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REVIEW PAPER

Evidence
based cardiovascular risk assessment

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Summary

In order to best identify persons at risk for cardiovascular disease (CVD), it is important to understand the guidelines for CVD risk assessment and evidence-based methods for evaluation of risk in asymptomatic individuals. In this report, we will 1) review the role and limitations of global risk assessment, 2) review the evidence and recommendations for biomarkers in CVD risk assessment, and 3) review the evidence and recommendations for subclinical disease evaluation / imaging in CVD risk assessment.

Keywords

Screening, atherosclerosis, prevention, risk assessment

In 1961, Dr. William B. Kannel from the Framingham Heart Study introduced the concept of cardiovascular risk factors from some of the early longitudinal data showing the importance of elevated cholesterol, blood pressure (BP), and smoking in relation to future coronary heart disease (CHD) risk [1]. The concepts of multivariable and global risk assessment, based on estimating risk from the combination of several risk factors (Figure 1) developed over succeeding decades cumulating in the development of the Framingham Risk Scores, as well as other risk scores used in other parts of the world, including the Systematic COronary Risk Evaluation (SCORE) algorithms in Europe [2–4], which all differ according to the endpoint used, length of follow-up, and risk factors included. The U.S. National Cholesterol Education Program was one of the first groups to recommend use of global risk assessment scoring specifically for persons at suggested intermediate risk based on the presence of 2 or more risk factors [5]. For example, one can apply different risk scoring systems to a given case study, a 67-year old woman, nonsmoker, with total cholesterol of 210 mg/dL, systolic BP of 138 mm Hg, and high-density lipoprotein (HDL) cholesterol of 42 mg/dL. She also has a triglyceride level of 201 mg/dL, waist circumference of 36 inches, and fasting glucose of 109 mg/dL which do not factor into these risk scores, but show that she has all five metabolic syndrome risk factors. Depending on what risk score is used, one gets dramatically different results, ranging from only 1–2% of the European SCORE algorithm for fatal CVD is used, to 3% if the 10-year CHD Framingham risk score is used [6], 10% if the Framingham 10-year total CVD risk score is used, to

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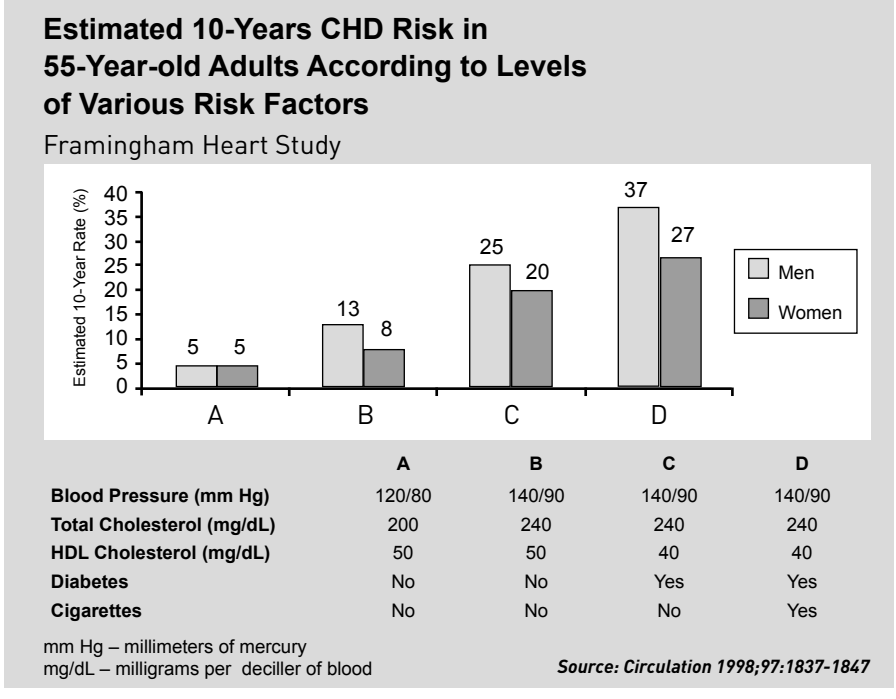

