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Cardiovascular Disease Risk Assessment: Review of Established and Newer Modalities

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Opinion statement

Cardiovascular disease (CVD) risk assessment has changed substantially in recent years. Statins are recommended for a larger proportion of Americans based on a recently recommended CVD global risk calculator derived from studies of multiple large, diverse, community-based cohorts. Recent research shows that patients that are intermediate risk for CVD events may benefit from net reclassification of risk based on circulatory biomarkers like c-reactive protein, interleukin-6, lipoprotein(a), and lipoprotein-associated phospholipase A_2. In addition, multiple imaging biomarker modalities, including coronary artery calcium and carotid intima-media thickness, may play an important role in further risk stratification for patients in the later stages of CVD development. The data obtained from these markers could play an important role for deciding how aggressive a physician should be with pharmacological therapy. Here, we discuss many of the current recommendations of CVD risk assessment including those included and excluded from recent guidelines, while addressing the most recent data supporting renewed and newer modalities for CVD risk assessment.

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients in the USA [1]. The annual costs for CVD hospitalizations was estimated to be $320.1 billion in 2011 alone, approximately $100 billion more than estimated hospitalization costs for cancers and benign neoplasms in a recent year [1].

CVD presents a large burden to our society and our healthcare system, and while great strides have been made to meeting goals like the American Heart Association's (AHA) 20 % improvement in cardiovascular health by the year 2020, such goals rely on improved strategies and implementation of CVD risk assessment.

In 2008 that the National Heart, Lung, and Blood Institute commissioned three expert panels (regarding cholesterol treatment, overweight management, and blood pressure treatment) to create updated guidelines meant to address the CVD burden. In November of 2013, the American College of Cardiology (ACC) and AHA released guidelines for cardiovascular risk assessment based on a systematic review and synthesis of high-quality medical literature [2•]. These guidelines, and the associated controversy with them, have played a pivotal role in redefining global risk assessment. Additional guidelines have also addressed specifically risk assessment for those who are asymptomatic, most notably diabetic patients [3]. These guidelines appreciate their shortcomings and leave open the possibility of diagnostic tests that may more reliably predict CVD. This future may involve diagnostic modalities that are able to move past long-term CVD risk assessment and address short-term risk, such as perhaps helping to predict CVD risk in the next 6 months to a year. The purpose of this review is to analyze current recommendations for global risk-assessment of CVD, while addressing newer circulatory and imaging biomarkers that may add to an individual's CVD risk assessment.

Current guidelines for global risk assessment

The new equations for risk assessment set forth by the 2013 ACC/AHA Cardiovascular Risk Assessment Guideline are based on pooling cohorts from the Framingham, the Atherosclerosis Risk in Communities, the Coronary Artery Risk Development in Young Adults, and the Cardiovascular Health Studies [2•]. The large sample size these studies provide together gives this new Pooled Cohort Risk Score greater precision than previous risk scores such as Framingham based on a single population. As compared to the ATP III Framingham Risk Score (FRS), the new Pooled Cohort Risk Score predicts 10-year risk of both coronary heart disease (CHD) and stroke together rather than just CHD. However, CHD in this case includes non-fatal MI and CHD death, meaning it does not include outcomes of PCI, CABG, and unstable angina requiring hospitalization, so had the latter been included, actual predicted risk would be greater.

Ultimately, the outcome of atherosclerotic cardiovascular disease (ASCVD) was defined as the first occurrence of non-fatal myocardial infarction, CHD death, fatal stroke, or non-fatal stroke. The ASCVD risk calculator is based on traditional risk factors including a patient's sex, age, race, total cholesterol, high-density lipoprotein cholesterol (HDL), systolic blood pressure, treatment for high blood pressure, diabetes, and smoking status.

Ultimately, the calculator produces a 10 year and lifetime risk for ASCVD. The concept of lifetime risk is particularly interesting as it has been shown that individuals aged <50 have a low predicted 10-year risk for CVD despite significant risk factors [4]. However, in the setting of cumulative exposure to modifiable risk factors at younger and younger ages, the committee included lifetime risk as not a replacement for 10-year risk assessment but a form of risk communication that may help motivate the patient towards better adhering to lifestyle and other therapies. Indeed, the ASCVD risk calculator should be used within a clinician-patient discussion about the potential risks and benefits of beginning or intensifying therapy, lifestyle management strategies, and personal preferences regarding treatment.

