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State-of-the-Art Review

Imaging subclinical coronary atherosclerosis to guide lipid management, are we there yet?

Pamela Piña [a], Daniel Lorenzatti [a], Rita Paula [a], Jonathan Daich [a], Aldo L Schenone [a], Carlos Gongora [a], Mario J Garcia [a], Michael J Blaha [b], Matthew J Budoff [c], Daniel S Berman [d], Salim S Virani [e,f], Leandro Slipczuk [a,*]

[a] Cardiology Division, Montefiore Medical Center/Albert Einstein College of Medicine. Bronx, NY, USA
[b] Johns Hopkins Ciccarone Center for the Prevention of Heart Disease. Baltimore, MD, USA
[c] Department of Medicine, Lundquist Institute at Harbor UCLA Medical Center, Torrance, CA, USA
[d] Department of Imaging, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[e] Section of Cardiology, Department of Medicine. Baylor College of Medicine, and Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA
[f] The Aga Khan University, Karachi, Pakistan

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ABSTRACT

Atherosclerotic cardiovascular disease risk (ASCVD) is an ongoing epidemic, and lipid abnormalities are its primordial cause. Most individuals suffering a first ASCVD event are previously asymptomatic and often do not receive preventative therapies. The cornerstone of primary prevention has been the identification of individuals at risk through risk calculators based on clinical and laboratory traditional risk factors plus risk enhancers. However, it is well accepted that a clinical risk calculator misclassifies a significant proportion of individuals leading to the prescription of a lipid-lowering medication with very little yield or a missed opportunity for lipid-lowering agents with a potentially preventable event. The development of coronary artery calcium scoring (CAC) and CT coronary angiography (CCTA) provide complementary tools to directly visualize coronary plaque and other risk-modifying imaging components that can potentially provide individualized lipid management.

Understanding patient selection for CAC or potentially CCTA and the risk implications of the different parameters provided, such as CAC score, coronary stenosis, plaque characteristics and burden, epicardial adipose tissue, and pericoronary adipose tissue, have grown more complex as technologies evolve. These parameters directly affect the shared decision with patients to start or withhold lipid-lowering therapies, to adjust statin intensity or LDL cholesterol goals. Emerging lipid lowering studies with non-invasive imaging as a guide to patient selection and treatment efficacy, plus the evolution of lipid lowering therapies from statins to a diverse armament of newer high-cost agents have pushed these two fields forward with a complex interaction. This review will discuss existing risk estimators, and non-invasive imaging techniques for subclinical coronary atherosclerosis, traditionally studied using CAC and more recently CCTA with qualitative and quantitative measurements. We will also explore the current data, gaps of knowledge and future directions on the use of these techniques in the risk-stratification and guidance of lipid management.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) is an ongoing epidemic, and atherogenic lipoproteins are its root cause. Most first cardiac events occur in asymptomatic individuals, and therefore waiting for symptoms to develop is not a feasible strategy. Risk scores have been developed from the Framingham Risk Score to the Pooled Cohort Equation (PCE) to estimate the likelihood of a person developing ASCVD over a defined period. However, they have shown significant limitations, including over or underperforming in ethnic minorities, the lack of acknowledgment of dynamic changes in risk factors, and the over-reliance on age. The development of coronary artery calcium scoring (CAC) and later CT coronary angiography (CCTA) surged as potential complementary tools to visualize coronary plaque and provide the basis

* Corresponding author.
E-mail address: lslipczukb@montefiore.org (L. Slipczuk).

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for individualized management directly. The major scope of this review is the evaluation of such risk in asymptomatic individuals using CAC and more recently CCTA to improve risk prediction and potentially guide lipid-lowering medical therapy.

2. Risk estimators in asymptomatic individuals

European [1] and American [2] guidelines recommend using mathematical tools to predict ASCVD risk in asymptomatic patients. ASCVD risk calculators are derived from data pooled from multiple cohort studies; due to their inherent limitations, they must be interpreted in light of specific circumstances for individual patients.

The American College of Cardiology and American Heart Association (ACC/AHA) have endorsed the PCE for primary clinical risk assessment since 2013 [2]. The PCE is a race- and sex-specific traditional risk calculator derived from the data of 5 large US cohort studies. It should be used mainly for non-Hispanic African American and White adults aged 40 to 79 with low-density lipoprotein cholesterol (LDL-C) 70–190 mg/dL and only for individuals without prior ASCVD. It estimates the 10-year risk of developing a first hard ASCVD event (e.g., nonfatal MI, coronary heart disease, fatal or nonfatal stroke) and stratifies individuals into 4 absolute risk categories: low (<5%), borderline (5–7.4%), intermediate (7.5–19.9%), and high (≥20%). However, total ASCVD risk is a continuum, and the elements included in the equation are dynamic and should not be interpreted in a restricted way. The risk category cut-offs are mainly based on practical considerations concerning the net benefit of preventive therapies but with limited predictive performance in the individual patient.

The PCE has been shown to overestimate [3] or underestimate [4] ASCVD risk for certain subgroups. Thus, the 2019 ACC/AHA Guideline on the Primary Prevention of CV Disease advocates for the use of use additional risk-enhancing factors (family history [FH] of premature ASCVD, chronic kidney disease, chronic inflammatory conditions, etc.) to guide decisions about preventive interventions for borderline- or intermediate-risk adults. However, the value of preventive therapy may remain uncertain in this group, and some patients may be reluctant to take medical therapy without evidence of increased ASCVD risk. At the same time, most ASCVD events occur in patients who would have otherwise been considered intermediate or low-risk [5].

CAC and CCTA have emerged as tools to improve risk prediction and potentially guide therapy in the individual patient. Given the low cost of statins, a treat-all versus test-guided approach has been considered. Pletcher et al. demonstrated that CAC testing in intermediate-risk patients is cost-effective, especially when statins are costly or when there is significant statin dysutility [6]. In asymptomatic patients without prior ASCVD, with CAC=0 and intermediate risk, statin therapy has a proven low benefit (with certain exceptions such as diabetics and patients with LDL-C>190 mg/dL). The EISNER trial demonstrated that compared with no scanning, randomization to CAC scanning was associated with improved coronary artery disease (CAD) risk factor control without increasing downstream medical testing [7]. In the ROBINSCA trial [8], CAC scoring significantly reduced the number of individuals indicated for preventive treatment compared to the SCORE model. Additionally, testing provides the benefit of a treat-to-goal approach and guidance on adding non-statin lipid-lowering therapies. Recently, in the DANCAVAS trial [9], screening with CAC, among other non-invasive methods, was performed in men 65 to 74 years of age living in 15 Danish municipalities. The authors demonstrated that after more than 5 years, the invitation to undergo comprehensive cardiovascular screening did not significantly reduce the incidence of death from any cause. However, the results of subgroup analyses suggested the possibility of a greater benefit of screening among participants in the younger age group (65–69 years of age).

Polygenic risk scores (PRS) are a newly attractive tool for quantifying inherited risk. One advantage of genetic risk scores is that they can be measured early in life (even at birth), and they remain constant over a lifetime [10]. In older adult populations, these scores add relatively little to risk prediction; by that stage of life, lifetime exposure to risk factors predominates, and such cumulative risk may be best captured by a direct measure of subclinical disease burden (e.g., CAC). However, at young ages, genetic risk scores appear to convey unique data—distinct from family history—that could be used to drive downstream behavior. For example, PRS may inform when the first CAC scan should be obtained, thereby potentially improving the efficiency of CAC for early detection of conversion to CAC >0 [11].

3. Coronary artery calcium

We have known about the presence of vascular calcification for centuries. Before the development of the light microscope, the pathological diagnosis was made based on macroscopic observation with the naked eye.

High circulating lipids, specifically APOB-containing lipoproteins, including LDL-C, have been implicated as an important modifiable risk factor for coronary atherosclerosis. Coronary artery calcium has been promulgated as a specific marker of atherosclerosis since the 1940s. The extent of coronary artery calcification reflects the lifetime effect of all known and unknown factors that cause CAD. Lifelong exposure to LDL-C has been demonstrated to simultaneously promote vascular calcification and skeletal bone dimerization, explaining the paradoxical coexistence of osteoporosis and atherosclerosis in many patients [9].