Figure 1. Multivariable CHD risk assessment

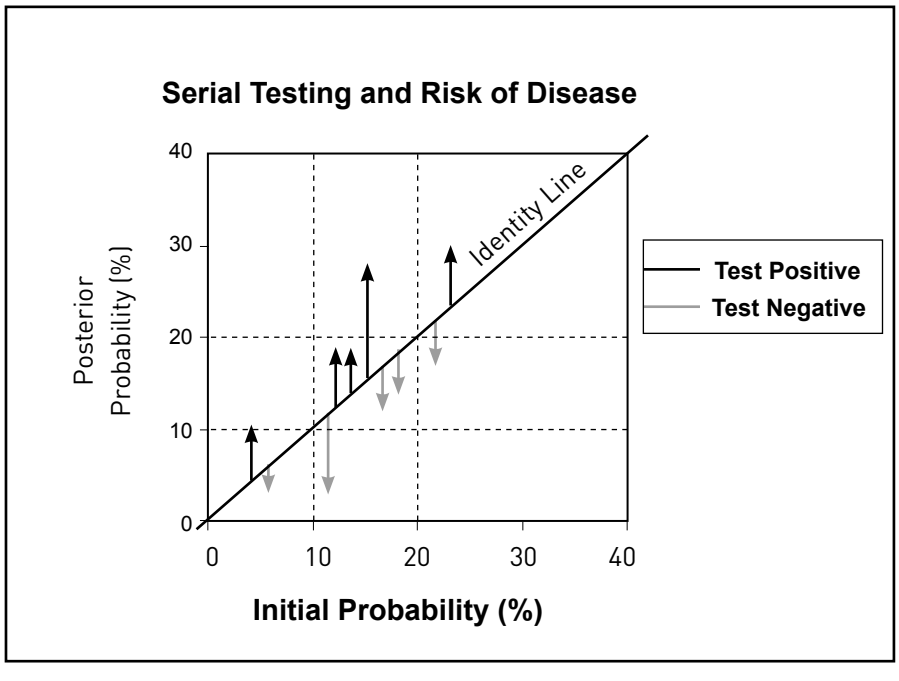

Figure 2. Reclassification of risk by a screening test

39% if lifetime risk is estimated. Many persons who suffer CVD events are not at high risk; in fact, 56% or 87 million persons in the U.S. have low short-term but high lifetime risk [7] and lifetime risk for total CVD is approximately 60% in men and 50% in women [8]. One can suggest possibly considering use of a short-term (e.g., 10-year) risk score initially, and in those at low or intermediate risk, then applying a lifetime risk estimation to decide who should be treated. Persons initially at high risk by the short-term score or lifetime risk score would be treated, whereas those at lower risk by both short-term and lifetime risk scoring would receive lifestyle management.

Global risk scoring algorithms are therefore only moderate accurate for identifying those who will eventually suffer a major coronary event. There are a number of criteria that are required for a good screening test for evaluation of CVD risk. These criteria include sensitivity in identifying those who have the condition of interest, providing reproducible results, detecting those where early intervention is likely to have a beneficial impact, and being able to provide incremental value to risk predicted by office-based risk assessment (e.g., risk scores) [9]. One example of how a screening test may work is that it can be applied to those initially at intermediate (e.g., 10–20%) risk and if positive, would stratify that person to a higher risk category, and if negative would stratify them to a lower risk category (Figure 2). A new metric for clinical utility, the net reclassification