Population for assessment

The guidelines suggest that among non-Hispanic African Americans and non-Hispanic whites free from ASCVD who are 20–79 years of age, traditional ASCVD risk factors should be addressed, and in adults 40–79, 10-year ASCVD risk should be done every 4–6 years assuming (ACC/AHA Class IIa-B Recommendation). Of note, the authors address the lack of ethnic-specific risk algorithms given insufficient data and do note that Hispanic-Americans and Asian-Americans have a lower and American-Indian ethnicities a higher 10-year risk for ASCVD as compared to non-Hispanic Whites that should be taken into consideration when the risk calculator is used in these groups.

Included additional screening modalities for uncertain quantitative risk assessment

Currently, the 2013 guidelines state that after quantitative risk assessment, if a risk-based treatment decision is uncertain, assessment of additional modalities may be indicated for those at intermediate risk. Based on the patient's history, the most straightforward inclusion was a patient's family history of premature cardiovascular disease (ACC/AHA Class IIb-B Recommendation). This was defined as a first-degree relative male <55 or female <65 years of age, which Kashani et al. was shown to be an independent contributor to risk appraisal of CVD risk [5]. Importantly, one should always quantitate the number of first-degree affected relatives since the greater the number with a premature family history, the greater the person's risk [6].

With regard to circulatory biomarkers, high-sensitivity c-reactive protein (hs-CRP) has been well established as being associated with CVD risk and is a recommended measure when the treatment decision on the basis of global risk assessment alone is uncertain (ACC/AHA Class IIb-B Recommendation). It has been shown that there is a clear additional benefit of adding hs-CRP to traditional FRS when predicting CVD risk, but hs-CRP was not included in the original calculator secondary to unclear cost-effectiveness in high- and intermediate-risk populations who would use low cost statins [7, 8]. As the association between hs-CRP and CVD risk is strongest for hs-CRP as a continuous variable, the appropriate cut-off for ease of clinical decision-making has been unclear [9, 10]. The 2013 ACC/AHA Guidelines support a value of ≥2 mg/L for hs-CRP in this case. While elevated hs-CRP identifies higher risk persons, we still do not have definitive information that lowering hs-CRP reduces CVD event risk; the currently ongoing Cardiovascular Inflammation Reduction Trial will help answer this [11]. Other circulatory biomarkers such as ApoB were not included by the 2013 ACC/AHA Guideline panel largely because there was no evidence that other biomarkers had additional predictive value for CVD events beyond standard risk factors [12].

With regard to imaging modalities, detection and quantification of coronary artery calcium (CAC) has had a large wealth of evidence showing the added benefit to the c-statistic in traditional models for CVD risk evaluation within the intermediate-risk groups (ACC/AHA Class IIb-B Recommendation) [8]. However, given that prior studies have focused on an outcome of purely CHD (rather than ASCVD), and there is continued uncertainty regarding safety and cost-effectiveness, the panel labeled this as a Class IIb Recommendation. Those patients with ≥300 Agatston units of ≥75th percentile for age, sex, and ethnicity [based on the Multi-Ethnic Study of Atherosclerosis (MESA) coronary calcium risk calculator—http://www.mesa-nhlbi.org/cacreference.aspx] may benefit

from upward risk stratification for the purposes of initiation or intensification of therapy. The guideline did note that coronary calcium screening was likely to be the most useful of the additional modalities proposed for cardiovascular risk stratification beyond global risk assessment.

The 2013 ACC/AHA Guidelines has also included ankle brachial index (ABI) as a modality for better risk stratification, however, the added benefit beyond the FRS is most predominant in females (ACC/AHA Class IIb-B Recommendation). While an improvement in the c-statistic did occur for both men and women, the added benefit was only statistically significant in women when the ABI was added to the FRS for CVD risk [0.605 (0.644–0.672) vs 0.658 (0.644–0.672)] [13]. An ABI cut-off of <0.9 was included as support for revising a patient's initial risk assessment, although clearly data from the recent ABI Trialists Collaboration also shows significant increases in risk even at borderline ABI levels of 0.9–1.0 [14].

