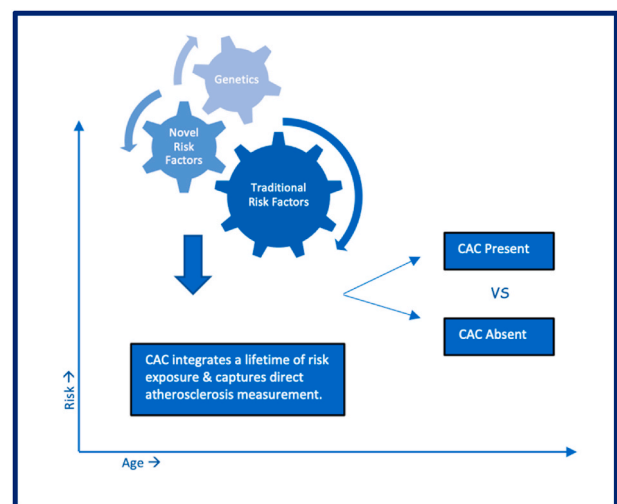


Fig. 3. CAC as an integrator. The coronary artery calcium score (CAC) bypasses isolated risk assessment. Instead, CAC directly measures atherosclerosis and integrates a lifetime of risk exposure.

pharmacotherapy usage. Thus, CAC is put forward as such by the 2018 Guidelines on Blood Cholesterol Management.

### 2.3. Biochemical aspects of atherosclerosis

With the early identification of high risk coronary plaques and the 2018 Guidelines for CAC, it is also vital to understand vascular calcification and the pathophysiology of atherosclerosis. The first stage of atherosclerosis includes the deposition of lipoproteins in the sub-endothelial matrix [14]. This is subsequently followed by monocyte migration to the site [14]. Monocytes then differentiate into macrophages, and they begin lipoprotein phagocytosis [14]. After the lipoprotein-cholesterol complex oxidizes, the now lipid-laden macrophages (foam cells) begin to die [15]. Abnormal apoptosis of these macrophages releases toxic material, activates T cells, and triggers further inflammation [16]. Next, smooth muscle cells begin to proliferate and migrate to the intima, where they secrete collagenous material and form a fibrous cap [14].

In high risk lesions, the lipid pools tend to join and grow into necrotic cores [14]. This lesion may be converted into fibroatheroma [17] if there is further deposition in the necrotic core along with macrophage infiltration [14]. With the influence of vascular endothelial growth factor, placental growth factor, and oncostatin M [18], the lesions become more unstable and angiogenesis occurs [14,19]. If the fibrous cap is thick, however, the plaque becomes stable [14]. Myocardial infarction is associated with thin-cap fibroatheroma and, depending on coronary hemodynamics and the patient's thrombotic state, can lead to either lesion healing or thrombi formation [14,20].

It is this necrotic core of the atheroma that creates a site for calcification development [14]. Impaired macrophages and vascular smooth muscle cells release extracellular vesicles, on which the deposition of amorphous calcium phosphate or crystalline hydroxyapatite occurs [14, 21]. This balance of pro- or anti-calcification factors determines whether calcification occurs and whether unstable, microcalcified plaque converts to stable, macrocalcified plaque [14].

### 2.4. Radiological detection of atherosclerosis

Radiological detection and imaging modalities are crucial for directly measuring atherosclerotic burden, identifying high risk coronary plaques early, and offering a more personalized approach than risk factor-based calculations. While CAC scoring indicates the presence and degree of calcified coronary plaque, coronary CT angiography (CTA) is an imaging modality able to visualize both calcified and non-calcified lesions [22]. CTA can also assess luminal stenosis, plaque burden and progression, but it is typically only completed for patients with symptoms that indicate coronary heart disease. In contrast, due to its noninvasive and lower radiation requirement, CAC is most commonly performed for risk assessment in asymptomatic patients [22].