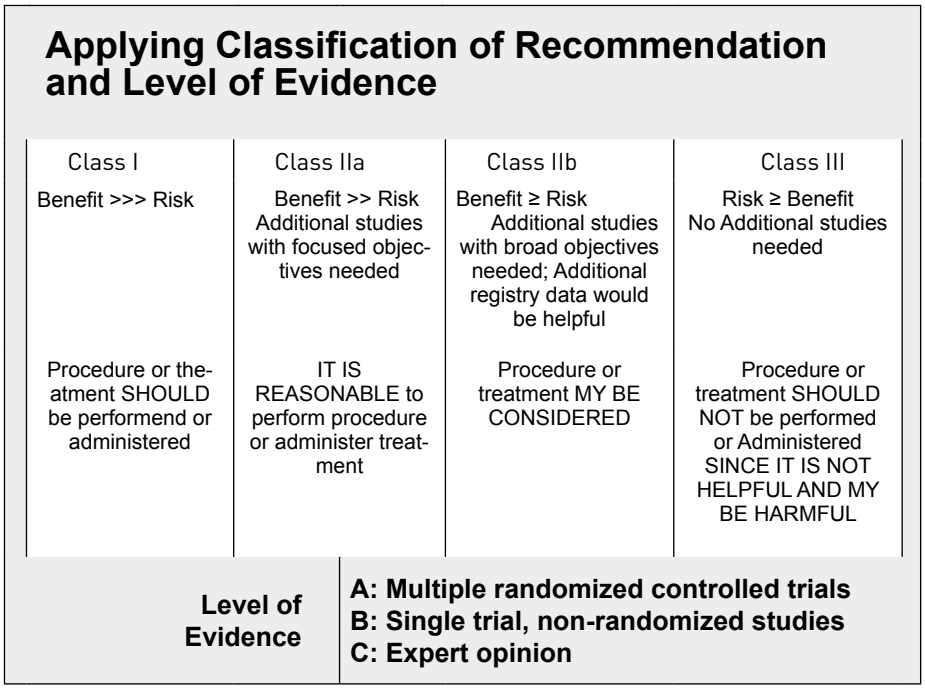

Figure 3. American Heart Association / American College of Cardiology Classification of Recommendations and Levels of Evidence

index, is defined as the net proportion of persons who are correctly reclassified from the new test, or the sum of 1) cases whose risk is stratified upward (correct) by the test being positive minus the cases where risk is stratified downward (incorrect) and 2) controls whose risk is stratified downward (correct) minus those who are stratified upward (incorrect) [10].

In 2010, the *American College of Cardiology Foundation* (ACCF) / *American Heart Association* (AHA) guidelines for CVD risk assessment in asymptomatic adults were published and form the basis for the recommendations and screening tests discussed in this report [2]. They graded a large number of screening tests according to the strength of recommendation or size of effect (Class I being strongest, III being weakest) and level of evidence (A being strongest and C being weakest) (Figure 3).

Inflammatory factors and other biomarkers

Numerous prospective studies have documented high sensitivity C-reactive protein as an independent risk factor for CVD events with approximately a two to four-fold greater risk associated with being in the highest vs. lowest quartile [11]. These studies, as well as the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) clinical trial involving rosuvastatin given to persons with normal low-density lipoprotein (LDL) cholesterol but elevated high-sensitivity C-reactive protein (hs-CRP) resulting in significant CVD event reduction, have led to the hs-CRP recommendations from the *ACCF / AHA* statement and the *National Lipid Association* expert panel. They do recommend (Class IIa or IIb, level of evidence B) hs-CRP assessment in men aged 50 years or over or women aged 60 years and over not on lipid-lowering therapy but with an LDL cholesterol <130 mg/dL, as well as younger intermediate risk persons. Measurement, however, is not recommended in higher or lower risk persons [2].

Elevated levels of lipoprotein associated phospholipase A2 (LpPla2) are also shown from a large meta-analysis to confer excess risk of CVD events, and to provide additive value in combination with hs-CRP for identification of higher risk persons [12]. The guideline panels did give LpPla2 a class IIb level of evidence B recommendation for measurement in those at intermediate risk [2].

B-type natriuretic peptides or BNP have also been shown to be positively associated with CVD risk both in persons with and without existing CVD from large meta-analyses [13], but only very modest improvements in discrimination as measured by the C-statistic have been noted, and the *ACCF/AHA* panel did not recommend (Class III) its measurement for CHD risk assessment in asymptomatic adults [2].

It is possible that a multimarker approach utilizing biomarkers representing complementary, but different pathologies may be practical in the future and numerous groups are trying to identify the "cocktail" of biomarkers that will serve to significantly enhance risk reclassification. For example, such a combination of biomarkers might involve inflammation, myo-

cyte necrosis, hemodynamic stress, accelerated atherosclerosis, and vascular damage. An example from the Framingham Heart Study utilizing five distinct biomarkers (BNP, C-reactive protein, urine albumin / creatinine, homocysteine, and renin) shows an index consisting of the biomarkers to be independently associated with risk of CVD events; however, only a very modest improvement in C-statistic was observed [14].

While somewhat obvious, but poorly documented in the medical history, a premature family history of CHD is strongly associated with future risk and a careful evaluation of family history in all first degree relatives is recommended; however, genomic screening, despite its popularity, as failed to be proven to provide incremental predictive utility for CVD events over standard risk assessment and is not recommended. Modest recommendations, however, are made for the assessment of HbA1c in persons without diabetes, as well as urinary albumin excretion, especially in those with hypertension or diabetes [2].