New and renewed modalities for CVD risk assessment

There have been other circulatory and imaging biomarkers that have been proposed for CHD and CVD. Ultimately, the clinical value of a risk marker should be assessed by its effect on patient management and outcomes. In order to achieve this, risk markers should have proof of concept, have prospective validation in independent populations, provide significant incremental information when added to standard risk factors, be readily available and inexpensive (or at least cost-effective), and be based on studies with a large number of outcome events [15]. While many of the following predictors may only meet part of these criteria at this point, within a subset of patients they may provide additional information regarding CVD risk. Often times, these groups of patients may be those who are asymptomatic but still at intermediate risk based on comorbidities such as diabetes or metabolic syndrome.

Circulatory biomarkers

Numerous circulating biomarkers representing a variety of pathophysiological pathways including inflammation [CRP, interleukin-6 (IL-6), and lipoprotein-associated phospholipase A_2 (Lp-PLA_2)], lipid metabolism [lipoprotein(a)], and endothelial dysfunction (urinary microalbuminuria) have been shown to promote atherogenesis. In more recent years, some of these biomarkers have had additional evidence to signify utility for CVD risk assessment.

Interleukin-6

A large amount of focus has been placed on "downstream" markers of inflammation, such as CRP with the risk of CHD. However, more recently, "upstream" markers such as pro-inflammatory cytokines like IL-6 have been shown to be related with CHD because their role in the inflammation cascade [16]. Analyses via systematic reviews have shown IL-6 to be as strongly correlated with CHD risk after traditional risk factor adjustments and with a similar magnitude of prediction of traditional risk factors [17]. Furthermore, a causal role for IL-6 signaling in CHD has been supported via genetics [18]. A more recent meta-

analysis including 29 studies showed that the relative risk of non-fatal MI or CHD death per standard deviation increase from baseline of IL-6 resulted in a relative 25 % (1.19–1.32) increase of CHD events despite adjustment for standard risk factors [19]. Although these results further support the inflammation hypothesis in vascular disease, the causal role of the "upstream biomarker" IL-6 in CHD or CVD is yet to be established.

Lipoprotein-associated phospholipase A_2

Similar to CRP, Lp-PLA_2 is an example of "downstream" inflammatory biomarker. Lp-PLA_2 is unique and highly specific for vascular inflammation and atherosclerosis. Lp-PLA_2 plays a large role in plaque instability as is found predominately adjacent to areas with massive macrophage aggregation and oxidized LDL accumulation [20, 21]. Multiple studies and pooled analyses of these studies have consistently shown that Lp-PLA_2 is significantly associated with CVD risk [22]. A recent meta-analysis has shown that increases in Lp-PLA_2 mass and activity, after adjustment for conventional risk factors, significantly increase the relative risk (RR) of CHD events, ischemic strokes, vascular mortality, and non-vascular mortality. Importantly, this meta-analysis showed that Lp-PLA_2 was comparable to systolic blood pressure and non-HDL cholesterol in magnitude for prediction off CVD events [23]. Despite these findings, Lp-PLA_2 was not included in the pooled cohort model for CVD risk prediction. Interestingly, hs-CRP, another marker of general inflammation, was included in the 2013 ASCVD guidelines as a biomarker that may be helpful to better define risk [as well as is the Reynolds Risk Score (RRS) calculator] given its strong predictive association with CVD events [24]. However, Lp-PLA_2 has been shown to be more specific for vascular inflammation than CRP, which can be increased in conditions such as rheumatic disease or infections [22]. In fact, studies have shown that the addition of Lp-PLA_2 to hs-CRP leads to better risk stratification for CVD risk than Hs-CRP alone [25, 26].

Despite these epidemiological findings, a recent international phase 3 drug trial of darapladib, an inhibitor of Lp-PLA_2 activity, showed no effect on combined outcomes in patients with stable CHD [27•]. While this drug does not necessarily reflect the utility of Lp-PLA_2 in those without baseline CVD, some have suggested that Lp-PLA_2 activity may be a biomarker related to lipoprotein metabolism and inflammation but not causal in the pathway of CHD events [28]. Yet, that is still not clear. Recently, a prospective study using a healthy, CVD-free, multi-ethnic cohort showed that both Lp-PLA_2 mass and activity were associated with CVD risk regardless of standard risk factors and the presence of coronary artery calcium or carotid intima-media thickness [29•].

