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Coronary Artery Calcium: Where Do We Stand After Over 3 Decades?

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ABSTRACT

In 2018, cardiovascular society cholesterol guidelines recommended the use of coronary artery calcium to guide statin therapy in patients 40-79 years of age who are at intermediate risk by multiple risk factor equations (ie, estimated 10-year risk for atherosclerotic disease of 7.5%-19.9% but in whom statin benefit is uncertain). Many such patients have no coronary calcium and remain at <5% risk over the next decade; hence, statin therapy can be delayed until a repeat calcium scan is conducted. Exceptions include patients with severe hypercholesterolemia, diabetes, and a strong family history of atherosclerotic disease. If coronary calcium equals 1-99 Agatston units, the 10-year risk is borderline (5% to <7.5%) and statin therapy is optional pending a repeat scan. If coronary calcium equals 100-299 Agatston units, the patient is clearly statin eligible (7.5% to <20% 10-year risk). And finally, if coronary calcium is ≥300 Agatston units, a patient is at high risk and is a candidate for high-intensity statins. Risk factor analysis combined judiciously with coronary calcium scanning offers the strongest evidence-based approach to use of statins in primary prevention.

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KEYWORDS: Atherosclerotic disease; Coronary artery calcium; Primary prevention; Statin therapy

Coronary artery calcium is a surrogate for coronary artery atherosclerosis burden. More than 40 years ago, investigators showed that coronary calcium detected by fluoroscopy enhanced the predictive accuracy of treadmill exercise testing to indicate coronary lesions ≥50% in patients with hypercholesterolemia.[1] Agatston et al[2] showed that ultrafast computed tomography scans were better than fluoroscopy in detecting and evaluating coronary atherosclerosis. In the 1990s, several smaller studies further found that coronary calcium predicted coronary heart disease and atherosclerotic cardiovascular disease (atherosclerotic disease);[3-9] these studies laid the foundation for several larger studies. One of the most important of the latter was the Multi-Ethnic Study of Atherosclerosis (MESA);[10] this study measured serial coronary calcium in more than 6000 men and women from 6 communities in the United States. It has many investigators and has published more than 1800 papers, a large fraction of which involve coronary calcium.[11] Other informative investigations are the Heinz Nixdorf RECALL Study (4200 participants in Germany).[12] and the BioImage study (6102 participants).[13] Finally, the Coronary Calcium Consortium has assembled a database of 66,636 asymptomatic adult participants free of cardiovascular disease at baseline.[14] It is a multicenter, retrospective, cohort study designed to study the association between coronary calcium and long-term cause-specific mortality.

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The major use of coronary calcium scoring at present is to guide the clinician in a decision to initiate statin therapy for primary prevention of atherosclerotic disease. Committing a patient to a lifetime of statin therapy is not a trivial undertaking. Several factors stand in the way of successful long-term compliance with statins. These include a variety of impediments in the health care system as well as complaints of statin side effects. Because of the investment in clinical management of patients started on statin therapy, it is important to maximize the accuracy of risk assessment to better refine statin eligibility.

CLINICAL SIGNIFICANCE

- Coronary artery calcium can be a useful adjunct for identifying statin eligibility in primary prevention of atherosclerotic disease.
- Patients at apparent higher risk, as suggested by standard risk factors, may have no coronary calcium, indicating a low-risk status. Statin therapy can be delayed for up to a decade before repeat calcium scanning.
- A positive coronary calcium confirms a higher risk status and supports statin eligibility.

For many years, risk assessment as a guide to statin therapy was carried out with an algorithm based on prospective population studies. The first algorithm used in the United States was that of the Framingham Heart Study.[15] More recently, this tool was replaced by algorithms derived from prospective studies in 5 large cohorts in the United States.[16,17] These algorithms, called "pooled cohort equations" were distinguished by ethnicity and gender. Pooled cohort equations were first used in 2013 American College of Cardiology and American Heart Association cholesterol guidelines.[18] In this guideline, the threshold for starting statin therapy was identified as a 10-year risk for hard atherosclerotic disease events of ≥7.5%. This threshold was based on data obtained from randomized controlled trials of statin therapy in patients without atherosclerotic disease.[18] The 2018 American Heart Association/College of Cardiology/Multiple Cardiovascular Societies cholesterol guidelines[19] used the same pooled cohort equations to stratify risk in patients 40-75 years of age into 4 categories of 10-year risk for atherosclerotic disease: low (<5%), borderline (5% to <7.5%), intermediate (7.5% to <20%), and high (≥20%).