Subclinical CVD assessment methods

Screening tools have been developed for evaluating subclinical CVD in just about every part of the body, ranging from carotid ultrasound to aortic and carotid magnetic resonance imaging (MRI), coronary calcium screening by computed tomography (CT), ankle brachial index for peripheral artery disease, and brachial artery reactivity and radial tonometric techniques for assessing endothelial function. We will review the principal screening modalities (namely carotid ultrasound, ankle-brachial index, and coronary calcification screening) that have the greatest evidence base for cardiovascular risk assessment.

Carotid ultrasonography. Probably the most established method for examining subclinical atherosclerosis is carotid B-mode ultrasound (Figure 4). It is noninvasive without radiation and of moderate cost and there are numerous clinical trials that have used this as a surrogate endpoint for examining effects of therapeutic interventions such as lipid-lowering on retarding progression of atherosclerosis. While the accuracy of assessments of carotid intima-media thicknesses (IMT) depends on the operator, easier more automated devices are being developed which will make its assessment more standardized and applicable to the office-based practitioner. The *ACCF/AHA* guidelines give IMT measurement a class IIa level of evidence B recommendation in asymptomatic intermediate risk persons [2]. Increased carotid IMT has long been shown to be associated with greater

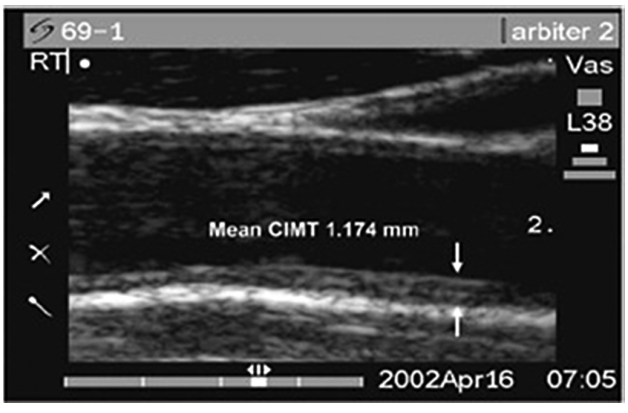

Figure 4. Example of carotid B-mode ultrasonography for assessment of carotid intimal media thickness

CVD event risk, such as shown by the Cardiovascular Health Study in the elderly, where among those in the 5th quintile for carotid IMT, one quarter had suffered a MI or stroke within 7 years [15]. More recently, the Atherosclerosis Risk in Communities study demonstrated the combined importance of both carotid IMT as well as carotid plaques for prediction of CHD events; at each level of carotid IMT, there was added prediction offered by the presence of carotid plaques [16]. The combination of both was able to reclassify 23% of individuals over traditional risk factors.

Ankle brachial index. Measurement of subclinical peripheral arterial disease can help identify persons more likely to have vascular disease in other areas as well as increased CVD risk. Ankle brachial index (ABI) measurement involves a simple Doppler tool and is completely noninvasive, with the ratio of the higher of the systolic BP measures from each ankle forming the numerator for the left and right ABI and the higher of the systolic BP measures taken in each arm being the denominator. An ABI < 0.9 is diagnostic of peripheral arterial disease. Studies such as the Cardiovascular Health Study have shown the lower the ABI the worse the survival, with <80% of subjects alive after 6 years among those with an ABI < 0.9 [17]. The more recently reported ABI Collaboration showed that compared to a reference group of 1.1–1.2, those with an ABI <1.0 were at significantly higher risk of total mortality, even those in the borderline 0.9-<1.0 range, there was nearly a two-fold increase in the risk of mortality [18]. From this study, 19% of men and 38% of women were reclassified in their risk category from the addition of ABI.

Coronary artery calcium. Coronary artery calcium (CAC) measured by computed tomography (Figure 5) has established itself as a potent subclinical disease predictor of future CVD events. The extent of CAC correlates with overall atherosclerotic burden,