Even though triglycerides are independently associated with CV events, their role in the process of vascular calcification remains unclear. In the MESA study, individuals with TG >400mg/dL were excluded, and therefore findings should be analyzed with caution. However, high TG levels (≥175 mg/dL) were not associated with CAC in the intermediate CV risk population included in the study [12]. Recently, a Taiwanese study of 3586 patients showed that higher level of TG and lower level of HDL-C were significantly associated with the risk of CAC>100, particularly in patients younger than 65 years and with normal-weight [13].

3.1. Detection and quantification of CAC

The potential value of CAC in predicting future coronary events was first acknowledged in the 70s and 80s using chest radiography and fluoroscopy [14,15]. It was not until 1990 that CAC could be precisely detected and quantified with the introduction of cardiac gated electron-beam computed tomography (EBCT) [16]. Later, multidetector computed tomographic (MDCT) scanners replaced EBCT and were documented to provide CAC quantification that correlated well with the EBCT [17]. Nowadays, thanks to the increasingly larger numbers of detectors and faster gantry speeds in current MDCT scanners, even nongated studies can provide accurate semi-quantitative or quantitative measurements [18].

The Agatston score remains the reference standard and the most commonly used CAC score in clinical practice; it is a summed score of calcified coronary lesions, accounting for both the total area and the maximal density of coronary calcification [16]. A CT attenuation threshold of 130 Hounsfield units (HU) is used for calcium detection [19]. The traditional CAC risk categories are: 0=very low risk, 1–99=mildly increased, 100–299=moderately increased, 300–1000=moderate to severely increased, and >1000=severely increased [16]. Additionally, CAC percentiles based on age, gender, and ethnicity, are also routinely reported, given that individuals in the ≥75th percentile are considered of increased risk [20]. The calcium area and density values may have wide inter-observer variability within a CAC score category, with implications for coronary heart disease (CHD) development and the probability of culprit lesion events. It has been shown recently that for a given CAC score, high CAC density relative to plaque area (called “discordant”) confers lower long-term ASCVD risk, likely serving as an imaging marker of biological resilience for lesion vulnerability [21].

Non-gated studies provide already existing valuable data and can be used to calculate semiquantitative (ordinal scores) or quantitative CAC (Agatston scoring), with a high correlation with ECG-gated CT studies and CVD outcomes [22]. At a minimum, a visual assessment analysis should be performed as follows: 0=none with very low risk, 1=mild with mildly increased risk, 2=moderate with moderately increased risk, and 3=severe with moderately to severely increased risk, and the corresponding 2018 Coronary Artery Calcium Data and Reporting System (CAC-DRS) categories range from 0-3 [20].

Given its wealth of evidence regarding risk stratification, low cost, and wide availability, CAC plays a central role in determining long-term ASCVD risk and mortality [23,24] in asymptomatic patients. It has been shown to be stronger in risk prediction over hs-CRP, carotid intima-media thickness, and other biomarkers [5], as well as clinical risk scores.

3.2. Power of Zero to de-escalate risk

In 2009, the landmark studies by Blaha et al.[25] and Sarwar et al. [26] provided the first glimpse into the potential value of the absence of CAC for "de-risking" otherwise at-risk individuals. This concept was coined as the "power of zero" and is firmly supported by the fact that the absence of CAC is the strongest negative risk marker in clinical practice, identifying patients at very-low 10-year risk. Consequently, recent AHA/ACC guidelines (2018 & 2019) recommended CAC scoring to aid in the decision-making regarding statin in borderline- or intermediate-risk patients for whom the indication to recommend therapy is unclear.

In a 2016 study from MESA, CAC zero was better than 12 other negative risk markers, including the absence of family history, healthy lifestyle, hsCRP>2 mg/L, low N-terminal pro-brain natriuretic peptide, and absence of carotid plaque in reducing an individual patient's post-test risk of developing clinical CVD [27] (Table 1). Along the same line are the results from the BioImage study, where 86% of the study participants qualified for statin therapy for primary prevention due to an ASCVD risk of ≥7.5%. In this population, CAC=0, as well as CAC <10, were the strongest negative risk factors for the development of CVD over a median follow-up of 2.7 years [28].

The value of CAC=0 to re-classify ASCVD risk in those at borderline and intermediate ASCVD risk, the group for whom its use has been deemed most appropriate in the 2018 AHA/ACC Cholesterol Guideline, was initially shown in a study of the MESA population. Of participants eligible for statins, a total of 1316 (44%) had CAC=0 at baseline and were reclassified to lower risk with a resultant observed 10-year ASCVD event rate of 4.2 per 1,000 person-years [40].

Furthermore, recent studies have demonstrated the prognostic significance of CAC scoring in low-risk individuals with a family history of CHD, a group identified for potential CAC scoring in the new Society of Cardiovascular Computed Tomography (SCCT) guidelines. In this population, CAC=0 maintains its strong prognostic capacity [41].

3.3. CAC in higher risk groups

A 2020 study from the CAC Consortium characterized individuals with CAC scores >1000. They found that individuals with CAC>1000 have a higher area and density of calcification than the other CAC groups. In addition, those with CAC scores >1000 are at an almost 2-fold higher risk of CVD mortality than those with CAC scores of 400 to 999 [42]. Notably, CAC scores ranging from 775 to 900 for a general at-risk primary prevention population and CAC scores of 300–375 in persons with diabetes were associated with an ASCVD mortality risk equivalent to the overall FOURIER trial population of patients with clinical

Table 1
Main studies reporting prognostic role of CAC among asymptomatic patients.

Authors	Publication Year	Population Number	Endpoints	Follow-up	Main results
Prospective Army Coronary Calcium Project [29]	2005	2000	CAD: SCD, MI, UA	3.0 ± 1.4 years	CAC was associated with an increase in coronary event risk by a factor of 12 ($p = 0.002$).
Rotterdam Study [30]	2005	1795	Hard CAD: MI, CAD mortality	3.3 ± 0.8 years	Relative risk of coronary events for CAC 101–400, 401–1000, and >1000 (compared with scores of 0–100) were 3.1, 4.6, and 8.3, respectively.
Cooper Clinic Cohort [31]	2005	10,476	Hard CAD: CHD death, nonfatal MI	3.5 years	Age-adjusted rates (per 1000 person-years) of hard events for CAC 0 and incremental sex-specific thirds of detectable CAC were 0.4, 1.5, 4.8, and 8.7, respectively.
St. Francis Heart Study [32]	2005	4903	Coronary death, nonfatal MI, revascularization procedures, stroke, and vascular surgery	4.3 years	Subjects with ASCVD events had higher baseline CAC scores than those without events. Relative risk for all ASCVD events of CAC ≥100 was 11.1 compared to CAC <100.
Budoff *et al.* [33]	2007	25,253	All-cause mortality	6±3 years	CACS provides independent incremental information in addition to traditional risk factors in the prediction of all-cause mortality.
MESA [34]	2008	6814	Major CAD events: MI, CAD death; coronary events: major CAD events	3.9 years	Adjusted risk of a coronary event increased by 7.73 when CAC 101–300 and 9.67 when CAC >300 regardless of ethnicity.
Heinz Nixdorf Recall [35]	2010	4129	Hard CV events: nonfatal MI, coronary death	5.1±0.3 years	Reclassifying intermediate-risk subjects with CAC <100 to the low-risk category and CAC >400 to high-risk yielded a reclassification improvement of 21.7% and 30.6% for the FRS, respectively.
CARDIA [36]	2017	3043	CAD events: MI, ACS, CAD death, revascularization	12.5 years	In adults 32 to 46 years, those with any CAC had a 5-fold increase in CHD events and a 3-fold increase in CVD events.
CAC Consortium [37]	2020	66,636	CVD and CHD mortality	12.5 years	CAC was the most reliable predictor for long-term mortality.
Impact of statins treatment by CAC					
Mitchel et al. [38]	2018	13,622	MI, stroke CVD	9.4 years	ARR and RRR proportional to CAC, 8.5% ARR when CAC >100 (NNT = 12)
Zhou et al. [39]	2020	6301	ASCVD events	14.2 years	ARR and RRR proportional to CAC, 10% ARR when CAC >400 (NNT = 10)

ACS: acute coronary syndrome, ARR: absolute risk reduction, ASCVD: atherosclerotic cardiovascular disease, CAC: coronary artery calcium, CAD: coronary artery disease, CHD: coronary heart disease, CV: cardiovascular, CVD: cardiovascular disease, MI: myocardial infarction, NNT: number needed to treat, RRR: relative risk reduction, UA: unstable angina.

cardiovascular disease [43]. The threshold for CAC scoring to mimic secondary prevention risk varies according to risk factors, and the population studied. Although there are no published randomized trials of PCSK9i in primary prevention populations free of familial hypercholesterolemia, current ACC/AHA and ESC/European Atherosclerosis Society guidelines already recommend consideration of this therapy in some asymptomatic populations without FH. Using CAC in this population could enhance the identification of potential candidates likely to derive the smallest and largest absolute benefit from aggressive LDL-C lowering with PCSK9i improving cost-effectiveness [44].

