The central principle of primary prevention is that treatment decisions must be carefully matched to accurate estimates of risk. The currently accepted method for determining coronary heart disease (CHD) risk among asymptomatic individuals is through calculation of the risk factor–based Framingham Risk Score (FRS). The FRS relies predominantly on age, sex, and to a lesser degree the traditional modifiable CHD risk factors (smoking, blood pressure, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus) to derive a statistical probability of developing a myocardial infarction or CHD-related death in the ensuing 10 years. Although the FRS has proven to be a useful tool, its overall predictive value in modern cohorts is modest (C-statistic, \( \approx 0.70–0.75 \)). Risk factor profiles widely overlap in those with and without CHD events, with the FRS failing to identify many truly high-risk individuals who are likely to benefit from preventive therapy. For example, 75% of younger patients presenting with ST-elevation myocardial infarction were considered low risk the day before their event. The majority of all CHD events continue to occur in patients considered either low or intermediate risk at baseline FRS assessment.

Improving the FRS by adding risk factors has proven difficult largely because of the fundamental limitations inherent to any risk factor–based approach. The most important limitation is the reliance on 1-time measurements of a small collection of routinely available risk factors taken at a relatively late stage in life (Figure 1A). This strategy may seem fundamentally at odds with the pathophysiology of atherosclerosis. For example, we know from Mendelian randomization studies, cohorts of young patients, and autopsy studies that CHD risk exposure begins early, varies in intensity over the course of development and adulthood, and includes many poorly accounted for genetic and environmental determinants. Common clinical measurements may not capture this time-dependent risk exposure. For example, routine clinical measurements of blood pressure are notoriously variable and tell us little about the lifetime exposure to hypertension and likelihood of end-organ damage. The emerging data suggest that CHD risk is likely best expressed as a function of cumulative exposure to all risk determinants over a lifetime.

A recent advance in risk prediction is the concept of lifetime risk. For example, there is now a 30-year risk calculator from the Framingham Heart Study and a risk stratification tool provided by the Cardiovascular Lifetime Risk Pooling Project. However, these models capture only 1 element of risk.
Biomarkers Are Not Enough for Risk Stratification

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lifetime risk—the extension of risk forecasting further into the future (Figure 1B). Although termed lifetime risk, these models offer no advance in the integration of time-dependent risk exposure over one’s lifetime. Rather, they continue to emphasize 1-time measurement of traditional risk factors typically collected in an older patient.

One strategy for improving risk prediction is through the use of novel serum biomarkers. Serum biomarkers may offer insight about a new pathophysiologic pathway (inflammation with high-sensitivity C-reactive protein [hsCRP]) or may indicate hemodynamic stress (pro-brain natriuretic peptide) or end-organ myocardial damage (high-sensitivity troponin). However, 1-time measurements of serum markers suffer from lack of specificity, repeat-measurement variability, and modest ability to reflect cumulative risk exposure. To date, serum biomarkers have offered little improvement over the FRS. Among ≈250,000 individuals from the Emerging Risk Factors Collaboration, adding hsCRP to the FRS improved risk classification by just 1.5%, with the authors estimating that ≈500 intermediate-risk people would need hsCRP testing to prevent 1 cardiovascular disease (CVD) event during a 10-year period. An alternative strategy for improving risk prediction involves the use of imaging to directly measure the accumulated burden of atherosclerosis. Atherosclerosis imaging tests seek to personalize risk assessment by integrating the cumulative interaction of early risk determinants (ie, genetics and epigenetics) with lifetime exposure to measured (ie, blood pressure and serum cholesterol levels) and unmeasured (ie, air pollution and secondhand smoke) risk factors and directly displaying the resultant effect on the chosen vascular bed in an individual patient (Figure 1C). In this way, atherosclerosis imaging tests may mitigate imprecision in quantifying early-life risk exposures, especially those that accrue before medical encounters, as well as our imperfect ability to measure risk exposure severity in the clinic setting. Equally importantly, direct visualization of the vascular bed allows clinicians to identify individuals who, for unclear reasons, do not develop atherosclerosis despite seemingly significant risk factor exposure.
Serum biomarkers and imaging tests represent fundamentally different types of risk information that require distinct terminology. Serum biomarkers are more similar to traditional risk factors, signaling increased risk of developing a disease and attempting to describe a distinct pathophysiologic process. Atherosclerosis imaging tests are best considered disease scores, offering direct measurement of the disease of interest and offering integration rather than separation of distinct pathophysiologic mechanisms.