As mentioned above, non-calcified plaque characterization is typically based on coronary computed tomographic angiography. Non-calcified lesions can be further divided into fibrous, fibrofatty, or low attenuation based on Hounsfield Unit (HU) [14]. With regard to attenuation pattern, noncalcified plaques may also be categorized as homogeneous or heterogeneous [14]. Radiologically, heterogeneous plaques can be further divided into having or lacking the Napkin-ring sign (NRS). NRS plaques have low attenuated centers, due to their lipid-rich and rupture-prone necrotic core [14,23]. High-risk calcification is visualized on CCTA as “spotty” calcification. This is a coronary CTA marker of histological microcalcifications (<3 mm of calcified plaque and >130 HU density surrounded by noncalcified plaque) [14,24]. Of note, visualized “positive remodeling” refers to high-risk plaque with a large lipid core that grows outwards but does not cause luminal narrowing [14].

### 3. CAC in reclassifying ASCVD risk

With a thorough understanding of the pathophysiology and radiological detection of atherosclerosis, let us transition back to CAC: an independent predictor of ASCVD.

Here, this manuscript examines the role of coronary calcium in reclassifying ASCVD risk (Fig. 4), as put forward by recent cholesterol guidelines. Although coronary artery calcium has been broadly verified as a predictor for clinical events, most studies examine CHD rather than ASCVD events. Moreover, they do so on only a short-to intermediate-term follow-up basis. In addressing both of these concerns, the Multi-Ethnic Study of Atherosclerosis (MESA) cohort established a 10-year association of coronary artery calcium with ASCVD events [25]. This population-based sample of healthy adults aged 45–84 years allowed for the evaluation of CAC event variability with age, sex, or race/ethnicity [26]. This Budoff et al. [25] study was the first to determine a strong 10-year predictive ability of CAC score cut points, with the same magnitude of effect in all age groups, sexes, and races. Moreover, this paper demonstrated that CAC is similarly predictive of ASCVD in both on- and off-lipid-lowering therapy patients. To that end, the MESA cohort study eliminated prior concerns regarding CAC's non-predictive function for statin patients; statin-causing micro-calcifications are nonsignificant [25].

Coronary artery calcium (CAC) scoring guides treatment decisions and serves as an arbitrator for ASCVD risk.

Regardless of sex, race/ethnicity, or age, CAC is strongly correlated with major adverse cardiovascular events. Budoff et al. CAC cutpoints are therefore increasingly relevant to the clinical setting. With their inclusion of MESA's entire baseline pool (over 6800 participants), the study's analysis authenticates CAC cutpoints for predicting CHD risk in a general population [25]. Research indicates that one such cutpoint—zero CAC, for instance—yields an extremely low-cardiovascular event rate [27]. With about 50% baseline zero CAC and mostly <5% over the 10-year follow-up, MESA elucidates this negative risk factor's potential to ‘de-risk’ the appropriate subjects [25]. In essence, a CAC score of zero yields the most precise downward risk classification; it prompts the suggestion that a patient reconsider lifelong statin

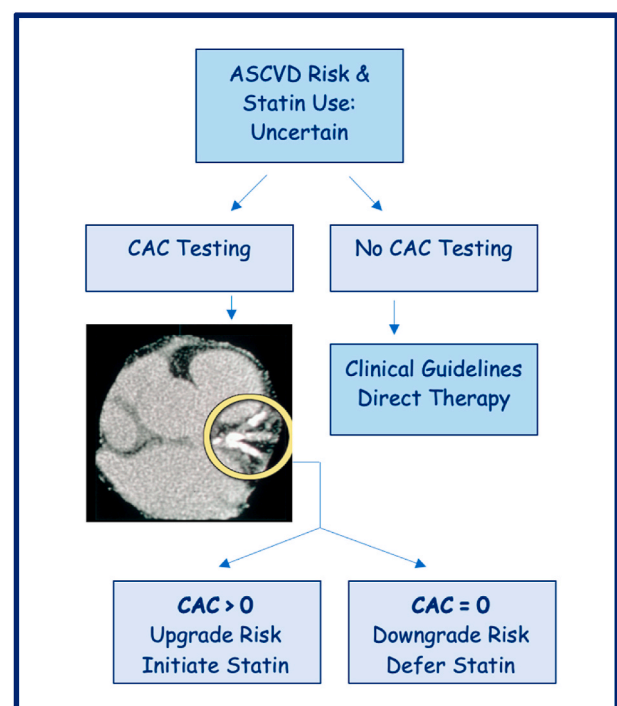


Fig. 4. CAC as a grader or risk.

treatment if otherwise uncertain.