Likewise, CAC is able to improve current risk stratification and therapy allocation paradigms among individuals with hypertriglyceridemia without clinical ASCVD. In a pooled analysis of 2345 individuals from MESA, CARDIA, Dallas Heart Study, and Heinz Nixdorf Recall study cohorts with hypertriglyceridemia and no clinical ASCVD, the role of CAC in further risk stratification was evaluated. Among participants eligible for icosapent-ethyl (EPA), 38% had CAC >100, their event rates were markedly higher (15.9% vs. 7.2%), and the NNT for 5 years was 2.2-fold lower (29 vs. 64) than those of the 25% eligible participants with CAC=0 [45].

Considering the exposed above, guidelines from medical societies, notably the American Association of Clinical Endocrinologists and the European Society of Cardiology, have begun recommending very low LDL-C goals (<55 mg/dl) in those who are at "extreme or very high risk".

3.4. CAC in special groups (Diabetes, LDL-C >190mg/dL, and young)

Patients with diabetes are at particular risk for developing ASCVD; however, this risk has been recognized as heterogeneous. CAC has been proposed to accurately classify a diabetic individual's ASCVD risk compared to traditional ASCVD risk factors. Notably, up to 40% of patients with diabetes have CAC=0, and even though they portend a higher risk than non-diabetes individuals, they still have a lower risk than the different categories of CAC-positive patients. This could be useful for selecting a lower-intensity statin therapy or seeking less restrictive LDL-C targets in this population [27]. In a trial including participants from MESA, Malik et al. demonstrated that the addition of CAC scoring to global risk assessment was associated with significantly improved risk classification in those with metabolic syndrome (MetS) and diabetes [46]. Similarly, Wong et al. evaluated sex differences in this population and revealed that women had higher total and CVD death rates than men when CAC >100. CAC predicted CHD, CVD, and all-cause mortality in patients with diabetes [47]. Likewise, other authors indicated that the mortality risk increased significantly for diabetic individuals even with a baseline CAC=0 after 5 years [48]. Hence, in these patients rescanning should be considered for a shorter period. Guidelines recommend, in adults aged 40 to 75 years with diabetes, the initiation of statin therapy before a clinical ASCVD assessment, but further risk assessment is required for other decision-making, like statin intensity and the addition of higher-cost nonstatin lipid-lowering therapies [49].

Patients with LDL-C ≥190 mg/dL have been traditionally excluded from risk calculators and considered high-risk. Recently, it has been suggested that this represents a heterogenous risk group. CAC scoring has been shown to stratify CVD risk in asymptomatic patients with LDL-C effectively ≥190 mg/dL [50]. In a recent study, individuals with CAC=0 had a lower risk for future CV events (incidence rate per 1000 person-years = 4.7; 10-year risk = 3.7%; risk/year = 0.4%) [50]. These results do not indicate that subjects with CAC=0 and severe hypercholesterolemia should not be treated with statins, especially younger patients, given their lifetime risks. In this scenario, imaging can help guide the use of more expensive therapies, such as PCSK9 inhibitors, for those who still have elevated LDL-C levels after subsequent follow-up.

Moreover, in a retrospective study of 811 patients aged ≥40 years with LDL-C ≥190 mg/dL evaluated with non-gated chest CT, visual CAC and thoracic aorta calcification (TAC), quantified using simple "ordinal scores" were found to be independently associated with all-cause mortality [51].

Although universal screening for CAC in young adults has not been endorsed, we suggest certain "CAC benefit groups" in which ASCVD risk may be sufficiently high to warrant an assessment of CAC assessment from a shared-decision discussion. These groups include the following: 1) those with diagnosed familial hypercholesterolemia; 2) those with a family history of premature ASCVD; 3) those with multiple risk factors; and 4) those aged 40–45 years who are identified as borderline-intermediate risk by the current PCE. Identifying the presence and degree of CAC in adults ≤45 years in these elevated risk groups provides the opportunity to initiate early preventive efforts with greater potential to change the natural history of ASCVD than if started later in life. The exact age for initial testing has however not been studied and more data is needed but is usually considered in the 30s to early 40s. Considering that in a large cohort of U.S. adults aged 30–45 years without symptomatic ASCVD, the probability of CAC >0 varied by age, sex, and race ranging from 7% to 26% [52].

3.5. CAC progression & the re-scan interval

In patients whose development or progression of CAC would support intensification or alteration in preventive management, it may be appropriate to consider repeat CAC scanning. The interval is still a matter of debate, but initially, data supported repeat CAC scanning at an interval of 5 years for patients with CAC=0 and a 3–5 year interval for patients with CAC>0 [23].

In PESA, a large, middle-aged, and asymptomatic population (40–54 years employees of Santander Bank) was evaluated using comprehensive serial multimodality imaging of multiple vascular territories. At baseline, 63% of the asymptomatic participants showed evidence of atherosclerosis, defined as the presence of atherosclerotic plaque in any of the screened territories by ultrasound (carotids, iliofemoral, aorta) or evidence of CAC in the coronary tree. CAC was detected in only 18% of the cohort (CAC 1-99 in 14%, 100–399 in 3%, and ≥ 400 in 0.7%), in line with previous data from the CARDIA and MESA studies. Importantly, at the 3-year follow-up visit, >40% of the healthy middle-aged PESA cohort showed evidence of disease progression [53]. In a recently published work using the MESA cohort, it was suggested that the so-called "warranty period" of a CAC=0 could be as long as 6–7 years for the low-risk population and as short as 3 years for high-risk and diabetic individuals. Family history of CHD and smoking affected the estimation for both men and women. The conversion from CAC=0 to a CAC score of >10 took an average of 5 to 8 years (depending on ASCVD risk category and age), and the conversion to CAC >100 would take at least 9 years for high-risk individuals [54].

An important limitation in assessing CAC progression has been the measurement variability in detecting real changes in patients with CAC>0. A study by Budoff et al. showed in 4609 asymptomatic individuals that CAC progression added incremental value in predicting all-cause mortality over baseline score, demographics, and CV risk factors [55]. On the contrary, the analysis of CAC progression did not add any benefit to risk prediction models for coronary and cardiovascular events prediction when compared to 10 published algorithms using HNR data. Nevertheless, the best coronary disease prognosis was found for participants with "double zero," meaning CAC=0 at baseline and the CT scan 5 years later [56]. Therefore, a repeat scan after 5 years seems to be of additional value, except for those who already have a double-zero CAC scan or have already been classified at high risk because of CAC ≥400.

3.6. Limitations and new perspectives

Although CAC has many strengths (it can be performed rapidly, in a reproducible fashion with minimal radiation exposure, without the need

for intravenous contrast, and at a low cost), it is not without limitations. Its use for ruling-out CAD has been challenged in the past. In MESA, up to a third of total events occurred in patients with a CAC zero prior to the performance of a subsequent scan at 3 to 5 years [54]. In the CAC consortium cohort, 0.09% of CV deaths occurred in participants without evidence of coronary calcium in a 12-year follow-up period [57]. In the recent Miami Heart Study (MiHEART), 2359 middle-aged and predominantly low-risk (74% in ASCVD risk<5%) asymptomatic individuals were evaluated with CAC score and CCTA. The prevalence of any coronary plaque on CCTA was 16% among those with CAC=0. Furthermore, in this group, 0.8% had stenosis ≥ 50%, 0.1% stenosis ≥70%, and 2.3% high-risk plaque features [58]. It could be argued then that using CAC similar to risk scores can underestimate the youngest individuals with the most to gain from preventive therapies [59], as the presence of isolated non-calcified plaque is more frequent in that population. Finally, the absolute event rates in these studies are likely modified by high baseline use of statin therapy and significant statin drop-in in most studies. For these reason, even that CAC can play a central role in patient selection for lipid lowering therapies, its utility for potentially monitoring progression/regression of disease while on therapy may be limited.