In this editorial review, we argue that traditional risk factors and serum biomarkers are insufficient for guiding modern risk-based treatment in primary prevention. To support this hypothesis, we point to data demonstrating the following: (1) marked heterogeneity between age/traditional risk factors and atherosclerosis burden; (2) marked heterogeneity in event rates within traditional risk strata, with the predominant driver of event rates being atherosclerosis burden; and (3) inability of serum biomarkers to produce clinically meaningful risk reclassification beyond the FRS.

In our discussion, we use coronary artery calcium (CAC) scoring from noncontrast cardiac computed tomography as the current prototype of subclinical atherosclerosis imaging in primary prevention. The use of CAC for risk stratification is currently supported in national guidelines by a class IIa recommendation.

Heterogeneity Between Traditional Risk and Atherosclerosis Burden

A fundamental observation is that atherosclerosis burden is not an obligatory finding in older patients or those with many risk factors. Likewise, young patients and those with 0 or 1 risk factor may have an increased burden of atherosclerosis (Figure 2). Although there is a direct relationship between predicted FRS and the presence and severity of CAC, the distribution of CAC within FRS groups remains heterogeneous.

The National Heart, Lung, and Blood Institute (NHLBI)-funded population-based Multi-Ethnic Study of Atherosclerosis (MESA), which enrolled apparently healthy adults with no known CVD, is an optimal study to observe this heterogeneity. For example, when MESA participants are stratified by age and risk factor burden, 2 of the most important components of the FRS, a substantial amount of disagreement is noted with the directly measured atherosclerosis burden.

The number needed to scan (NNS) to detect a CAC score=0 among older individuals aged 75 to 84 is ≈5. Similarly, among individuals with ≥3 risk factors, the NNS to detect a CAC score=0 is just ≈3. Nearly identical trends can be observed for increasing low-density lipoprotein levels, smoking status, and diabetes mellitus status. Among those traditionally classified as intermediate to high risk based on age, conventional risk factor burden,
or calculated risk score, the NNS to detect a CAC score=0 remains <6. Among individuals with no modifiable risk factors, the NNS to identify 1 individual with CAC >100 is 9.

Again using data from MESA, Okwuosa et al\textsuperscript{22} have demonstrated that among individuals with 10-year FRS estimates of 5% to 7.5%, 7.5% to 10%, 10% to 15%, and 15% to 20%, the prevalence of CAC ≥100 was 18%, 25%, 33%, and 41%, respectively, translating into an NNS of 5.5, 4, 3, and 2.5 to detect a CAC score ≥100. At the same time, individuals with a 10-year FRS estimate of 10% to 15%, 15% to 20%, and >20% had a prevalence of CAC=0 of 36%, 27%, and 17%, translating into a respective NNS of 2.8, 3.7, and 5.6 to detect a CAC score=0. To put this in perspective, for a patient with an intermediate FRS of 10% to 15%, one is about as equally likely to discover CAC=0 as an elevated burden of atherosclerosis as indicated by CAC >100.

The Coronary Artery Risk Development in Young Adults (CARDIA) study, a population-based cohort of young asymptomatic individuals aged 33 to 45 years, demonstrates this conundrum in young patients. Given the importance of chronologic age in the FRS, it is difficult for patients aged <45 years to be considered anything but low risk. Likewise, many argue that CAC is a late finding in atherosclerosis and cannot be used to identify young patients at risk. Despite this, 19% of CARDIA participants with an FRS of 5% to 10% had some CAC (NNS≈5), whereas 17% of these young individuals with an FRS >10% already had a CAC score of ≥100 (NNS≈6).\textsuperscript{23}

**Effect of Heterogeneity on Risk Prediction**

Even more important is the heterogeneity between traditional risk and observed events, with discrepant event rates driven by the directly observed burden of atherosclerosis. This concept was highlighted in an observational cohort of ≈44,000 asymptomatic individuals free of known CHD who were referred for CAC testing and followed up for all-cause mortality.\textsuperscript{20,21} Across age categories and risk factor burden, there is a marked variation in mortality rate that is most strongly associated with CAC burden (Figure 3). Of great importance is that all individuals with a CAC score ≥100 have a substantially elevated mortality rate regardless of age or risk factor burden.

