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Discordance between Risk Factors and Coronary Artery Calcium: Implications for Guiding Treatment Strategies in Primary Prevention Settings

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ABSTRACT

Preventive efforts including smoking cessation campaigns, increased awareness of healthy lifestyle habits, risk factor modification, and the appropriate use of statins have been successful in reducing cardiovascular mortality over the last decade. The coronary artery calcium (CAC) scan has reliably been an additive predictor to traditional risk estimation methods, partly because of the heterogeneity between risk factor burden and atherosclerotic burden. The focus of this review is to highlight this heterogeneity by focusing on groups in which risk factor burden and subclinical atherosclerosis burden, as measured by CAC, are discordant. In high-risk groups with 0 CAC, the event rates are consistently low; in low-risk groups with elevated CAC (CAC > 100), the event rates are consistently high. We conclude with our clinical perspective of the considerable heterogeneity between risk factors and atherosclerotic burden in the context of the 2013 ACC/AHA cholesterol treatment and risk assessment guidelines.

Although the burden of atherosclerotic cardiovascular (CV) disease (ASCVD) remains substantially high, the last decade has seen a significant decline in mortality due to ASCVD.[1] Moreover, recent outcomes-based clinical trials in primary prevention and in patients with suspected coronary heart disease (CHD) have "suffered" from lower-than-expected ASCVD event rates.[2–4] The discrepancy between expected and actual event rates is almost certainly related to improvements in preventive measures including public health efforts to reduce smoking, promote healthy lifestyle habits, increase awareness of risk factors, and the success of statin therapy in appropriate patients.

In 2013, updated guidelines by the American College of Cardiology and American Heart Association (ACC, AHA) led to a significant paradigm shift among the primary prevention population with the release of a new pooled cohorts risk estimator and substantial changes in the approach to determine eligibility for statin therapy.[5,6] In recognition of the potential side effects of widespread statin therapy, particularly increasing concerns over diabetes mellitus (DM),[7] the principle shift was from a low-density

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Abbreviations and Acronyms

ACC = American College of Cardiology

AHA = American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CHD = coronary heart disease

CRP = C-reactive protein

CV = Cardiovascular

CVD = Cardiovascular disease

DM = Diabetes mellitus

HDL-C = High-density lipoprotein cholesterol

HNR = Heinz Nixdorf Recall

hs-CRP = High sensitivity C-reactive protein

HTN = Hypertension

LDL-C = Low-density lipoprotein cholesterol

MESA = Multi-Ethnic Study of Atherosclerosis

MetS = Metabolic syndrome

MI = Myocardial infarction

lipoprotein cholesterol (LDL-C)-target based approach to an approach that matches intensity of statin therapy with the absolute 10-year risk of an ASCVD event in the majority of the primary prevention population.[8] This well-intentioned approach seeks to limit the small, but noteworthy potential harm of statins in those who would not benefit from statin therapy while only exposing those who stand to gain significant greater benefit to the potential risks. Accurate risk estimation is critical to this approach.

While calibration of the new 2013 ACC/AHA pooled cohorts ASCVD risk estimator has been questioned, discrimination is also still lacking with a C-statistic of approximately 0.7, which has not significantly improved over prior risk estimators.[9–11] In particular, there have been concerns regarding overestimation of risk and significant overexposure to statins.[12,13]

When the decision to start a statin is uncertain an alternative approach that is supported by the recent US guidelines is to test for subclinical coronary atherosclerosis in the form of coronary artery calcium (CAC), a specific marker of atherosclerosis. Multiple studies have shown significant discordance between risk factors/risk estimation and the burden of atherosclerosis as measured by CAC. This discordance is a testament to the heterogeneity between risk factors and ASCVD. In this review, a broad overview of CAC scanning and its prognostic value is presented, followed by a summary of data examining discordance between risk factors and CAC burden, along with event rates in these discordant groups.

Coronary artery calcium

Atherosclerosis is the result of a complex interplay between risk factors, environmental exposures, and genetic susceptibility. In response to the rise in CVD in the mid-20th century, the landmark Framingham Heart Study was undertaken to identify the "factors of risk", which have evolved to include modifiable factors such as smoking, hypertension (HTN), DM, and cholesterol as well as the non-modifiable gender and age.[14,15] More than 50 years since the seminal Framingham work, these same risk factors serve as the basis for the updated 2013 ACC/AHA risk estimator. The 2013 cholesterol treatment guidelines suggest more recent markers of risk including family history of CHD, ankle-brachial index, C-reactive protein (CRP), lifetime risk for ASCVD and CAC as adjunct considerations when the decision to start a statin is uncertain based on the updated risk estimator. Among these additional risk markers, CAC is the only marker to significantly improve discrimination and substantially reclassify risk beyond traditional risk estimation.[16]

Biologically, it is reasonable to expect CAC to improve significantly upon traditional risk-factor based risk estimators. Atherosclerosis is the necessary mediator between risk factors and the majority of preventable ASCVD events. It therefore stands to reason that regardless of risk factor burden, the presence of atherosclerosis signifies elevated risk for ASCVD, while the absence of atherosclerosis confers minimal to no risk for ASCVD. As a specific marker of atherosclerosis and a strong correlate of the burden of atherosclerosis, CAC scanning is the most practical non-invasive test in primary prevention for identifying subclinical coronary atherosclerosis.[17] Whereas the traditional approach to risk estimation uses a snapshot of risk factors such as cholesterol and blood pressure measured at one office visit, quantification of subclinical atherosclerosis provides an integrated view of risk factor exposure over the lifespan.[18]

While there have been several proposed changes to the CAC scan, the elegant method described by Agatston et al. nearly 25 years ago remains the most widely employed and the clinical standard.[19,20] It essentially consists of a non-contrast enhanced CT scan of the heart that is gated to the cardiac rhythm; CAC appears as a bright white attenuation on the acquired images and is quantified in the coronary artery territories using a simple formula based on the density of the calcification (Fig 1). The semi-automated method makes for a simple, quick test that has become relatively cheap in recent years ($75–$125 in most major cities) with a radiation exposure that is equivalent to approximately 2–3 mammograms with modern technology (~1 millisievert). Most importantly, the last two decades have allowed for extensive validation of the Agatston CAC score with important prospective cohort data for CV disease (CVD) events.

CAC and risk prediction

The Multi-Ethnic Study of Atherosclerosis (MESA) has contributed immensely to the prognostic implications of CAC scanning. MESA was the first population-based cohort study to show a graded association between increasing CAC scores and ASCVD events.[21] Over a median follow-up of 3.9 years in MESA, compared with a CAC score of 0, a score of 1–100 conferred a nearly 4-fold higher risk for events, and a score of >100 conferred a nearly 7-fold higher risk for events. After 5.8 years median follow-up in MESA, Polonsky et al. showed that CAC scoring resulted in significant improvements in reclassification of those participants at intermediate risk for CHD.[22] Compared to a risk-factor based model, a predictive model inclusive of CAC scores classified an additional 23% of participants who experienced events as high risk, while an extra 13% of participants not experiencing events were classified as low risk.