Another potential limitation of CAC is the non-rare presence of subtle calcified plaque below the Agatston score threshold of 130 HU, which, even when minimal, is associated with increased adverse CV outcomes. Although modern imaging technology has advanced, the Agatston scoring method has remained unchanged since its introduction, and consideration of a change in CAC scoring methodology has been recommended. Lately, it has been proposed that smaller and less dense calcified plaques below the conventional detection threshold can be identified by eliminating the size threshold and reducing the HU threshold to ≥120 [60].

4. Coronary computed tomography angiography

CCTA is currently the modality of choice to exclude disease in symptomatic patients with low to intermediate-risk pretest probability (15–50%) for obstructive CAD. Compared to functional ischemia tests, CCTA allows the detection of non-obstructive coronary plaques and the reliable ruling-out of left main disease. In recent large randomized clinical trials, such as the PROMISE [61] and SCOT-HEART [62], the use of CCTA was associated with a lower risk for myocardial infarction than conventional pharmacological management, mostly due to the intensification of preventive therapies. Importantly, in the SCOT-HEART trial, the findings were also present in patients with non-cardiac chest pain, raising the possibility of its value in plaque detection to guide preventative therapies initiation in asymptomatic individuals [62].

Given low radiation with newer scanners (down to 1 mSv with some scanners and safety protocols), the possibility of performing CCTA over CAC has gained momentum in patients in whom CCTA has been previously not commonly used. These include selected asymptomatic high-risk or younger individuals, especially those with a higher likelihood of having a large amount of non-calcified plaque. The presence of predominantly non-calcified plaque is more prevalent in young (age< 45–50 years) and female individuals [63]. Moreover, the burden of CAC and the relationship to non-calcified plaque may differ between ethnicities. Other groups of patients who have risk factors such as diabetes, HIV, smoking, inflammatory conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis, or psoriasis), familial hypercholesterolemia, or those working in high-hazard occupations or a strong family history of premature ASCVD, may also present underlying CAD without CAC [64] and may benefit from CCTA screening instead of CAC. Testing such asymptomatic individuals should be performed in the context of shared decision-making if there is uncertainty regarding initiation and intensity of lipid lowering therapies (**Table 2**).

4.1. Visual assessment of coronary plaque burden

Beyond stenosis and clinical variables, recent data suggests that the overall amount of coronary plaque by CCTA is a lead predictor of incident CHD events [71]. Indeed, the ability to detect calcified and non-calcified plaque is a unique attribute of CCTA.

Standard plaque burden estimation on CCTA is based on a visual or semi-quantitative assessment of coronary segments using the Segment Involvement Score (SIS), Segment Stenosis Score (SSS), and CT-adapted Leaman score (CT-Leaman) [72]. The SIS provides independent prognostic information above and beyond the presence of obstructive CAD [73].

The SCAPIS trial, conducted in middle-aged individuals without known CHD (50.6% women), demonstrated any CCTA-detected atherosclerosis in 42.1% and any significant stenosis (≥50%) in 5.2%. Atherosclerosis was more prevalent in older individuals and increasingly detected with higher CAC scores [74]. Similarly, the MiHeart study included asymptomatic individuals with independent predictors plaque: older age, male sex, tobacco use, diabetes, overweight, and obesity. Overall, 49% of participants had coronary plaque [58]. Larger studies, such as the SCOT-HEART 2 trial (NCT03920176), are currently underway to provide evidence on whether a CCTA-based strategy for asymptomatic patients with at least one risk factor is of benefit in clinical practice. It hopes not only to answer the question of whether CCTA is better than risk scoring but also how to apply an imaging-based screening tool.

Epicardial adipose tissue (EAT) and pericoronary adipose tissue (PCAT) are inflammation features evaluated by CCTA that have proven to be associated with coronary atherosclerosis and CV events [75].

Table 2
Main studies reporting prognostic role of CCTA among asymptomatic patients.

Authors	Publication Year	Population	Endpoints	Follow-up	Main results
CONFIRM [65]	2012	7590	Death Non-cardiac MI	2 years	CCTA predicts mortality and non-fatal MI in asymptomatic patients with moderately high CAC, but not for lower or higher CAC.
Min et al. [66]	2014	27,125	Cardiac death, revascularization, ACS	2.4 ± 1.1 years	For asymptomatic diabetic individuals, CCTA measures of CAD severity confer incremental risk prediction.
Kang et al. [67]	2016	591	Cardiac deaths, Nonfatal MI, UA, late coronary revascularization	6 years	Results suggested long-term prognostic value of CCTA for asymptomatic DM
Halon et al. [68]	2019	630	ACS	9.2 years	In asymptomatic DM pts, CCTA plaque volume, %low-density content and mild calcification predicted late plaque events.
Impact of statins treatment by CCTA					
Chow et al. [69]	2015	10,418	All-cause mortality	2.2 years	ARR and RRR proportional to nonobstructive plaque burden, 0.57% ARR with nonobstructive plaque.
Øvrehus et al. [70]	2014	33,552	All-cause mortality, MI	3.5 years	ARR proportional to CAC and nonobstructive plaque burden, RRR similar across groups, ARR 7.8% when CAC >400 (NNT = 13)

ACS: acute coronary syndrome, ARR: absolute risk reduction, CAC: coronary artery calcium, CCTA: coronary computed tomography angiography, CAD: coronary artery disease, DM: type 2 diabetes mellitus, MI: myocardial infarction, NNT: number needed to treat, RRR: relative risk reduction, UA: unstable angina.

Tzolos et al. demonstrated that PCAT attenuation of the RCA was predictive of myocardial infarction (HR: 1.55; p=0.017, per 1 SD increment) with an optimum threshold of −70.5 HU (HR: 2.45; p=0.01) [76] (Fig. 1).

4.2. Qualitative high-risk features of coronary plaque

Similar to invasive studies, analysis of coronary plaque by CCTA for risk assessment may be divided into two different approaches: (1) qualitative assessment with identification of "high-risk" plaque features and (2) quantitative measurement of total coronary plaque volume and burden [72].

Qualitative analysis typically focuses on detecting stenosis and estimating overall plaque volume and composition. More recently, this has included identifying specific plaque findings associated with high-risk plaques (HRP). These characteristics include four specific imaging findings, namely the presence of low-attenuation plaque (LAP), outward or positive remodeling (PR) of the coronary wall, small "spotty" plaque calcification, and the napkin-ring sign (NRS) (Fig. 2). Currently, the presence of two or more of these features is required to define a HRP [77].

Low-attenuation plaque identifies the presence of a large necrotic core, one of the hallmarks of vulnerable, rupture-prone coronary plaques in pathology studies [78]. Motoyama *et al.* were the first to suggest using the currently widely used threshold of <30 HU for LAP [79] (Fig. 3). However, other studies have used various, typically higher HU cut-offs to differentiate LAP from other non-calcified (fibrous or fibro-fatty) plaque. These cut-offs range from 30 to 75 HU. Based on this definition, LAP is more often observed in patients with ACS than those with stable angina and has been associated with an eight-fold increased risk for ACS in patients with acute chest pain undergoing CCTA [80].

Positive remodeling is the expansion of the external elastic membrane area and the compensatory enlargement of the vessel wall at the site of atherosclerotic lesions. This vascular remodeling dissociates plaque size from the degree of luminal stenosis during the early stages of plaque growth [81]. The remodeling in the vascular wall is defined as a remodeling index >1.1 (i.e., the ratio of the smallest vessel cross-sectional area of the lesion to the proximal reference luminal area). In the ROMICAT-II study, this high-risk feature was associated with an 11-fold increased risk for ACS [80].

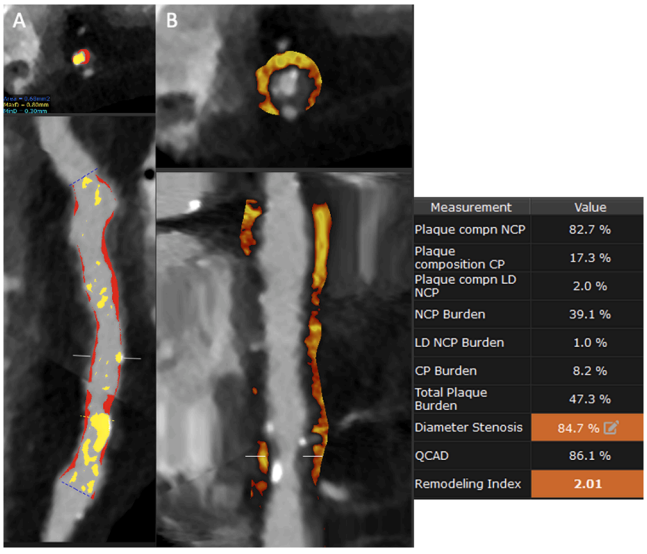

Fig. 1. A. Curved MPR with Autoplaque analysis demonstrating right coronary artery ectasia with an obstructive lesion in the distal segment. The yellow pattern describes the calcified components of the plaque, and the red one indicates the noncalcified. A 2% is composed of low attenuated plaque (<30HU) with a remodeling index of 2.01, indicating high-risk plaque. **B.** Straight MPR PCAT analysis with AutoPlaque demonstrating an attenuation higher than -70 HU.