The above mortality studies have been limited by self-reported risk factor status, potential referral bias, and lack of CHD-specific mortality. However, strikingly similar results have been observed in the population-based prospective MESA cohort where risk factors were rigorously measured and hard CHD events were adjudicated by committee.\textsuperscript{18,19} Again, the presence of increased atherosclerosis burden (CAC ≥100) was associated with a significant increase in event rate across any given age group or risk factor burden status.

![Figure 3. Effect of coronary artery calcium (CAC) on event rates within traditional risk factor strata.](http://circimaging.ahajournals.org/) Within traditional risk strata, as identified by age group and risk factor burden, the quantity of CAC is the primary driver of adverse events. Adapted with permission from Nasir et al\textsuperscript{20} and Tota-Maharaj et al.\textsuperscript{21} Authorization for this adaptation has been obtained from both the owner of the copyright in the original work and the owner of copyright in the translation or adaptation.
important heterogeneity of events by CAC burden has also been observed among low-risk women, across lipoprotein cholesterol levels, and the traditional FRS categories.\textsuperscript{24,25}

### Statistical Risk Marker Validation

Most biomarkers do not require advanced statistical testing because they fail \(\geq 1\) of 2 important initial steps: (1) documentation of sufficient heterogeneity between traditional risk estimates and values of the risk marker; and (2) documentation of substantial heterogeneity between traditional risk and CHD events, with the disparity driven by the biomarker. However, as shown above, CAC fulfills both of these criteria. Furthermore, validation is then justified and provided by more advanced statistical tests.

In MESA, the Rotterdam study, the Heinz Nixdorf Recall Study, and the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) study, CAC has been shown to enhance overall risk discrimination (using the C-statistic) and to improve classification of individuals into more appropriate risk groups for clinical decision making (using net reclassification improvement).\textsuperscript{25–28}

In the landmark article from MESA, Detrano et al\textsuperscript{29} noted that individuals with a CAC score \(\geq 100\) had a multivariable-adjusted hazard ratio of \(>7\) for major coronary events and a concomitant improvement in the C-statistic from 0.77 for models using the individual traditional risk variables to 0.82 adding CAC. These results have been replicated in other cohorts.\textsuperscript{26–28} Also from MESA, and again replicated in other cohorts,\textsuperscript{26–28} Polonsky et al\textsuperscript{25} demonstrated a net reclassification improvement of 25% for the entire cohort and 54% for the intermediate-risk group.

### The Imaging Hypothesis—the Power of CAC=0

A common feature of all anatomic imaging modalities is a high sensitivity for detecting clinically important disease. The imaging hypothesis states that given the high sensitivity of imaging tests, the greatest value lies in the negative predictive value, determining who is at low risk for developing an adverse outcome. The imaging hypothesis holds true for atherosclerosis imaging. In asymptomatic individuals, it is highly unlikely for a patient to have clinically important coronary disease and have an adverse event when CAC=0.\textsuperscript{30}

The so-called power of 0 has been demonstrated in multiple studies (Table 1). In a pooled analysis of 71,995 patients, the overall mortality rate at 4.2 years when CAC=0 was 0.5% \textsuperscript{31}

Likewise, in a retrospective cohort study of 44,052 patients referred for clinical CAC scans, the mortality rate was just 0.5% at mean 5.6 years of follow-up.\textsuperscript{32} In 2 of the largest population-based cohort studies using baseline CAC assessment, \(<1\%\) of individuals had a hard CHD event during 5 years of follow-up.\textsuperscript{33,34} Importantly, studies have shown that mortality in young patients aged <45 years with CAC >100 is actually higher than for older patients aged >75 years with CAC=0.\textsuperscript{21} Patients with 0 risk factors but CAC >100 have worse survival than those with \(\geq 3\) risk factors but CAC=0.\textsuperscript{22}

Identifying a low-risk primary population is extremely important because it provides clinicians and policymakers a rationale for using less healthcare resources in a population of patients unlikely to receive net benefit from intervention. Although CAC testing achieves this goal, the existing data suggest that biomarkers (such as hsCRP) cannot reliably rule out either atherosclerosis or future CVD events. Rather than identifying those who do not need treatment, serum biomarkers are nearly exclusively added to the FRS to raise risk estimates and thus are inextricably tied to more treatment and downstream cost.