Precluding statin therapy when unnecessary maximizes cost-effectiveness, and coronary artery calcium screening successfully re-classifies asymptomatic patients into low-, intermediate-, and high-risk groups. A zero score carries a low 10-year risk, and it allows for possible down-stratification of a patient's risk based on global risk assessment—regardless of age group, gender, or ethnicity. It is recommended that they repeat CAC screening in 5–10 years [25]. In contrast, a score of  $\geq 100$  represents a minimum of 7.5% 10-year risk of ASCVD—for which patients may qualify for preventative statin therapy [25]. With these determinants, Budoff et al. evidences a 0 CAC scoring value as an invaluable marker for refining ASCVD risk assessment.

Also important to consider is Nasir et al.'s 2015 study in MESA. This study directly examined the implications of CAC testing among statin candidates, according to then-current ACC/AHA Cholesterol Management Guidelines. 2014 cholesterol guidelines accentuated the importance of ASCVD risk, derived only from Pooled Cohort Equations, in classifying candidates for statin therapy [28]. The ACC and AHA recommended statins for an estimated 10-year ASCVD risk of  $\geq 7.5\%$ , and considered statins for an estimated risk of 5%–7.5% [28]. Without CAC as a re-classifier, it was estimated that approximately 45 million adults free of established CVD were now recommended for statin treatment [29]. Nasir et al. utilized the aforementioned MESA cohort, excluding patients on lipid-lowering medication for a new total of 4758 (age  $59 \pm 9$  years; 47% males) [29]. At the time, current guidelines recommended 2377 (50%) MESA participants for moderate-to high-intensity statins, of which 41% had CAC = 0 and had 5.2 ASCVD events/1000 person-years [29]. Among the 12% of participants considered for moderate-intensity therapy, 57% had a CAC = 0, with an ASCVD event rate of 1.5 per 1000 person-years. Of participants eligible (recommended or considered) for statins, 44% had CAC = 0 at baseline and an observed 10-year ASCVD event rate of 4.2 per 1000 person-years [29].

When guidelines based on Pooled Cohort Equations alone were applied, nearly two thirds of MESA participants without CVD became eligible for statins. Yet, Nasir et al. determined that half of these candidates had no coronary artery calcium, and a lower 10-year observed ASCVD risk than the guidelines initially recommended for statin therapy [29]. This study crucially demonstrates the ramifications of CAC absence in recategorizing ASCVD risk. A CAC score of 0 effectively reclassified about 50% of candidates as *unqualified* for statin therapy. Clearly, statin eligibility is heterogeneous when CAC is not used to stratify ASCVD risk. Without coronary artery calcium as a key arbitrator for statin use, the number needed to treat to prevent 1 event increases significantly.

#### 4. CAC in reducing cardiovascular NNT

Perhaps most remarkable is coronary artery calcium's unparalleled effect upon the number of patients needed to treat (NNT). Unlike any other risk factors, high coronary artery calcium scores astoundingly reduce the NNT required to prevent one cardiovascular event. By decreasing NNT and refining ASCVD risk stratification, pharmacotherapy efficiency and proper allocation is maximized. CAC's effect upon NNT is one crucial reason for following the 2018 Cholesterol Guidelines and advocating CAC to guide preventative therapy.

##### 4.1. The JUPITER MESA study

Similar to the aforementioned MESA ASCVD study, Blaha et al. demonstrated CAC's predictive power of ASCVD outcomes in the JUPITER cohort of the MESA population [11]. Although the mean follow-up duration was only 5.8 years for a subcohort of 950 individuals—compared with Budoff et al.'s 10-year duration for MESA's full 6800 sample—this study nevertheless established CAC as promising means of further stratifying ASCVD and a method to guide statin use in clinical practice [11].

Approximately half of the MESA JUPITER sample had zero coronary artery calcium, a low event rate, and therefore an adverse 5-year NNT with rosuvastatin 20 mg of 549 patients to prevent one CHD event [11]. Most CHD events (74%), in fact, occurred in the small (25%) subset of JUPITER-eligible individuals with CAC > 100. This particular MESA JUPITER pool, in contrast, found an extremely favorable 5-year NNT: as low 24 for CHD and 19 for CVD [11]. Compared to the entire MESA JUPITER pool with NNT of 549, CAC screening-based risk stratification yielded a dramatically favorable 19 NNT: only 19 individuals required treatment to prevent one cardiovascular event.