Spotty calcification is the initial stage of a calcified plaque occurring due to active local inflammation. On CCTA, SC has a density greater than 130 HU and a diameter of <3 mm surrounded by non-calcified components [82]. The use of SC as a marker for the vulnerable plaque is, however, limited by its high prevalence and low specificity in predicting future events [83].

The most notorious HRP feature is the NRS, which is currently considered the CCTA hallmark of the vulnerable atherosclerotic plaque [84]. Studies employing CCTA and intracoronary imaging have shown that the NRS is predominantly found in high-risk lesions such as in thin cap fibroatheroma (44% vs. only 4% in non-thin cap fibroatheroma). This finding is characterized by a plaque core with low attenuation surrounded by a rim-like area of higher attenuation, potentially representing thin-cap fibroatheroma [85].

Combining HRP features with data on stenosis severity maximizes the prognostic value of CCTA-derived information. In one of the most significant to-date studies on the prognostic value of HRP, they were proven to be an independent predictor of MACE [86]. The risk reclassification provided by HRP features seems to be greatest in the lower-risk groups, such as younger patients, women, and those with non-obstructive CAD.

In 2016, vulnerable plaque (LAP, PR, spotty calcification, or the NRS) was incorporated into the SCCT CAD-RADS [77]. The "V" modifier was used to communicate the presence of vulnerable plaque as part of CAD-RADS and prompted more aggressive management or investigation to be considered. Recently, Cury *et al.* published a modified and actualized version named CAD-RADS 2.0, where the V modifier was replaced by the letters HRP referring to high-risk plaques. This new version also includes a grading scale for plaque burden (P1-P4), a modifier for the presence or absence of ischemia in CT-FFR, and a modifier for exception, indicating other causes of non-atherosclerotic coronary abnormalities, such as coronary fistulae, dissection or anomalous origin, among others [87].

These HRP features should be considered to start or expand aggressive preventative medical therapies and not in isolation to pursue downstream testing such as invasive coronary angiography.

4.3. Semi-quantitative and quantitative measurement of coronary plaque burden

For a semi-quantitative assessment and reporting of plaque burden, several visual scores were developed. The SIS offers a simple method of determining the extent of atherosclerosis throughout the coronary tree with an increased risk of subsequent cardiac events with a higher segment-involved score [88]. Others, such as the CT-Leaman score, also consider the severity of stenosis and the type of atherosclerotic plaque [89]. These semi-quantitative scores are currently quicker to perform than quantitative assessments, but they only provide an estimate of the disease burden.

Quantitative analysis of individual coronary plaque has now been described using a variety of software approaches. They allow the measurement of calcified, noncalcified, low-attenuation plaque and total plaque volume. In a post-hoc analysis of a cohort of 1769 patients with stable chest pain undergoing CCTA in the multicenter SCOT-HEART trial, LAP burden was the strongest predictor of fatal or nonfatal myocardial infarction [90]. Patients with LAP burden greater than 4% were nearly five times more likely to have a subsequent myocardial infarction. In a further analysis of patients undergoing CCTA in the SCOT-HEART trial [76], PCAT-RCA of ≥-70.5 HU added to LAP burden of >4% provided an improved prediction of future myocardial infarction (HR: 11.7; p< 0.0001). It still remains unknown if these particular features can predict events in asymptomatic individuals and whether they can be used to select intensity of preventative treatments such as lipid lowering therapies.

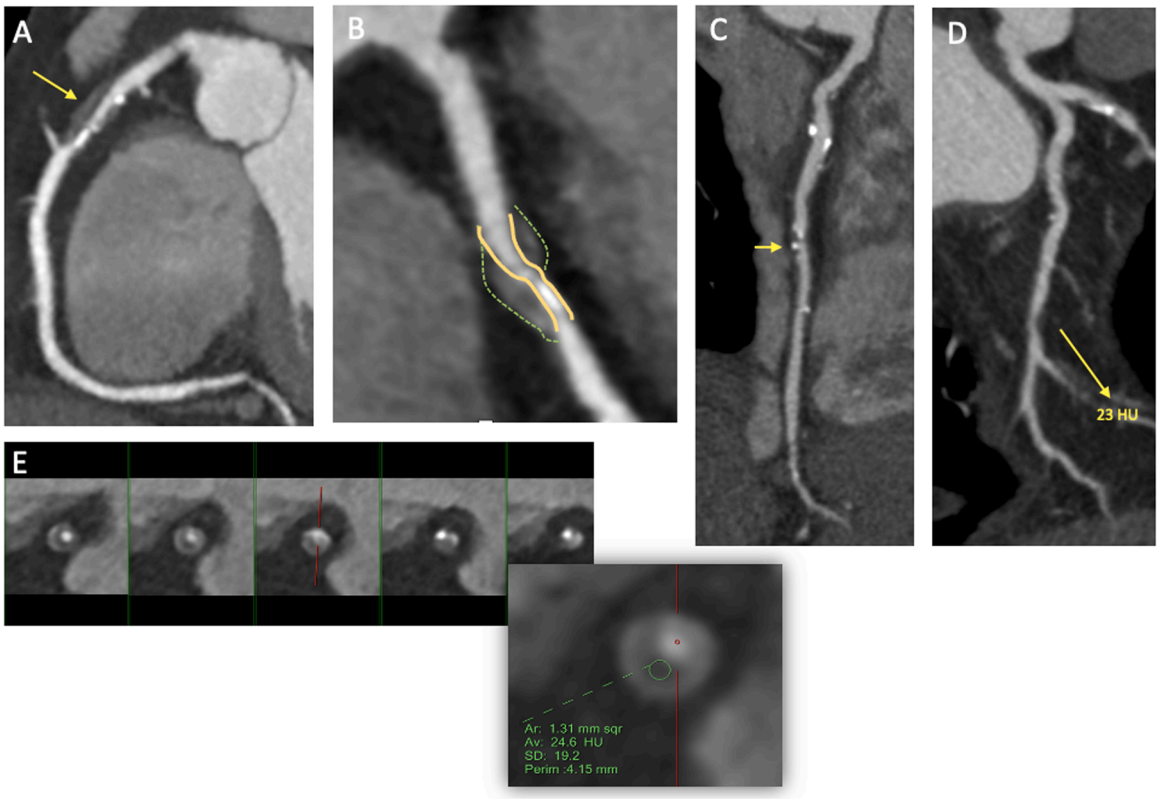

Fig. 2. **A-B.** Curved MPR with a severe mixed plaque at the proximal LAD (*arrow*) exhibiting positive remodeling and spotty calcification. **C.** Curved MPR showing a mid-LAD plaque with spotty calcification (*arrow*). **D.** Curved MPR with a severe noncalcified plaque at the distal LCx (*arrow*) with low attenuation plaque (<30HU). **E.** Cross-sectional view at different levels of the LAD demonstrating a napkin-ring sign.

For intermediate stenoses diagnosed on invasive angiography, performing Fractional Flow Reserve (FFR) measurements is recommended to assess their functional relevance [85]. However, FFR-CT (HeartFlow, Redwood City, California) is a technology whereby patient-specific blood flow models are constructed from CCTA images and used to estimate FFR noninvasively without requiring an additional scan [91]. In a meta-analysis, the AUCs of CTA-derived FFR at the patient and vessel level were 0.90 and 0.91, respectively, in identifying obstructive stenosis as identified by invasive FFR [92]. Also, in another meta-analysis, Noorgard *et al.* demonstrated the prognostic value of this tool. Still, it should be noted that this was not shown in the respective individual trials included [93]. Therefore, recently published American multi-society guidelines for the Evaluation and Diagnosis of Chest Pain stated that for intermediate-high risk patients with stable chest pain and known coronary stenosis of 40–90% in a proximal or middle coronary segment on CCTA, FFR-CT can be useful for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization (IIaB) [94]. There is however almost no data on the use of FFR-CT in asymptomatic patients and for now its potential use is only speculative.