Lp-PLA_2 has been recommended by the 2010 AHA/AHA Guidelines for Cardiovascular Risk Assessment for risk stratification only in groups with moderate or high CV risk [3]. This is largely because of secondary analyses of the Women's Health Study and Atherosclerosis Risk in Communities (ARIC) Study, which showed that the addition of Lp-PLA_2 to traditional risk factors only had modest to no increase in the predictive power for future CVD in healthy individuals. However, this in no way detracts from Lp-PLA_2's utility in those at risk for CVD. Particularly in those patients with some inflammatory burden such as those with metabolic syndrome or diabetes, Lp-PLA_2 could play an important role in risk stratification especially where the use or intensity of statin therapy based in LDL-C or global risk alone may be unclear.

Lipoprotein(a)

The evidence for the causal role of lipoprotein(a) [Lp(a)] with CHD is based on Mendelian randomization studies and from large epidemiological databases [30, 31]. Lp(a) is composed of apolipoprotein B-100 and the attached glycoprotein apolipoprotein(a) [apo(a)]. Although unclear, the mechanism through which Lp(a) may be proatherogenic is based on the proinflammatory effects of the apo(a), as well as Lp(a)'s preferential binding to proinflammatory and proarthrogenic oxidized phospholipids which help to destabilize atherosclerotic lesions [32].

While the causal effects of Lp(a) have been well documented, not until recently has it been shown that Lp(a) could add to CVD reclassification. Prior studies have shown modest reclassification of subjects for CVD and increase in c-index for intermediate/high-risk FRS categories when Lp(a) was added to predictors of total cholesterol and HDL-C [33]. More recently, Lp(a) was shown to have significant discrimination and reclassification of CVD risk when added to the FRS and RRS [34•]. The prospective 15-year follow-up study in a general population noted a 39.6 % significant net reclassification index afforded by Lp(a) in those at the intermediate risk for CVD. Nearly 2 in 5 of patients classified as intermediate risk by traditional algorithms moved into either lower or higher CVD risk categories. Nonetheless, it is unclear how such measurements will change clinical practice given no clinical trial exist to determine the optimal use of Lp(a). The utility of Lp(a) may be best in high-risk patients who would benefit from intensive use of established preventive therapies.

Microalbuminuria

Microalbuminuria is most commonly defined as an albumin excretion rate of 30–300 mg/day or an albumin:creatinine ration of 2.5–25 mg/mmol in men or 3.5–25 mg/mmol in women. Multiple studies have shown microalbuminuria to be predictive of CHD and CVD [35–37]. However, discrepancies in results have arisen based on gender, age of participants, and diabetes status.

Microalbuminuria appears to significantly increase the risk for CHD in women vs men with impaired glucose tolerance the most. Increased mortality in women (RR=6.10; 95 % CI, 2.62–15.19) vs men (RR=1.77; 95 % CI, 0.91–3.44) was seen in one study of diabetic patients and may be possibly related to differences in cut-off definitions for microalbuminuria [38]. Another study showed that in those with metabolic syndrome, microalbuminuria was predictive for both CHD and CVD, while for men no association existed [39]. However, other studies have indicated that microalbuminuria is predictive of cardiovascular events in those with or without diabetes after adjustment for gender [40].

More recent studies have also shown the predictive nature of the simple marker for subclinical CVD parameters. After adjustment for standard risk factors, including age, gender, and diabetes status, microalbuminuria was shown to be independently associated with left ventricular mass index, carotid intima-media thickness, and arterial stiffness by carotid femoral pulse wave velocity [41]. Given these findings, the ACC/AHA 2010 Recommendations for cardiovascular risk assessment have indicated this as a reasonable test for adults with hypertension or diabetes, from a urinalysis to detect microalbuminuria for CVD risk assessment [3, 42].

Other imaging strategies

Radiological advances through non-invasive vascular imaging provide a distinct advantage over circulatory biomarkers for improved predictive accuracy of clinical events in the short to medium term in patients with subclinical disease. The most widely studied form of imaging is that of CAC. However, in recent years, other modalities such as myocardial perfusion imaging, coronary computed tomography angiography, and carotid intima-media thickness have shown benefit for risk stratification in selected intermediate-risk patients although the evidence for these modalities in improving risk assessment is less striking than for CAC.