The potential clinical implications associated with CAC=0 are broad and include more selective use of aspirin and statin for primary prevention and more selective use of downstream testing. For example, among individuals with nonoptimum risk factors but CAC=0, we would recommend against the initiation or continuation of aspirin given the likelihood that the risk of bleeding will outweigh the anticipated cardiovascular benefit. About statin use, we would recommend treating those with CAC=0 to less aggressive targets with low-dose statins given that the side effects of statins seem to be dose dependent. Given the extremely low risk, there should be essentially no downstream testing in the CAC=0 group.

### CAC Versus hsCRP

hsCRP has been championed as one of the most promising serum biomarkers. To assess the comparative effectiveness of hsCRP, one must identify studies that directly compare hsCRP and CAC in populations where these tests are likely to be used in clinical practice.

Such analyses have been performed in MESA.\textsuperscript{35} In MESA participants with normal low-density lipoprotein cholesterol \(<130\) who otherwise fit criteria for enrollment in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, the presence of CAC was associated with a 4.3-fold increase in CHD events, whereas hsCRP \(\geq 2\) mg/L was not associated with either CHD

#### Table 1. Outcome Studies Demonstrating Risk of CAC Score of 0

<table>
<thead>
<tr>
<th>Study (Study Type)</th>
<th>Study Size</th>
<th>Number With CAC=0</th>
<th>Study With CAC=0, %</th>
<th>Follow-Up Time, y</th>
<th>Outcome</th>
<th>Events (Event Rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarwar et al\textsuperscript{35} (pooled analysis)</td>
<td>71,995</td>
<td>29,312</td>
<td>41</td>
<td>4.2</td>
<td>CVD events</td>
<td>154 (0.5%)</td>
</tr>
<tr>
<td>Blaha et al\textsuperscript{28} (retrospective cohort)</td>
<td>44,052</td>
<td>19,898</td>
<td>45</td>
<td>5.6</td>
<td>All-cause mortality</td>
<td>104 (0.5%)</td>
</tr>
<tr>
<td>MESA\textsuperscript{35} (prospective cohort)</td>
<td>68,094</td>
<td>34,141</td>
<td>50</td>
<td>4.1</td>
<td>CHD events, hard</td>
<td>10 (0.3%)</td>
</tr>
<tr>
<td>Heinz Nixdorf Recall\textsuperscript{35} (prospective cohort)</td>
<td>44,052</td>
<td>13,222</td>
<td>50</td>
<td>5.0</td>
<td>CHD events, hard</td>
<td>11 (0.8%)</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; and MESA, Multi-Ethnic Study of Atherosclerosis.
or CVD after multivariable adjustment. In the Heinz Nixdorf Recall Study (mean FRS, 11%), hsCRP values of 1 to 3 mg/L did not predict events compared with hsCRP <1 mg/L after multivariable adjustment. Although hsCRP >3 mg/L was associated with a modest 82% increased CHD risk in this study, CAC >400 was associated with a hazard ratio of 5.9 for CHD events. Furthermore, adding CAC to the FRS + hsCRP improved risk discrimination, whereas adding hsCRP to the FRS + CAC had no effect on risk discrimination, suggesting that not only does CAC provide a greater improvement in risk discrimination but adding hsCRP on top of CAC adds little benefit.

Proponents of hsCRP argue that the true value of this test lies in its ability to selectively identify patients who will receive benefit from statin therapy. However, the often-quoted JUPITER trial is not a biomarker trial and thus cannot substantiate this claim. For example, JUPITER exclusively enrolled patients with high hsCRP ≥2 mg/L, and it is unknown whether patients with low hsCRP would have received a similar benefit from rosuvastatin. Subsequent analyses from JUPITER and other trials have shown no evidence of effect modification by hsCRP level. In fact, statins display remarkably consistent relative risk reduction in nearly all patient groups. In the absence of evidence that the relative benefit of statins is dependent on hsCRP status, the question becomes one of the predicting absolute benefits.

In this light, Blaha et al further demonstrated the potential treatment implications of using CAC to guide statin use in clinical practice. In MESA participants fitting criteria for the JUPITER trial (older age, low-density lipoprotein cholesterol <130 mg/dL, and hsCRP ≥2 mg/L), ≈50% had CAC=0. These individuals had a low event rate and thus had a highly unfavorable estimated 5-year number needed to treat (NNT) of 549 to prevent 1 CHD event with rosuvastatin treatment. In contrast, most CHD events (74%) occurred in the small group of JUPITER-eligible patients with CAC>100; treatment in this group would be associated with a highly favorable 5-year NNT of 24. The authors argue that focusing treatment of the subset of individuals with measurable atherosclerosis might represent a more appropriate allocation of resources and might reduce healthcare cost compared with traditional risk factor or hsCRP-based approaches.