FFR-CT analysis can also evaluate the coronary artery lumen volume to left ventricle myocardial mass ratio (V/M). This value represents a measure of the ability of the epicardial coronary arteries to supply blood in relation to myocardial demand and could be used as an additional metric of coronary circulatory function. Patients with low V/M ratios following coronary vasodilation mediated by nitrates have been found more likely to have FFR values ≤0.80 than patients with high V/M, regardless of the presence or absence of focal stenosis. Importantly, while subjects with a low V/M were found to have significantly greater atherosclerosis than patients with high V/M, the ratio is considered an independent predictor of FFR ≤0.80 [95]. These intriguing findings motivate further research on the role of V/M and FFR-CT in other patient populations, such as asymptomatic patients with borderline obstructive plaques but its role over plaque burden and characteristics remains to be determined.

4.4. Limitations and new perspectives

Although the presence of high-risk plaque features has been widely recognized in the prediction of clinical events, its positive predictive value for ASCVD events is still limited. Longitudinal imaging studies have recently demonstrated that plaques with at least one adverse feature are, in fact, relatively common and appear dynamic, with the ability to revert to a more stable phenotype spontaneously or in response to medications, such as statin therapy [96]. Further CCTA randomized trials are needed to investigate the pathophysiology of the rapid progression of high-risk coronary plaques leading to ASCVD events, which will offer clinical utility in the management of asymptomatic patients.

There are several barriers to progressing from a risk score-based approach to one that incorporates CCTA. Exposure to radiation requires some consideration, along with the use of contrast and medications, such as beta-blockers and nitrates, to optimize image quality brings a small risk of adverse reactions. Finally, the use of CCTA has the potential for further downstream testing in patients felt to have a 'severe' burden of disease or have clinically important incidental findings [97]. This would require careful consideration and may be the subject of future research.

The SCOT-HEART [98] and PROMISE [99] trials were sufficiently large to assess the impact of CCTA on hard clinical outcomes in symptomatic individuals. In asymptomatic patients, there has only been one randomized trial assessing the use of CCTA in a primary prevention setting. The FACTOR-64 study recruited asymptomatic patients with diabetes and failed to demonstrate a clinical outcome benefit [100].

In addition, CCTA, potentially provides information to assess

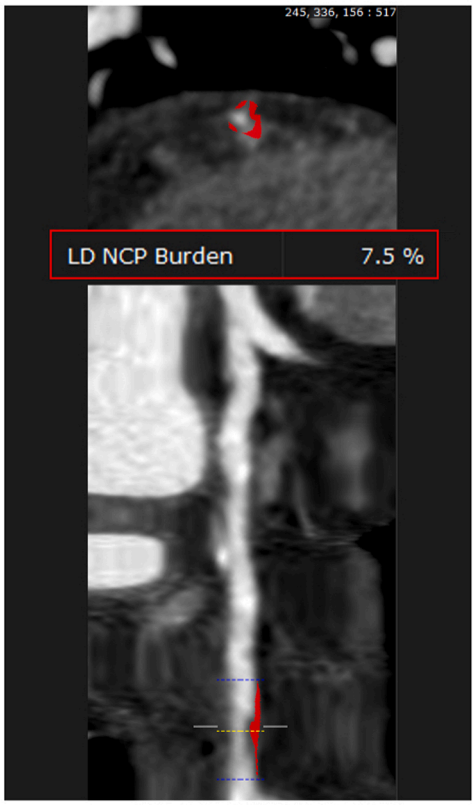

Fig. 3. Straight MPR with AutoPlaque analysis demonstrating noncalcified stenosis of the left anterior descending artery with a 7.5% low attenuation plaque burden (<30HU).

progression or regression of coronary atherosclerosis as response to medical therapy and its been recently used as an endpoint in clinical trials. In this particular feature, it is superior to CAC providing unique information as listed above. However, further trials are needed to standardize and evaluate the clinical implications of these findings as response to medical therapy.

Consequently, we still need more prospective randomized trials in asymptomatic populations like the ongoing SCOT-HEART 2 to evaluate the clinical impact of a CCTA-based strategy in hard outcomes.

5. Lipid management according to CAC/CCTA results

Even that the added value of risk stratification by coronary atherosclerosis imaging has been described above, this assessment can do little for our patients without the appropriate preventative interventions. The studied effects of most lipid therapies (as shown on Table 3) on lipid parameters and cardiovascular risk are derived from studies in symptomatic patients. Until newer data is available, this secondary prevention effect size can be considered to guide therapeutic selection for patients with high-risk subclinical coronary atherosclerosis.

The relationship between lipid disorders and non-invasive coronary plaque imaging has been previously established. A cross-sectional analysis of the MESA showed that participants with combined hyperlipidemia, simple hypercholesterolemia, and dyslipidemia of MetS had a statistically significant probability of having a multivessel CAC (2 or more) as compared to the normolipidemia reference group, even after adjusting for the demographic and cardiac risk factors [115]. Additionally, in patients with optimal LDL-C levels, remnant cholesterol (total cholesterol minus LDL-C minus high-density lipoprotein cholesterol) levels are associated with a significant coronary atherosclerotic burden as assessed by CCTA [116]. On the other hand, isolated hypertriglyceridemia was not associated with CAC extent [115,116]. There also seems to be an association between the time course and duration of elevated lipid levels and CAC. Measurements of lipid levels done early (15–30 years before the CAC study), followed by long-term averaged measurements, are strongly associated with CAC in a middle-aged to elderly adult population (mean age 63 years). However, contemporary lipid measures were associated with elevated CAC only in younger adults (mean age 42–43 years) [117,118]. It has been proposed that this lack of association between the presence of CAC and a more recent measurement of lipid values in older people could be explained by other risk factors and changes throughout life [117].

As mentioned above, CAC is helpful in tailoring the decision to start or withhold statin therapy and the selection of lipid-lowering therapy intensity [119]. For a given CAC score, diffuse distribution of CAC suggests a higher risk than more localized CAC. The presence of left main coronary calcification, especially when >25% of the total score is in the left main, also suggests a higher risk. The National Lipid Association, in a consensus document, underpins the importance of CAC regarding lipid management [119].

Similarly, in a more recent expert consensus, the ACC provides a treatment pathway according to the CAC results (**Central Illustration**). For those with intermediate risk and CAC scores of 0, in the absence of high-risk profile features, it is reasonable to defer statin therapy with a plan for CAC reassessment in 3–5 years [120]. For those with a CAC score of 1-99 AU, moderate-intensity statin therapy is reasonable. Based on data from MESA and consistent with the recommendations of the 2018 Cholesterol Guideline, a CAC score >100 is a clear indication to engage in a clinician-patient discussion about the initiation of statin therapy [121]. For those with a CAC score of >300 per MESA or >400 per Heinz Nixdorf Recall Study, with greater than the 75th percentile for their age/sex/race group, initiation or titration to high-intensity statin therapy may be considered [120,122]. In the higher risk groups, non-statin therapies should be considered if the LDL-C level remains ≥70 mg/dl and/or less than 50% LDL-C reduction from baseline is achieved on maximally tolerated statin therapy [120]. Of note, when CAC=0 or CCTA is without evidence of plaque, lifestyle modifications, including dietary changes, can play a central role without the immediate need for medications [121].

Serial CAC measurement in patients already treated with statin therapy has limited utility [123]. Although statins are associated with slower progression of overall coronary atherosclerosis volume and reduction of high-risk plaque features, they increase plaque density and thus increase the CAC score.

It has been proven that a CAC score >100 is associated with ≥7.5% 10-year ASCVD risk, the guideline-based threshold of statin benefit in primary prevention. Individuals with a CAC score ≥300 are associated with proportionately higher ASCVD risk than those with scores >100, suggesting a benefit from greater LDL-C lowering. Increases in Agatston CAC scores caused by statins are generally modest, and very elevated CAC scores (eg, >400 or >1000) should still be interpreted as indicative of extensive atherosclerosis and prompt aggressive preventive therapies. When the goals of therapy in the clinician-patient discussion have been achieved, it is reasonable to continue to monitor adherence to lifestyle modifications, medication, and LDL-C response to therapy [120].