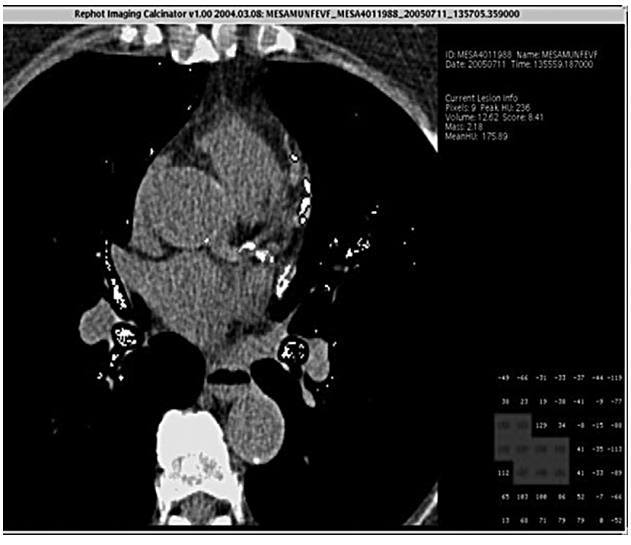

Figure 5. Example of coronary calcium evaluation by computed tomogrphy

although the greatest CAC deposits may not necessarily be present where the tightest stenosis are located and not all atherosclerotic lesions necessary contain CAC. While numerous "commercial" scanning cohorts have shown a direct relation between CAC scores and future CHD events, the Multiethnic Study of Atherosclerosis (MESA) was the first population-based prospective study to demonstrate this with successively higher rates of CHD events associated with greater CAC scores [19]. Those with a CAC score >300 compared to 0 had nearly a 7-fold greater risk of major CHD events and 10-fold greater risk of any CHD events. Moreover, incremental discrimination from higher C-statistics were noted in the four major ethnic groups included in MESA over and above standard risk factors. Overall, 23% of persons with events were reclassified as high risk and 13% without events reclassified as low risk [20]. More recently, we demonstrated CAC scoring to stratify risk in those with metabolic syndrome and diabetes; there was a 10-fold or greater gradient in risk from those without CAC to those with CAC scores of 400 or greater, thus demonstrating that diabetes is not a CHD risk equivalent but is associated with significant heterogeneity in risk (Figure 6) [21]. More than one-third of our cohort with diabetes had CAC scores of 0 and CHD risk was lower than many persons without diabetes or metabolic syndrome; thus, this raises question regarding whether diabetes is in fact a CHD risk equivalent. The *ACCF/AHA* statement has noted with a Class IIa level of evidence B recommendation that measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk, as well as at low to intermediate risk based on 6-10% (class IIb), but not in those at low risk. However, those with diabetes aged >40 are also appropriate for CAC measurement (Class IIa level of evidence B) (2). Progression of CAC has also recently been demonstrated to be independently associated with future CHD event risk [22]; however, guidelines thus far have not endorsed repeat CAC scanning for stratification of risk or treatment [23].

The identification of CAC has also been shown to be related in an observational study to be related to the subject's greater likelihood of practicing preventive behaviors, such as starting aspirin or cholesterol medicine, losing weight, and seeing a doctor, with the extent of calcification also shown to be related to the likelihood of certain behaviors [24]. More recently, in the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) prospective randomized trial, where over 2,000 asymptomatic subjects were randomized 2:1 to calcium scanning or not to scanning, those who received scanning showed no increase in their Framingham risk score 4 years later, compared to an increase in the risk score seen among those not received scanning [25]. Also, in a very recent report, the greater the lifestyle score (number of healthy lifestyle behaviors), the less the incidence or progression of CAC seen from serial CAC scanning in MESA [26].

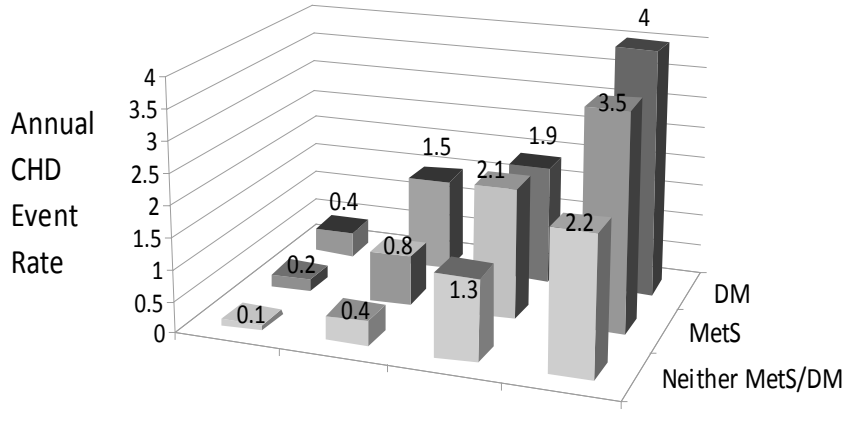

Figure 6. Stratification of CHD risk by coronary calcium levels in persons with and without metabolic syndrome and diabetes. Adapted from Malik et al. [21]

Some have argued that CAC testing might increase the utilization of other testing, but this has not been proven. In fact, the Eisner Study of subjects randomized to CAC testing or no testing showed no significant difference in the incidence of downstream testing over 4 years of follow-up [25]. In addition, the radiation dose from CAC scanning has been shown to be similar to that of a mammogram or a long distance air flight.