Blaha et al.'s findings, along with those of the St. Francis Heart Trial and Walter Reed Study, underscore the importance of treatment towards individuals with measurable atherosclerosis, and permit most efficient statin allocation. This JUPITER subcohort study similarly concludes that risk refinement by CAC can effectively identify those expected to benefit most and least from statin therapy [11]. With statin use often broadened to low-risk populations, personalized and accurate assessment of absolute cardiovascular risk is vital.

##### 4.2. The St. Francis Heart Trial

Other studies similarly evidence high CAC score's ability to reduce NNT in preventing cardiovascular events. Like the JUPITER study, the St. Francis randomized trial examined the effect of lipid-lowering therapy and antioxidants upon ACSVD events in asymptomatic, high CAC patients [30]. With an average treatment duration of 4.3 years, the study evidenced a reduction of major cardiovascular events in patients on active atorvastatin therapy (incidence of 6.9%) vs. those on placebo (incidence of 9.9%) [30]. This St. Francis trial demonstrated an overall absolute risk reduction as high as 3%, and a 36 NNT.

It is important to note that participants with the *highest* coronary artery calcium scores (over 400) benefited most from statin therapy: 8.7 vs 15.0% event rate; 6.3% absolute risk reduction; 42% relative risk reduction;  $p = 0.046$ . Compared with the overall cohort's 36 NNT, this select high-CAC group yielded NNT of 16 at 4 years [13,30]. Treating as few as 16 individuals with atorvastatin 20 mg to prevent one cardiovascular event is highly significant.

##### 4.3. The Walter Reed study

Both the JUPITER MESA and St. Francis studies were available at the time of the 2018 Cholesterol Guidelines, and contributed to their decision-making. Since the guidelines were released, however, additional studies have been conducted that provide still *more* evidence of CAC in markedly reducing CV NNT. The Walter Reed Study is one notable example.

Like JUPITER MESA and St. Francis Heart, the Walter Reed trial demonstrates a markedly favorable NNT and absolute risk reduction, when employing CAC testing to guide preventative therapy. The Walter Reed retrospective study examined the impact of statins on cardiovascular outcomes, following coronary artery calcium scoring [31]. Upon comparing patients with and without statin treatment, pharmacotherapy was associated with reducing risk of major cardiovascular events *only* for patients with coronary artery calcium [31].

With these results in mind, the study did pose a few limitations. For instance, Walter Reed was an observational study rather than a randomized controlled trial. Participants were also quite healthy overall, which may limit generalizability to patients with underlying disease. Perhaps this explains the estimated lack of statin benefit in Walter Reed's diabetic participants with CAC = 0 [31].

Though these limitations are important to consider, Walter Reed's significance cannot be discounted. Of note, the impact of statin therapy on adverse cardiovascular events was significantly related to CAC severity ( $p < 0.0001$ ). Even among this relatively lower-risk population, CAC > 100 was persistently correlated with greater CVD risk reduction with statin therapy, as opposed to CAC < 100. Compared to an NNT of

100 for CAC 1–100, only 12 patients for CAC >100 would require treatment with statin therapy to prevent 1 CVD outcome [31].

Walter Reed, JUPITER MESA, and St. Francis, among others, repeatedly indicate that the presence and severity of coronary artery calcium is a promising screening marker. CAC pinpoints patients that will most likely derive long-term benefit from statin therapy, and plays an especially vital role in down-risking individuals without calcium. In turn, utilizing coronary artery calcium to guide preventative treatment yields a distinctly favorable absolute risk reduction. This lower number needed to treat strongly supports current guidelines that advocate the use of CAC screening in clinical practice and preventative therapy.

## 5. CAC cost effectiveness and value

Coupled with its vital roles in (1) reclassifying ASCVD risk and (2) reducing NNT, coronary artery calcium screening also (3) maximizes cost effectiveness, value, and patient adherence. With these three targets in mind, the rationalization behind 2018 ACC/AHA Guidelines becomes clear. Being years removed from 2018, our review now has the opportunity to examine recent guidelines' effect upon CAC cost effectiveness.