When starting lipid lowering therapies it is essential to understand the effects on lipid parameters and cardiovascular risk. In both primary and secondary prevention, it is established that for every 40 mg/dL LDL-C reduction in patients treated with statins, there is a 23% reduction of events in 5 years (Table 3) [124]. Furthermore, multiple trials have reported no systemic increase in adverse events in those achieving LDL-C <50 mg/dL [125], which may be appropriate for patients with high risk imaging findings. Many studies have confirmed that the lower the LDL-C, the lower the ASCVD risk and, with no evidence of any clinically significant harm, no matter how low the achieved LDL-C level is [126,127].

The FOURIER [106] and ODYSSEY trials [107] demonstrated in symptomatic patients with established ASCVD that even for patients

Table 3
Summary of Lipid Lowering Therapies: dosing, side effects, lipids, and cardiovascular outcomes reduction.

Category	Dosing	Potential Side effects	Usual Lipid reduction	CVD outcomes reduction
Statins Atorvastatin Rosuvastatin Simvastatin Pravastatin Pitavastatin Lovastatin Fluvastatin	*High intensity:* Atorva 40–80 and Rosuva 20–40 mg *Low/Moderate intensity:* Atorva 10–20 mg; Rosu 5–10mg; Simva 10–40mg; Fluva 20–80 mg; Lova 20–80 mg, Pitava 1–4 mg, Prava 10–80 mg	- Myalgias, myopathy - Dyspepsia - Myonecrosis, Rhabdomyolysis - Transaminase elevation - Increased risk of new-onset diabetes	*High intensity:* >50% *Moderate intensity:* 30–49% *Low intensity:* <30%	***Primary prevention*** JUPITER (Rosu) [101] HR: 0.56 (0.46–0.69) WOSCOPS (Simva) [102] HR: 0.69 (0.57–0.83) CARDS (Atorva) [103] HR: 0.65 (0.30 to 1.55)
Cholesterol absorption inhibitors Ezetimibe	10 mg daily	- Diarrhea - Back pain - Abdominal pain - Muscle pains	LDL-C reduction of 15–20% as monotherapy. Combined with statin, there is a 25% extra reduction.	***Primary prevention*** EWTOPIA 75 [104] HR: 0.66 (0.50–0.86) SHARP [105] HR: 0.83 (0.74–0.94)
PCSK9 Inhibitors Evolocumab Alirocumab	*Alirocumab*: dosed 75–150mg q 2 weeks or 300 mg q 4 weeks *Evolocumab* 140 mg q 2 weeks or 420mg q 4 weeks	- Injection site reactions - Nasopharyngitis - Back pain - New onset diabetes	LDL-C reduction of 40–65% when added on to statin and/or ezetimibe Mean LDL-C decrease is 30% with evolocumab in patients with HoFH	***Secondary prevention*** FOURIER [106] HR: 0.85 (0.79–0.92) ODYSSEY [107] HR: 0.85 (0.78–0.93)
Bile Acid Sequestrants Colesevelam Cholestyramine Colestipol	*Colesevelam:* 3.75gr daily or 1.87 gr twice a day *Cholestyramine:* 8–16 g/day orally *Colestipol:* 2–16 g/day orally	- Constipation, upset stomach - Triglyceride elevation - May bind other medications (Thiazides, Warfarin, Aspirin)	Typically lowers LDL-C by 15–20%	***Primary prevention*** LRC (Cholestyramine) [108] HR: 0.83 (0.09 to 1.37)
Bempedoic Acid	180 mg oral daily	- Hyperuricemia - Tendon rupture - Back pain - Anemia	Lowers LDL-C by -19% In combination with Ezetimibe by -38%	No outcomes trial CLEAR – Safety trial [109]
Inclisiran	284 mg SQ q 3months	- Injection site reactions - Transaminase elevation - Arthralgia	Lowers LDL-C by -50%	No outcomes trial ORION-9 – LDL reduction [110]
n-3 Fatty Acids Omega-3-acid ethyl esters (Lovaza) Icosapent ethyl (Vascepa)	*Lovaza* 4 g/day *Vascepa* 4 g/day	- Fishy taste in mouth - May prolong bleeding time	Neutral effect on LDL-C lowering TG lowering of 20–30%	***Secondary prevention*** REDUCE-IT (Icosapent ethyl) [111] HR: 0.75 (0.68–0.83) ORIGIN (Ethyl esters) [112] HR: 0.98 (0.87–1.10)
Fibrates Fenofibrate Gemfibrozil	*Fenofibrate* 50–160 mg/day *Gemfibrozil* 600 mg twice daily	- Myositis - Cholelithiasis	TG lowering of 40–50% Lowers LDL-C by 30%	***Secondary prevention*** ACCORD [113] HR: 0.92 (0.79–1.08)
Niacin	500 to 2000 mg/day	- Flushing, Pruritus - Hepatitis - Gout	TG lowering of 15–25% LDL-C 10–20%;	***Secondary prevention*** Systematic Review [114] RR 0.99; 95% CI 0.88–1.12)

CVD: cardiovascular disease. HoFH: Homozygous familial hypercholesterolemia, HR: hazard ratio, LDL-C: low-density lipoprotein cholesterol, RR: relative risk.

with LDL-C below 70–100 mg/dl, further reduction in LDL-C improved outcomes in several clinical scenarios. It seems logical that the same would be even more effective before clinically advanced atherosclerosis has developed. FOURIER and ODYSSEY clarified that no matter how low LDL-C, even below 20 mg/dl, there was no greater incidence of adverse events than from placebo. Mendelian randomization studies have also very convincingly showed that the lower the LDL-C, the less atherosclerosis and the fewer the resulting ASCVD-related events [128]. Moreover, when these changes are earlier in life and atherosclerosis stages, smaller LDL-C changes can lead to larger ASCVD risk reduction.

In a subgroup of the MESA cohort (n =4085), the 10-year number needed to treat (NNT) with statins to prevent an ASCVD event for CAC 0, 1 to 100, and >100 were 87, 37, and 19, respectively. These results are based on an average relative risk reduction of 30% for statin therapy in the referenced primary prevention trials [129]. Furthermore, in a large (n=13,644) relatively lower-risk cohort, CAC >100 was consistently associated with a greater reduction in the hazard for MACE with statin therapy relative to CAC <100. On the contrary, in the 10-year NNT analysis, statins had no significant effect among patients with CAC=0. Patients with a CAC of 1 to 100 had a trend toward benefit (NNT=100; p=0.095), whereas patients with a CAC >100 derived significant benefit with a NNT of only 12 ($p < 0.0001$) [38].

Mortensen *et al.* investigated the association between CAD severity assessed by CCTA in patients without prior CVD and ASCVD events, with low event rates (4.4 per 1000 person-years) among individuals with no CAD and CAC=0. In contrast, event rates were substantially higher in patients with 3-vessel disease (39.8 per 1000 person-years). Consequently, the NNT to prevent 1 ASCVD event in 6 years by treating LDL-C to targets varied greatly from 233 (ESC) and 110 (ACC/AHA) for patients with no CAD to 8-9 for patients with 3-vessel disease (both ACC/AHA and ESC) [130].

Despite being on statin therapy, many patients still have a residual risk for CV events, mostly integrated by residual LDL-C, triglycerides, lipoprotein(a) [Lp(a)], and inflammation. Omega-3 fatty acids have

been known to reduce TG levels, but until recently, it remained unclear if this translated to a reduction in CV events. The direct effect of EPA on reducing CV events was established by the REDUCE-IT trial [111]. The results of this trial, in turn, inspired the EVAPORATE trial [131]. The authors indicated that patients treated with EPA 4 g/day had a reduction in LAP volume compared with placebo at 18 months, as measured by CCTA. In the setting of a small sample size, there was no difference in TG levels; however, this research study served as a hypothesis generator and propelled the potential use for plaque measurements by CCTA as an endpoint in clinical trials. Similarly, but using invasive imaging, the HUYGENS trial demonstrated that the combination of statin and evolocumab after a non–ST-segment elevation myocardial infarction produces favorable changes in coronary atherosclerosis consistent with stabilization and regression [132]. Even though this trial is out of the scope of this literature review since it was done with symptomatic patients, it demonstrates the benefits of lipid-lowering therapies in plaque morphology. Further studies assessing the effects of PCSK9 inhibitor on plaque measured by CCTA are needed. A primary prevention trial with PCSK9 is currently in place (VESALIUS) to evaluate the impact of evolocumab on MACE in high-risk patients without prior MI or stroke (NCT03872401).