Further, CAC scanning can help identify those most likely to have a positive nuclear myocardial perfusion test; the likelihood of such a test being positive is quite low unless CAC scores exceed 400 [27]. Among those with diabetes or metabolic syndrome, a threshold CAC score of 100 is seen to identify those with an increased likelihood of a positive nuclear study [28]. Thus, CAC scanning may serve as a useful gatekeeper for identifying those most likely to benefit from nuclear myocardial perfusion testing.

There has also been interest in whether CAC testing can help identify those who may or may not benefit from statin therapy. In the Jupiter eligible population from MESA (e.g., LDL cholesterol <130, hs-CRP > 2, and no diabetes mellitus) it was shown that only 25% of subjects had a CAC >100 and when the Jupiter relative risk reduction was applied to the CHD event rates observed in this group, it would take only 24 persons treated with a statin to prevent one event; however, in the 27% with CAC 1-100, the number need to treat (NNT) was 94 and in the remainder with CAC=0, the NNT was 549 [29].

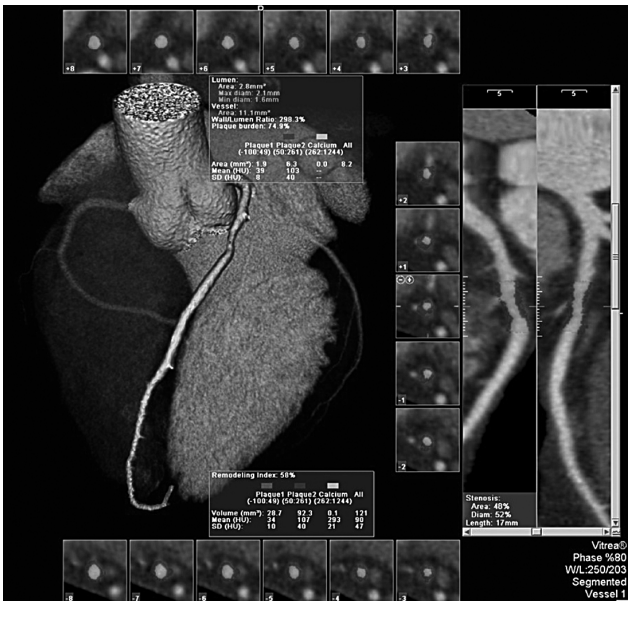

Figure 7. 3D vessel probe of the Left Main and left anterior descending (LAD) coronary artery from CT angiography. Curved Multi-planar Reconstruction (MPR) images are automatically rendered and quantify this LAD lesion at 48% diameter stenosis. SUREPlaque software is used to determine plaque burden and a vessel remodeling index at this lesion. Images courtesy of Courtesy of Toshiba America Medical Systems and Vital Images SUREPlaque and University of California Irvine, Cardiac CT Center.

When all the noninvasive screening modalities are examined together in MESA, a recent report shows CAC to be by far the strongest predictor and is associated with the greatest incremental value improvement by the C-statistic over Framingham Risk Score [30].

CT angiography and non-calcified plaque. CT angiography has paved the way for identification of non-calcified and vulnerable plaque characteristics (Figure 7) which quantification that compares well to that of intravascular ultrasound [31]; however, due to the radiation and contrast enhancement required, the *ACCF/AHA* recommendations still do not indicate it for CVD risk assessment in asymptomatic adults [2]. Nevertheless, the number of diseased vessels from CT angiography has been shown to be a strong predictor of prognosis [32], although information provided by CT angiography does not appear to add further information to prediction of CHD events over that of CAC [33].

Summary

The *ACCF/AHA* statement has made recommendations for screening certain populations with different imaging modalities and biomarkers. Most key imaging modalities have been recommended for CVD risk assessment in intermediate risk persons. It is important that screening tests be able to provide added clinical utility over global risk assessment and that screening be able to help identify persons most likely to benefit from more intensive therapy. However, it is not known whether screening for subclinical atherosclerosis will eventually result in improved clinical benefit. There will be newer guidelines for CVD risk assessment released in the near future by the U.S. National Institutes of Health in collaboration with U.S. cardiology professional societies.

Conflict of interest: None declared

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