Myocardial perfusion imaging

Stress myocardial perfusion imaging (MPI) through the use of the modalities of single photon emission computed tomography (SPECT) and positron emission tomography (PET) has been used to accurately diagnose coronary artery disease (CAD) for years. The utility of defining the risk for future events in conjunction with other risk factors has been less clear, particularly for SPECT-MPI. There has been a significant decrease in the frequency of abnormal SPECT-MPI over a recent 20-year period in patients with chest pain, including those with typical angina [43]. This was thought to reflect the possibility of a decrease in milder presentations of CAD (as compared to patient's presenting in prior years) or a decrease in the utility of SPECT-MPI in detecting patients at risk for CAD. The latter is supported by the fact that 78 % of patients with normal exercise SPECT-MP had evidence of atherosclerosis detected by CAC [43].

One of the advantages of PET MPI is the ability for myocardial flow reserve (MFR) analysis. One study showed that after stratifying groups with impairment (MFR<2) to those with preserved vasodilator flow (MFR>2), those with impairment had a significant higher number of hard cardiac events [44]. Further, after multivariable analysis, impaired MFR remained an independent predictor of hard events. However, this study was limited by a small number of events (27 in the cohort). Another larger study (*N*=2783 with 137 cardiac death events) also demonstrated the prognostic value of PET MPI as an independent predictor of cardiac mortality in patients with suspected CAD [45]. Those in the lowest tertile of MFR (<1.5) were associated with a 5.6-fold increase in the risk of cardiac death as compared with the highest tertile. The addition of MFR from PET MPI into cardiac risk assessment with standard risk factors did increase the c-statistic marginally from 0.82 to 0.84 but importantly helped reclassify 34.8 % of intermediate-risk patients.

Given these findings, one may expect to find that MPI is best suited for better risk assessment in those at high risk for CHD, such as diabetics. In the Detection of Ischemia Asymptomatic Diabetics study, those with small SPECT MPI defects did in fact have lower event rates than those with moderate or large MPI defects [46]. However, the positive predictive value of having a moderate or large MPI defect was only 12 % and the number events in the groups were quite small. This led authors to suggest that cardiac event rates were not significantly reduced with use of MPI screening in these asymptomatic diabetics. Interestingly, a

concern has been brought up for misclassification of high-risk patients, as one study showed stress MPI in outpatient diabetics (with and without baseline CAD) showed normal perfusion in 29.8 % of patients who ultimately had events [47]. Interestingly, given the concern for SPECT MRI, a recent study using PET MFR successfully showed that among diabetic patients without CAD, those with impaired MFR had event rates similar to patients without diabetes but prior CAD events [48]. In addition, those diabetics without CAD who had preserved MFR had very low annualized cardiac mortality.

While MPI may not be useful in risk stratification for those at low risk for CAD, it may play a role for individuals who are asymptomatic but at higher risk. This may in part be due to the fact that MPI reflects the severity of ischemia at the time of examination. A number of high-risk plaques are not obstructive and ultimately would be classified as a false negative result using MPI. However, in high-risk patients like diabetics who often have highly obstructive CAC burden, they may benefit from PET MPI for reclassification of risk stratification and ultimately high intensive pharmacological therapy. This is partly reflected in a Class IIb Recommendation for MPI in asymptomatic adults with diabetes or strong family history [3].

Coronary computed tomography angiography

Computed tomography angiography (CTA) has been a useful modality for assessing coronary artery stenosis but also plaque characteristics [49–51]. Plaques that have been associated with CHD events showed positive vessel remodeling (PR) and a variable extent of luminal narrowing [52]. In addition, the culprit lesion showed characteristics of low-attenuation plaques (LAP). CTA of non-calcified plaques with <30 HU have been highly correlated with the invasive technique of intravascular ultrasound identified low attenuated plaques [53]. While these plaque characteristics had been identified after event occurrence, more recently it has also been shown a possible modality for screening [54]. In 1059 patients who underwent CTA, atherosclerotic lesions were identified for PR and LAP. Among patients with both features, 22.2 % had an acute coronary event as compared to 0.5 % in those with neither feature. Among segments with either or both features, those resulting in ACS had significantly larger remodeling index, plaque volume, and LAP volume as compared to segments not resulting in ACS.