The cost value behind CAC testing resides in its reclassification of atherosclerotic cardiovascular risk. Namely, this occurs when risk stratification aligns with a change in statin therapy [32]. A calcium score of zero effectively re-allocates individuals to a lower risk category, providing patients additional cost flexibility in their treatment decisions [32].

In this regard, the *Hong* et al. study examined the effectiveness and opportunity costs of alternative treatment strategies, alongside the diagnostic performance of CAC testing. The study demonstrated that a CAC strategy is markedly more cost-effective than a treat-all strategy, especially among intermediate risk statin-eligible patients [32].

*Spahillari* et al., in turn, compared the cost-effectiveness of the 2013 ACC/AHA Guidelines (*without* recommendation for CAC screening) with the 2018 ACC/AHA Guidelines (*with* a recommendation for a non-0 CAC score to initiate statin treatment) [33]. After conducting a model-based economic evaluation, the study found that implementation of 2013 Guidelines without CAC assessment did provide a greater quality-adjusted life expectancy (0.0027 QALY). However, 2013 guidelines did so at a higher cost (\$428.97), when compared to 2018 guideline strategy with CAC assessment. This yielded a net cost-effectiveness ratio of \$158 325/QALY, which represents definitively low-value care by ACC/AHA definitions. When patients indicated a strong preference to avoid use of daily medication therapy, coronary calcium assessment yielded a markedly greater QALY and a lower cost than the CAC-blind strategy [33].

In summary, *Spahillari* et al. demonstrates the cost-effectiveness of CAC assessment-guided strategy, in place of initiating statin therapy for all individuals at intermediate risk of ASCVD. The 2018 Guidelines' placement of CAC as an arbitrator provides greater quality-adjusted life expectancy at a lower cost than non-CAC guided therapy. Calcium testing empowers patients to advocate for their own care, and it inspires clinician-patient shared decision making.

## 6. Utility of CAC: extended

This paper has focused on the use of CAC in the general population, yet its utility extends even further. Refining risk stratification with measurements of subclinical atherosclerosis is also immensely beneficial for patients with familial hypercholesterolemia, for instance. FH (familial hypercholesterolemia) is determined by inherited autosomal-dominant defects of LDL (low-density lipoprotein) metabolism [34]. Increased exposure to high concentrations of circulating LDL contributes to FH's classic indication of accelerated atherosclerosis and increased risk for premature CAD [34]. CAC, an independent predictor of ASCVD events, has been confirmed an effective ASCVD risk discriminator even for FH populations [35]. Thus, atherosclerosis imaging such as CAC

scoring helps risk stratify asymptomatic FH patients and identifies those who may benefit from more aggressive therapies [34].

## 7. Limitations

The 2018 AHA/ACC Guidelines have recommended CAC scoring to facilitate decision-making in initiating statins for intermediate-risk individuals. However, the guidelines also direct against CAC scoring among those who are high-risk and already using statins, citing minimal clinical utility [36]. Despite the many capabilities of statin therapy and CAC screening, prior studies indicate that statins may increase the rate of CAC progression [37]. *Lee* et al. demonstrated that, although percent atheroma volume advanced slower in statin users, advancement of calcified percent atheroma volume actually increased more rapidly with statin use [37].

Statin use may increase calcification in imaging and mechanistically-based studies, yet their influence upon CAC's clinically predictive value is still ambiguous [36]. To explore this potential limitation further, *Osei* et al. contrasted the risk prediction of area, volume, and density respectively—each a unique CAC scoring constituent. Because these components might be distinctly and variably impacted by statin use, examining each in an isolated manner is essential to determine true limitations of CAC screening for statin use adjudication [36]. *Osei* et al. thus tested the prognostic efficacy of CAC score's components for CHD and CVD mortality in statin users vs. non-users at the time of their CAC imaging event [36].