The potential for improved absolute risk reduction (and thus NNT) when using CAC to guide preventive therapy was further highlighted in a double-blind randomized controlled trial, whereby patients with CAC scores >80th percentile for age and sex were randomized to either atorvastatin 20 mg or placebo. In the subset with baseline calcium scores >400 (47% of the study population), treatment reduced the incidence of all CVD events by 42% (8.7% versus 15%; \(P=0.046\); estimated 5-year NNT =14). In this study, C-reactive protein did not predict events independently of CAC.

**CAC and hsCRP in Intermediate-Risk Patients**

Intermediate-risk patients represent the ideal target population for improved risk discrimination because treatment decisions in this subgroup are frequently uncertain. Using data from MESA, Yeboah et al performed a comparison of several risk markers in the broad intermediate-risk category. Although CAC, family history of CHD, ankle-brachial index, and hsCRP were each independently associated with increased risk for incident CHD, carotid intima–media thickness and brachial flow-mediated dilation were not associated. The corresponding net reclassification improvement statistics were as follows: CAC=0.659, family history=0.16, ankle-brachial index=0.036, hsCRP=0.079, carotid intima–media thickness=0.102, and brachial flow-mediated dilation=0.024.

We used the above MESA data to extend the comparison of CAC with hsCRP in the intermediate-risk population (Figure 4). Approximately 91% of all CHD events occurred in intermediate-risk individuals with CAC >0. In contrast, the majority of events occurred in patients with hsCRP <2 mg/L. As can be seen in Figure 4, focusing treatment with generic statins on patients with measurable atherosclerosis may potentially maximize the absolute benefit from statin therapy.

**CAC Versus Other Serum Biomarkers**

Although many serum biomarkers display modest associations with CHD events, studies of these markers commonly have small incremental effect sizes with substantial evidence of positive reporting and publication bias. Few serum biomarkers have shown sufficient heterogeneity with traditional risk models to demonstrate even modest incremental value over the FRS. For example, a recent study from the Rotterdam cohort evaluated the predictive ability of several novel risk markers (Table 2). Although several biomarkers were noted to have associations with increased CHD events, only CAC and possibly N-terminal pro-brain natriuretic peptide were noted to have a clinically meaningful effect on risk discrimination and recategorization compared with risk prediction based on conventional risk factors alone.

**Multiple Serum Biomarker Approach**

Given the limited benefit seen with individual serum biomarkers, researchers have investigated the use of combined biomarker scores. Previous cohort analyses have yielded generally unfavorable or mixed results on the ability for multiple biomarker scores to enhance risk prediction, and previous biomarker scores have not been directly compared with measures of subclinical atherosclerosis. However, Rana et al from EISNER recently compared CAC with a multiple biomarker score for the ability to further enhance CVD risk prediction. The multiple biomarker score was associated with a negligible nonsignificant improvement in risk prediction, whereas the addition of CAC was associated with a substantial improvement in risk discrimination and reclassification as noted by a net reclassification improvement of 35% and an improvement in C-statistic from 0.73 to 0.84 (Table 2). Notably, the addition of CAC to the FRS plus biomarker score resulted in improved risk discrimination, whereas the addition of biomarkers to FRS plus CAC had no effect on risk discrimination.
What are the barriers to more widespread use of subclinical atherosclerosis testing? Several potential roadblocks must be considered, including those specific to CAC (No. 1 and No. 2) and those applicable to all future tests (No. 3 and No. 4).

1. Exposure to radiation: The radiation exposure for a CAC scan is roughly 1 mSv, similar to that of a bilateral mammogram, and equivalent to \( \approx 120 \) extra days of background environmental radiation exposure. The potential benefits of preventing CHD morbidity and mortality, and deferring costly medical care when CAC=0, must be weighed against the potential for a small increase in lifetime cancer risk. Given the acceptance of frequent mammography for a disease responsible for a fraction of the total mortality attributable to CHD, selective CAC testing would seem to pose an acceptable risk.