While the risk of CHD events for asymptomatic patients have focused primarily on clinical and biochemical characteristics, non-invasive imaging like CTA could further stratify high-risk patients. A study of 120 asymptomatic diabetic patients who underwent CTA showed that 17.1 % of patients had high-risk plaques (PR and LAP) [55]. This same study showed that while high CAC burden was extremely common in this patient population, still 5.0 % of patients had a CAC score=0 while having significant stenosis. A recent large prospective 12-center international registry identified 400 asymptomatic diabetic individuals without known CAD and measured coronary stenosis prediction for CAD [56•]. After adjustment for CAD risk factors and CAC, maximal stenosis (HR=1.8), number of obstructive vessels (HR=1.85), and segmental stenosis score (HR=1.1) were significantly associated with increased number of CVD events. Furthermore, CTA increased the c-index from 0.64 (age, gender, CACS) to 0.77, as well as improved risk reclassification by per-patient maximal stenosis and number of obstructive vessels.

In some studies, asymptomatic diabetics have been reported to have similar or higher risk for CAD than symptomatic diabetics [57, 58]. Further, purely the number of risk factors for CAD is not associated with the prevalence of CAD in diabetic patients, given that the severity in each diabetic patient is different [59, 60]. If the high-risk plaques are an important factor for determining risk of events, CTA may be a useful screening test in diabetics and other high-risk patients as it may be able to detect silent vulnerable plaques, which are missed by functional imaging. However, recently, the FACTOR-64 Randomized Clinical Trial showed that among 900 asymptomatic patients with diabetes, the use of CTA to screen for CAD did not ultimately reduce all-cause mortality, non-fatal MI, or unstable angina [61•]. This was in the setting of a reduction in events (HR=0.80) but an insignificant one given the low number of events in the control and intervention group (<2.0 %). Given the additional risks such as radiation dosing, use of contrast media, and unclear cost-effectiveness, as compared to other clinical and biochemical screening tools, CTA for routine screening of CAD in even high-risk patients with diabetes is not recommended.

Carotid intima-media thickness

Carotid intima-media thickness (CIMT) was excluded from the 2013 ACC/AHA Risk Assessment Guidelines and given a ACC/AHA Class III-B Recommendation. This is contrary to the 2012 European and 2010 ACC/AHA CVD Prevention Guidelines that mark the recommendation of CIMT as reasonable form of CV risk assessment in asymptomatic adults at intermediate risk (Class IIa-B Recommendation) [3, 62]. This is after a meta-analysis of 14 cohorts (45,828 subjects with mean follow-up of 11 years) that showed that 10-year absolute risk to develop a MI or stroke (as predicted with the FRS) showed significant, although modest, reclassification of individuals at moderate risk when evaluated with CIMT [63]. However, conflicting results from several studies examining the added benefit of CIMT for reclassification of intermediate CVD risk patients in combination with the challenge of CIMT standardization lead the working group to not recommend CIMT even among the additional testing modalities for reclassification.

Importantly, what the above meta-analysis failed to consider was the contribution of the carotid plaque presence when calculating CHD risk. By adding plaque data to CIMT and traditional risk factors in 13,145 patients in the Atherosclerosis Risk in Communities study, Nambi et al. was able to show that 23 % of patients were reclassified, with a net improvement of 9.9 % [64]. Although the majority of these patients (61.9 %) were classified to a lower 10-year risk group, this is still relevant for clinical decision-making. Another study, using the MESA, showed that 6 different metrics of carotid artery plaque (including the combination of CIMT with presence of plaque >25 %) were independently associated with CHD events and increased the c-statistics when added to models including traditional risk factors [65•]. Furthermore, with the exception of 1 metric, these different metrics increased the net reclassification index by between 4.2 and 7.0 %. Only mean of the maximum IMT was incrementally added to the prediction of CVD beyond traditional risk factors. As more studies continue to evaluate CIMT with the combination of plaque metrics, it is possible that CIMT will be re-addressed as an important tool for CHD risk in intermediate to high-risk asymptomatic patients.

Conclusion

The use of predictive models plays an important role in clinical practice as they help to identify those at high risk for developing CVD. In addition, they motivate adherence to recommended lifestyle changes or therapies in populations that may be unaware of the significant morbidity and mortality burden of CVD. However, despite the great utility of established traditional risk factors such as hypertension and smoking status in predicting CHD events, the fact that as many as half of individuals who develop CHD have only one to none of these traditional risk factors indicates more complex prediction models are needed [66, 67]. And while the most recent guidelines for ASCVD risk recommend the use of CRP and CAC as tools for further risk stratification, they are not included in the initial risk stratification calculator. Inevitably, the fraction of patients who receive testing for CRP and CAC score for initial risk assessment will be small. However, the utility of these biomarkers and others previously discussed may be more informative partly as a function of the phase of the disease process.