5.1. Statin therapy considerations

Statins represent the backbone of lipid lowering therapies. Individual statin selection should be based on patients' risk, LDL-C goal and various conditions determined by patients' comorbidities. Risk of diabetes, chronic kidney disease (CKD) and statin-associated muscle symptoms (SAMS) represent some factors to considerate. In the JUPITER trial, the incidence of diabetes was 25% higher in the rosuvastatin group, and was associated with advanced age, increased fasting blood glucose, and metabolic syndrome. The risk of new-onset diabetes must be weighed against the risk of MACE and mortality [133]. In patients with CKD, a post hoc analysis demonstrated that the glomerular filtration rate remained stable with atorvastatin but significantly decreased in the rosuvastatin group (p=0.036). Atorvastatin but not rosuvastatin, has proven renoprotective effects in the CKD population [133].

Overall, statins as a class are associated with an increased risk of diabetes and hepatic transaminase elevations, with no statistically detectable effect on myalgia, myopathy, rhabdomyolysis, and cancer. Across the totality of the evidence, higher dose of statins result in higher odds of experiencing transaminase elevations, creatine kinase (CK) elevations, and discontinuations because of adverse events [134]. In head-to-head comparison and network meta-analyses, there were no differences among individual statins. Although rare, adverse events associated with statin therapy range from mild to moderate and seem to increase with treatment intensity [134]. Even though side effects are rare, CAC or CCTA can detect patients where the benefit is higher with a more advantageous risk/benefit ratio.

Statin intolerance is defined as one or more adverse effects associated with statin therapy, which resolves or improves with dose reduction or discontinuation. They can be classified as a complete inability to tolerate any dose of a statin or partial intolerance, with an inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective [135]. To classify a patient as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage [136]. An exception are cases of rare severe adverse events such as statin-induced necrotizing autoimmune myopathy, in which case patients should not be rechallenged with any statin.

The most frequently reported patient complaints in the clinical setting are SAMS. In most cases, they occur without CK elevation [135]. In the JUPITER trial, the incidence of myalgia in the statin- and placebo-treated groups were 16% and 15.4%, respectively [101]. In the Heart Protection Study, after 5 years, the incidence of SAMS was 32.9% and 33.1% in the statin- and placebo-treated groups, respectively [137]. Based on the placebo arms of these trials, SAMS are highly prevalent in general.

Less commonly, statin therapy has been associated with myopathy occurring in ~1/10,000 patients per year. A rare muscle-related side effect is rhabdomyolysis occurring in ~1/100,000 patients per year of treatment [134]. When adverse effects are present, clinicians should use the approach of reassessing, rediscussing (net clinical benefit), and rechallenge when appropriate [121]. The presence or absence of CAC or plaque in CCTA can aid in the discontinuation of a problematic statin for the individual patient versus the need to find a tolerated regimen.

5.2. Non-statin lipid-lowering therapies considerations

Based on the high ASCVD risk in individuals with CAC >100, if maximally tolerated statin and ezetimibe therapy results in inadequate lowering of LDL-C, with <50% LDL-C reduction or LDL-C ≥70 mg/dL, the addition of a PCSK9 inhibitors may be considered [120]. Doubling the dose of statin results in only approximately 6% further decrease in LDL-C levels. The addition of ezetimibe to statin therapy typically provides an additional 15% to 25% reduction in LDL-C. Much greater additive reductions occur by adding a PCSK9 inhibitor to statins. The maximum percentage change will occur 4 to 6 weeks after starting a statin or combined therapy. At this time, drug efficacy or initial adherence to therapy should be evaluated. Periodic remeasurements will make it possible to confirm adherence to therapy [138].

Ezetimibe is indicated in treating disorders of elevated cholesterol levels, including LDL-C and ApoB, as monotherapy or in combination with statins [138]. A meta-analysis of eight randomized placebo-controlled trials that included over 2700 subjects showed that monotherapy with ezetimibe 10 mg daily in hypercholesterolemic subjects for a minimum of 12 weeks was associated with a significant 18.5% reduction in LDL-C as compared to placebo [139].

In the wait for clinical outcomes trials, particularly for patients with possible non-compliance or difficulty with administration, the newer agent targeting PCSK9, Inclisiran, has demonstrated an LDL-C reduction of approximately 50% [110]. Similarly, Bempedoic acid demonstrated a decreased LDL-C by 21.4%, non-HDL-C by 17.9%, and apolipoprotein B by 15%. These drugs can be possible additions for those patients that wish to avoid frequent subcutaneous injections and/or statin-intolerant patients [140].

6. Progression/regression of plaque burden after treatment

When evaluating plaque progression, it is essential to consider the influence of remnant cholesterol (RC) on CAC progression as demonstrated by Hao et al. [141]. In a sample of 6544 ASCVD–free individuals from the CARDIA and MESA studies, 42.5% of patients had a high CAC score from baseline. After multivariable adjustment for demographics and CV risk factors, a 1-mg/dL increase in RC levels was associated with a 1.3% higher risk of CAC progression. In addition to RC, elevated TG levels were associated with an increased risk of CAC progression. Similarly, Won *et al.* revealed the TG glucose index was significantly associated with CAC progression in individuals with baseline CAC score ≤100 [142].

Zeb et al. [143] conducted a retrospective study on patients without known CVD and two consecutive CCTA. They demonstrated that the total plaque volume and the progression of non-calcified plaque were significantly reduced among statin users compared to non-statin users. However, there was a non-statistically significant increase in calcified plaque volume between treated and non-treated participants. In 2015, Lo et al. [144] reported the results of a randomized, double-blind clinical trial done in HIV patients with subclinical evidence of CVD defined by the presence of one or more plaques on CCTA and its relationship with statin treatment. In a group of patients in which LDL-C levels were not elevated as per the inclusion criteria of the trial (LDL-C <130 mg/dl), treatment with statins resulted in a reduction of coronary

non-calcified plaque volume by 19% in 1 year, compared with an increase of 20% in the placebo group. In addition, Atorvastatin reduced HRP features.

Although small, nonrandomized studies initially suggested that statin therapy may slow the progression of coronary calcification [145, 146], prospective, randomized studies disagree with this statement, showing no effect of any statin dose on the progression of coronary calcification [147,148]. More recently, in a cohort of 1255 subjects of the PARADIGM study, Lee et al. [149] analyzed the effect of statins treatment on plaque characteristics and found that statins were associated with slower progression of overall coronary atherosclerosis volume and reduction of HRP features but with increased plaque calcification. These findings go hand in hand with the procalcifying effect of statins, besides their known reduction of CV events.

In addition to the assessment of protective therapies such as statins, imaging of subclinical coronary atherosclerosis (in particular CCTA) can be used to monitor the potential deleterious effect of medical therapies on coronary plaque. In 2017, Budoff et al. [150] published a study in which 138 men >65 years old with symptomatic hypogonadism were treated with testosterone gel for 1 year and reported a statistically significant increase in coronary artery noncalcified plaque volume between two different scans (a baseline and a 12 month follow up CCTA), independent of statin use.

Similarly, a study that included patients with angiographically proven evidence of CVD found a relationship between higher levels (>70mg/dl) of Lp-(a) and accelerated progression of coronary LAP in comparison with the group of Lp-(a) < 70 mg/dl. This could, to some extent, explain the known increased risk of myocardial infarction in patients with elevated Lp-(a). In contrast, there was no change in total plaque volume or calcific and noncalcific plaque volumes between the high- and low-Lp(a) groups [151].

7. Conclusion

In summary, CAC and CCTA are highly reproducible tests that directly assess the total burden of coronary plaque and improve risk stratification of asymptomatic individuals over purely clinical risk estimators through the integration of lifetime exposure to the upstream modifiable risk factors, genetic determinants, and therapies. CCTA can provide additional information over and above the presence of calcium, including plaque burden, high-risk phenotypes, and progression/regression of the disease in response to lipid lowering therapies; hence this still remains to be proved in randomized clinical trials.

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CRediT authorship contribution statement

Pamela Piña: Conceptualization, Writing – review & editing. **Daniel Lorenzatti:** Conceptualization, Writing – review & editing. **Rita Paula:** Writing – review & editing. **Jonathan Daich:** Writing – review & editing. **Aldo L Schenone:** Writing – review & editing. **Carlos Gongora:** Writing – review & editing. **Mario J Garcia:** Writing – review & editing. **Michael J Blaha:** Writing – review & editing. **Matthew J Budoff:** Writing – review & editing. **Daniel S Berman:** Writing – review & editing. **Salim S Virani:** Writing – review & editing. **Leandro Slipczuk:** Conceptualization, 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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