Of 28,025 patients aged 40–75 years from the CAC Consortium, 6151 were statin users. The *Osei* et al. study used Cox regression models to examine the relation of CAC with CHD and CVD mortality, as well as the predictive performance of CAC components (area, volume, and density) [36]. After following participants for a median 11.2 years (395 CVD and 182 CHD deaths), one unit increase in log CAC score was correlated with increased risk of CVD mortality (HR, 1.2; 95% CI = 1.1–1.3) and CHD mortality (HR, 1.2; 95% CI = 1.1–1.4) among statin users [36]. Importantly, *Osei* et al. found a small negative interaction between CAC score and statin use for CHD and CVD mortality predictions (p-value = 0.036 and 0.025, respectively). Volume score and CAC area were similarly associated with outcomes in both statin users and non-users. However, density was associated with neither CHD nor CVD mortality in statin users, despite being strongly correlated in non-users [36].

Referencing prior studies, the 2018 AHA/ACC Guidelines recommended against clinical CAC screening for statin users [4]. They cited evidence suggesting that statins might encourage coronary calcification, while simultaneously slowing progression of non-calcified coronary plaque [38]. Possibly, this effect might subsequently contribute to plaque stabilization [38]. The *Osei* et al. study, however, indicates that higher CAC within statin users is still strongly predictive of mortality when compared to lower CAC score statin users [36]. The small negative interaction between CAC and statin use does indicate CAC's weaker prediction value in statin users. Yet, coronary artery calcium still prevailed as a strong prognosticator of CV risk for these statin users [36].

Notably, this negative association among statin use, CAC score, and mortality might be regulated by a progression towards more densely calcified plaque [36,37]. *Osei* et al.'s findings thereby emphasize critical uncertainties about the limitations and impact of statins upon CAC score components. Many questions remain regarding statins' biological effects on plaque, as compared to the natural etiology of plaque evolution [36]. *Osei* et al. suggests that, perhaps, the CAC increase in statin-users might protect against CVD through changing relationships of CAC density, area, or volume [36]. As such, mechanistic studies with longitudinal plaque imaging are well-worth an endeavor of future investigation. There are still many unanswered questions on the application of CAC scoring for statin users, as well as how it might be used to adjudicate the *intensity* of preventative pharmacotherapies [36].

## 8. Conclusion

Coronary artery calcium comprehensively tracks a patient's previous exposures and risk factors by directly measuring atherosclerosis. While a finding of zero CAC associates with very low future event rates, elevated CAC significantly increases risk even among typically low-risk patients.

It is important to note, additionally, the unanswered questions of CAC testing in the clinical setting. These include the concept and frequency of retesting patients with zero CAC score. For those who remain asymptomatic, this “warranty period” of a zero score is still a point of discussion; evidence suggests that calcium scoring should not be repeated frequently [39]. Though uncommon, the clinical significance of a zero calcium score in patients with chest pain is similarly controversial. Because of the low prevalence of zero calcium among symptomatic patients, a zero CAC score may not be the best test to confidently rule out obstructive CAD in this population [39].

Despite these limitations, CAC screening effectively reclassifies ASCVD risk, and it allots for the successful up- or down-risking of patients based on calcium score. CAC remarkably reduces absolute risk and the number of needed to treat (NNT) to achieve one event prevention. Last, CAC is shown to maximize not only cost effectiveness but also patient advocacy. These multifaceted considerations elucidate the 2018 Guidelines' rationale behind utilizing CAC testing in clinical practice to direct preventative therapy [13]. Specifically, this review has highlighted key points behind CAC scoring and its crucial role in guiding future preventative treatment.

This paper details numerous studies—each of which provide valuable information regarding the effect of statins in a real-world, CAC-screened population without known atherosclerotic CVD. It discusses CAC's ability to (1) reclassify ASCVD risk, (2), reduce NNT, and (3) improve cost effectiveness. Ultimately, coronary artery calcium possesses a vital role in adjudicating statin use on an individualized, personalized, and targeted basis. By summarizing the rationalization behind recent cholesterol guidelines for ASCVD risk assessment, this review seeks to help advocate the real-time application of CAC to both clinical setting and preventative therapy.

## CRedit authorship contribution statement

**Ilana Golub:** Conceptualization, and, Writing – original draft. **Suvasini Lakshmanan:** Investigation, and, writing review and editing, Writing – review & editing, Writing – review & editing. **Suraj Dahal:** writing review and editing, Writing – review & editing, and. **Matthew J. Budoff:** Supervision, writing review and editing, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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