Statin therapy was not recommended for patients at low risk. Although therapy may reduce events in borderline-risk patients, a significant reduction comes at the expense of a relatively high number needed to treat. Patients at intermediate risk by pooled cohort equations are potential candidates for statin therapy. But following release of 2013 guidelines,[18] several reports found that pooled cohort equations overestimate risk in selected subpopulations in the United States.[20,21] Among the latter were low-risk groups that differed in several respects from cohorts more representative of the US population as a whole. Thus, not only does baseline risk of various subpopulations of the United States differ, but the reliability of pooled cohort equations for individual patients within populations undoubtedly varies. For example, it is important to mention a particular limitation of risk assessment by pooled cohort equations; these equations provide a population-based risk estimate and do not necessarily apply to individual patients. Advancing age is a powerful risk factor in pooled cohort equations, but use of age in risk scoring can be misleading. In pooled cohort equations, age is basically a surrogate for atherosclerosis burden; yet the latter can vary greatly among individuals. Coronary calcium is also a surrogate for atherosclerosis burden, and when applied to individuals, it should be more reliable than age as a risk factor. Moreover, a series of studies have documented that coronary calcium measurements are most informative in patients at intermediate risk.[20,22] At still higher risk (ie, ≥20%), most patients already have advanced coronary calcium, and thus, starting statins does not require coronary imaging.[13]

Despite coronary calcium's potential to estimate risk for cardiovascular disease, its use in clinical practice so far has been limited. There are several reasons. These include a lack of understanding of appropriate coronary calcium usage, limited access to coronary calcium measurements, lack of insurance coverage, fear of radiation-induced cancer, and inadvertent discovery of chest lesions. In addition to these limitations, some researchers argue that use of statins for primary prevention has limited efficacy. These several limitations have been discussed extensively[23-25] and have been largely resolved.[26,27] A strong case can now be made that potential benefits of coronary calcium assessment outweigh any drawbacks.[22]

This document focuses on evidence that coronary calcium measurements are useful for shared decision-making in clinician-patient discussions for patients at intermediate risk by pooled cohort equations. The 2018 cholesterol guidelines[19] propose a stepwise method for assessing risk. First, 10-year risk for atherosclerotic disease is estimated with validated pooled cohort equations to triage patients into general-risk categories.[16,17] Second, attention is given to other independent risk factors called "risk-enhancing factors"; these factors help to personalize risk in patient discussion (Table). And third, when a decision about statin therapy is ambiguous, coronary calcium is a useful arbiter to better define statin benefit.

The following discussion summarizes categories of coronary calcium scores and makes suggestions for their use in each (Figure).

ZERO CORONARY CALCIUM

Perhaps the most important finding regarding coronary calcium in the past decade has been the observation that patients with zero coronary calcium have low rates of atherosclerotic disease events.[11-13,28-31] This finding, with few

Table Risk Enhancing Factors[19]

Family history of premature atherosclerotic disease; males age <55 y, females age <65 y
Metabolic syndrome
Chronic kidney disease (eGFR 15-59 mL/min/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
History of preeclampsia or premature menopause (before age 40)
Chronic inflammatory disorders such as rheumatoid arthritis, psoriasis or HIV/AIDS
High-risk ethnicity, such as South Asian ancestry
Primary hypercholesterolemia with LDL-C ≥160-189 mg/dL (≥4.1-4.8 mmol/L); non-HDL-C ≥190-219 mg/dL (4.9-5.6 mmol/L)
Triglycerides ≥175 mg/dL (≥2.0 mmol/L), persistently elevated
If measured,
1. elevations in apolipoprotein B ≥130 mg/dL, especially if triglycerides ≥200 mg/dL
2. high-sensitivity C-reactive protein ≥2.0 mg/L
3. lipoprotein (a) ≥50 mg/dL or ≥125 nmol/L, especially if family history of premature CHD
4. reduced ankle brachial index <0.9

ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; eGFR = estimated glomerular filtration rate; LDL-C/HDL-C = low-density lipoprotein cholesterol/high -density lipoprotein cholesterol.

exceptions, obviates the need for immediate statin therapy. Rescanning depending on individual characteristics may or may not reveal enough coronary calcium progression to justify initiation of a statin (ie, 10-year risk for atherosclerotic disease ≥7.5%).[32-34]

It takes a finite period of atherogenesis before calcification occurs. Sometimes, prior to calcification, plaques may rupture causing acute atherosclerotic disease events. Hence, the absence of calcium does not necessarily mean absence of unstable plaque. But in general, as shown in the MESA,[11] absence of coronary calcium generally signifies a low-risk state (ie, 10-year risk <5.0%). Accordingly, patients at intermediate risk by pooled cohort equations and who have zero coronary calcium are not necessarily "statin eligible." In most such patients, statin therapy can be deferred. However, there are exceptions as noted by the 2018 guideline, in particular, severe hypercholesterolemia, cigarette smoking, diabetes, and family history of premature atherosclerotic disease (especially with early age and with multiple close relatives).