2. Effect of incidental findings: Incidental findings with CAC are common, although the effect of these is less clear. MacHaalany et al\(^4\) noted that among \( \approx 1000 \) individuals who underwent CAC testing, 42\% had incidental findings of some sort, whereas just 1.2\% had clinically significant findings. The value of pursuing most findings is unclear because there is no difference in noncardiac death (including cancer death) between individuals with and without incidental findings. Furthermore, research on the necessity of reporting all incidental findings is needed.

**Table 2. Change in C-Statistic and NRI in the Rotterdam and EISNER Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in C-Statistic*</th>
<th>NRI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterdam(^26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarkers</td>
<td>0.00–0.02</td>
<td>0.4%–7.6%</td>
</tr>
<tr>
<td>CAC</td>
<td>0.05</td>
<td>19.3%</td>
</tr>
<tr>
<td>EISNER(^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker panel</td>
<td>0.02</td>
<td>4.0%</td>
</tr>
<tr>
<td>CAC</td>
<td>0.11</td>
<td>35.0%</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcium; EISNER, Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; and NRI, net reclassification improvement.

*Added to the Framingham Risk Score.

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**Figure 4.** Distribution of coronary artery calcium (CAC), high-sensitivity C-reactive protein (hsCRP), and hard coronary heart disease (CHD) events in intermediate-risk participants from MESA. Although CAC is evenly distributed in intermediate-risk individuals in MESA, the majority of hard CHD events occur in those with elevated CAC. This provides a rationale for directing primary prevention therapy at selected individuals in whom the majority of events occur. In contrast, the majority of events occurred in individuals with low hsCRP, arguing against selected treatment based on hsCRP. Using the relative event reduction (35\%) associated with generic statins, one can see that the 5-year number needed to treat (NNT) is favorable when CAC is high and unfavorable when CAC is low, whereas hsCRP does not provide strong rationale for targeting particular groups.
3. Increased cost of downstream medical testing: The use of any new test may potentially lead to increased downstream healthcare use, so-called layered testing. This is a legitimate concern with all novel serum biomarkers and new imaging tests. Importantly, the EISNER randomized control trial demonstrated that there is no difference in the rate of downstream testing, procedures, or resource use between individuals who did and did not undergo CAC testing. In fact, resources seem to be directed selectively at those at highest risk, which is the goal of primary prevention. For example, among individuals with CAC=0, there was lower downstream medical spending than those randomized to no scan. More research is clearly needed in this area.

4. Lack of evidence for improved outcomes: It is critical to note that no clinical trial has shown improved outcomes solely as a result of enhanced risk prediction. This applies not only to traditional risk scores but to new iterations such as the Reynolds Risk Score as well as serum biomarkers and atherosclerosis imaging tests. There must be a mandate across all risk prediction strategies for true biomarker-driven study designs. However, obtaining funding for these studies has proven difficult.

**Atherosclerosis Imaging—Challenging Existing Risk and Treatment Paradigms**

New risk markers must sufficiently move the risk needle to be expected to have any effect on clinical management of patients. For serum biomarkers, the consistent lack of effect on risk discrimination and reclassification, either individually or combined as a score, limits their value in helping guide treatment decisions for primary prevention. On the contrary, measurement of subclinical atherosclerosis by CAC testing seems to consistently lead to marked improvements in risk discrimination and reclassification. At the present time, only subclinical atherosclerosis imaging with CAC has the potential to truly tailor primary preventive strategies to individual patients based on personalized risk assessment, and these technologies are still rapidly improving.

There are tremendous public health implications in our choice of risk assessment strategies. No interventions in primary prevention are free of cost or risk. Commonly, our decision to treat with an aspirin or a statin is a lifelong commitment with absolutely no guidelines for guiding the safe withdrawal of such a risk-reducing therapy. As a result, the bar for instituting treatment in primary prevention must be set high. From a public health perspective, stakeholders will note that atherosclerosis imaging may help both those in whom the risk–benefit equation is favorable and also those in whom there be possibly a net harm of therapy (eg, CAC=0).

To illustrate this point, we use the controversial example of aspirin therapy for primary prevention in type 2 diabetes mellitus. Particularly in this patient population, aspirin is associated with definite harm (bleeding) and only marginal benefit, with absolute benefit relying heavily on underlying absolute risk. Contrary to the current dogma that all patients with diabetes mellitus are high risk, data from MESA suggest a heterogeneous distribution of CAC and

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**Figure 5.** Diabetes mellitus—a coronary heart disease (CHD) risk equivalent or risk nonequivalent? Although diabetes mellitus is commonly considered a CHD risk equivalent, the risk is, in fact, heterogeneous and is driven by the burden of subclinical atherosclerosis. CAC indicates coronary artery calcium. Adapted with permission from Malik et al. Authorization for this adaptation has been obtained from both the owner of the copyright in the original work and the owner of copyright in the translation or adaptation.
hard CHD events (Figure 5). The majority of hard CHD events occur in the small portion of people with elevated CAC >100. Focusing aspirin treatment on those individuals with a high burden of CAC might optimize the NNT while minimizing the exposure of lower-risk individuals to potential harm and little anticipated benefit. In fact, a recent analysis showed that among patients with diabetes mellitus at intermediate risk in whom guidelines state aspirin might be considered, CAC seems to identify those most likely to benefit. The use of CAC for further risk stratification in asymptomatic adults with diabetes mellitus ≥40 years of age is currently supported by national guidelines (class IIa recommendation).

Summary

Although risk factors have proven to be useful therapeutic targets, they are poor predictors of risk. Traditional risk scores are moderately successful in predicting future CHD events and can be a starting place for general risk categorization. However, there is substantial heterogeneity between traditional risk and actual atherosclerosis burden, with event rates predominantly driven by burden of atherosclerosis. Serum biomarkers have yet to show any clinically significant incremental value to the FRS and even when combined cannot match the predictive value of atherosclerotic imaging.

As clinicians, are we willing to base therapy decisions on risk models that lack optimum-achievable accuracy and limit personalization? The decision to treat a patient in primary prevention must be a careful one because the benefit of therapy in an asymptomatic patient must clearly outweigh the potential risk. CAC, in particular, provides a personalized assessment of risk and may identify patients who will be expected to derive the most, and the least, net absolute benefit from treatment. Emerging evidence hints that CAC may also promote long-term adherence to aspirin, exercise, diet, and statin therapy. When potentially lifelong treatment decisions are on the line, clinicians must arm their patients with the most accurate risk prediction tools, and subclinical atherosclerosis testing with CAC is, at the present time, superior to any combination of risk factors and serum biomarkers.

Disclosures

Dr Budoff has received a research grant from GE Healthcare. The other authors report no conflicts.

References


Response to Blaha et al

Charlotte Andersson, MD, PhD; Ramachandran S. Vasan, MD

Dr Blaha et al emphasize that a zero coronary artery calcium (CAC) score identifies individuals with a high risk factor burden who do not develop CVD, citing studies (comparing individuals aged >75 years with those aged <45 years) that are limited by referral bias. Other population-based studies indicate that individuals with a high Framingham risk score but CAC score of 0 have a greater risk of CVD than individuals with a low Framingham risk score but a high CAC score. Although CAC scoring improves risk reclassification, there is no evidence that such reclassification reduces morbidity/mortality or lowers healthcare expenditure. Overall, it may be unethical to ignore elevated risk factors in patients with a 0 CAC score because of potential atherosclerotic and nonatherosclerotic (target organ damage) sequel in the absence of long-term data demonstrating lack of adverse outcomes in this group. The specificity of the CAC score for obstructive coronary disease is limited, and it does not correlate with vulnerable plaque burden. The typical thin-capped fibroatheroma with an inflamed cap and a necrotic lipid-rich core that antedates acute coronary syndrome is not heavily calcified; it shows micro- or spotty calcification that is beyond the resolution capability of current scanners. In contrast, heavily calcified plaques are often stable. Furthermore, the calcification extent in vulnerable plaques does not increase with age, whereas the CAC score does. Finally, both CAC scoring and biomarkers yield complementary information on CVD risk because acute coronary syndrome arises from the conjoint interactions of local plaque vulnerability with humoral factors, and the latter (unlike CAC) can be targeted pharmacologically.
Is There a Role for Coronary Artery Calcium Scoring for Management of Asymptomatic Patients at Risk for Coronary Artery Disease?: Clinical Risk Scores Are Not Sufficient To Define Primary Prevention Treatment Strategies Among Asymptomatic Patients

Michael J. Blaha, Michael G. Silverman and Matthew J. Budoff

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