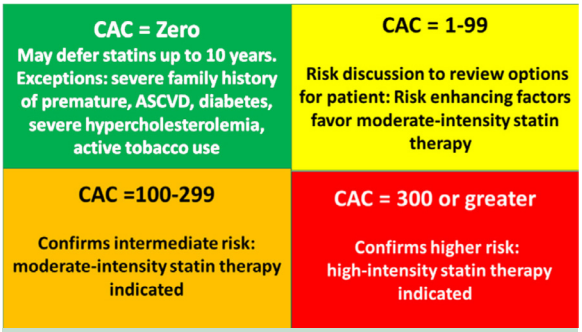

Figure Coronary artery calcium (CAC) categories for considerations for statin therapy. ASCVD=atherosclerotic cardiovascular disease.

The use of zero coronary calcium in a coronary calcium assessment-guided strategy for initiating statin therapy was examined in the Jackson Heart Study of African American adults, ages 40-75 years.[35] This analysis used a microsimulation model and noted that if a strong patient preference to avoid daily medication, zero coronary calcium may provide greater quality-adjusted life expectancy at cost savings than a noncoronary calcium-guided strategy. Moreover, in the Coronary Artery Calcium Consortium,[36] coronary calcium scoring of 53,487 individuals ages 45-79 years supported the guideline-recommended use of pooled cohort equations for initial risk assessment and coronary calcium for further risk assessment in intermediate as well as borderline-risk groups.

A critical question in intermediate-risk patients with zero coronary calcium is when to rescan for progression of coronary calcium. A so-called "warranty period" before conversion to positive coronary calcium score appears to vary, but on average is 3 to 7 years.[32,33] A recent report[33] suggests that patients with zero coronary calcium should be recommended at approximately 5 years to guide the decision about statin initiation. However, in MESA,[11] the average 10-year risk in patients with zero coronary calcium was <5.0%. This finding implies that remeasurement of coronary calcium can safely be made at 10 years for most patients. This period is attractive because it is analogous to the 10-year wait period between negative colonoscopies.

CORONARY CALCIUM OF 1-99 AGATSTON UNITS

MESA[11] showed that in patients with coronary calcium 1-99 Agatston units, the 10-year risk for atherosclerotic disease events falls in the borderline-risk zone. This relationship differs somewhat according to ethnicity, age, and gender. In patients at intermediate risk by pooled cohort equations, a coronary calcium score on 1-99 Agatston units falls in the borderline-risk or low-intermediate risk zones. Higher-risk levels are observed in men compared with women, in older compared with younger individuals, and in Hispanic compared with other ethnic groups. The decision to initiate statins depends on discussion between clinician and patient after consideration of patient preferences. Some experts[27] favor a decision to initiate statin therapy. This level documents the presence of coronary atherosclerosis, and statin therapy theoretically should delay plaque progression. Other authorities are more conservative and counsel delay of statin therapy with a focus on intensive lifestyle therapy.

Some investigators[37] contend that coronary calcium scores in the range of 1-9 Agatston units are ambiguous and are not appreciably different from zero coronary calcium. Nonetheless, follow-up studies[38] indicate that risk for

atherosclerotic disease events associated with coronary calcium 1-9 Agatston units often is in the borderline risk zone (10-year range of 5% to <7.5%).

CORONARY CALCIUM 100-299 AGATSTON UNITS

In MESA,[11] coronary calcium scores in the range of 100-299 Agatston units project 10-year risk for atherosclerotic disease events of approximately 15%. Thus, in patients at intermediate risk by pooled cohort equations, coronary calcium scores of 100-299 Agatston units clearly support statin therapy. Most primary prevention trials were carried out with a moderate-intensity statin. Thus, on the basis of strict evidence-based rules, moderate-intensity statins are favored compared with high-intensity statins. Moderate-intensity drugs also may be better tolerated over a period of many years. If moderate-intensity statins are not well-tolerated, an option is to combine a low-intensity statin with ezetimibe or bile acid sequestrant.

CORONARY CALCIUM ≥300 AGATSTON UNITS

If a patient with intermediate risk by pooled cohort equations has coronary calcium ≥300 Agatston units, this patient can be considered to be high risk and, thus, is a candidate for high-intensity statin therapy.[27] This level of coronary calcium approximates 10-year risk for atherosclerotic disease of ≥20%.

CONCLUSION

In the past 3 decades, many studies have documented a strong relation between coronary calcium and risk for atherosclerotic disease events. At present, however, it is difficult to recommend routine use of coronary calcium as the sole risk-assessment tool for primary prevention. A more measured approach, supported by evidence[36] is to employ coronary calcium to verify or negate risk in patients who have undergone prior screening with standard risk factors and especially in those with increased risk who do not wish to take a daily cholesterol medication. The 2018 cholesterol guidelines have proposed such an algorithm. There is no recommendation for routine coronary calcium screening in patients at low or borderline risk or at high risk found through risk-factor evaluation. Instead, the target population includes patients ages 40-75 years at intermediate risk according to risk factors. Because even this population is diverse, coronary calcium testing can better define precise risk status. This allows for a more targeted approach to primary prevention with statin therapy. The wider use of coronary calcium testing as suggested by the sequential approach in 2018 guidelines can fulfill the promise of focusing proven therapy on those who are likely to benefit most in a cost-effective way.

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