While published evidence continues to show the incremental benefit of different markers above standard practice, additional research is needed in asymptomatic and CVD-free individuals to quantify cost-effectiveness and the impact of these markers on CVD risk factor management and patient outcomes. This is particularly true for the current imaging modalities. Imaging biomarkers are likely to have little value for risk assessment in the earlier stages of the development of CVD, when subclinical disease is not even apparent. In contrast, circulating biomarkers such as CRP, Lp-PLA_2, IL-6, and Lp(a) can be additive to traditional risk factors throughout the disease process. Ultimately, the considerable evidence for CAC, CIMT, coronary CTA, and to a lesser extent MPI, for the added benefit in risk assessment, must be weighed vs the reality of their cost to our patients and healthcare system when determining if they would change clinical management.

As physicians move toward personalized medicine, it should be with the understanding that no risk assessment model is perfect. However, data from multiple broadly representative cohorts with excellent end-points show the importance of circulatory and imaging biomarkers for CVD risk assessment. As guidelines and risk calculators are updated, they will surely become more complex but will also help focus what biomarkers are best for risk assessment in what populations and what stage of CVD disease. Ultimately, this will allow for better clinical decision-making, including the use of aggressive pharmacologic therapy.

Compliance with Ethical Standards

Conflict of Interest
David M. Tehrani and Nathan D. Wong each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation. 2015;131:e29–322.
2.• Goff Jr DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2935–59.

Most recent widely publicized guidelines by the ACC/AHA describing the components for the 10 year and lifetime risk for ASCVD.

3. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56:e50–103.
4. Marma AK, Lloyd-Jones DM. Systematic examination of the updated Framingham heart study general cardiovascular risk profile. Circulation. 2009;120:384–90.
5. Kashani M, Eliasson A, Vernalis M, Costa L, Terhaar M. Improving assessment of cardiovascular disease risk by using family history: an integrative literature review. J Cardiovasc Nurs. 2013;28:E18–27.
6. Williams RR, Hunt SC, Heiss G, et al. Usefulness of cardiovascular family history data for population-based preventive medicine and medical research (the Health Family Tree Study and the NHLBI Family Heart Study). Am J Cardiol. 2001;87:129–35.
7. Schnell-Inderst P, Schwarzer R, Gohler A, et al. Prognostic value, clinical effectiveness, and cost-effectiveness of high-sensitivity c-reactive protein as a marker for major cardiac events in asymptomatic individuals: a health technology assessment report. Int J Technol Assess Health Care. 2010;26:30–9.
8. Peters SA, den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart. 2012;98:177–84.
9. Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375:132–40.
10. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107:499–511.
11. Everett BM, Pradhan AD, Solomon DH, et al. Rationale and design of the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis. Am Heart J. 2013;166:199–207. e15.
12. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes. 2011;4:337–45.
13. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300:197–208.
14. Lin JS, Olson CM, Johnson ES, Whitlock EP. The ankle-brachial index for peripheral artery disease screening and cardiovascular disease prediction among asymptomatic adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;159:333–41.
15. Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation. 2009;119:2408–16.
16. Libby P. Inflammatory mechanisms: the molecular basis of inflammation and disease. Nutr Rev. 2007;65:S140–6.
17. Danesh J, Kaptoge S, Mann AG, et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. PLoS Med. 2008;5, e78.
18. The interleukin-6 receptor as a target for prevention of coronary heart disease: a Mendelian randomisation analysis. Lancet 2012;379:1214–24.
19. Kaptoge S, Seshasai SR, Gao P, et al. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. Eur Heart J. 2014;35:578–89.
20. Mannheim D, Herrmann J, Versari D, et al. Enhanced expression of Lp-PLA2 and lysophosphatidylcholine in symptomatic carotid atherosclerotic plaques. Stroke. 2008;39:1448–55.
21. Kolodgie FD, Burke AP, Skorija KS, et al. Lipoprotein-associated phospholipase A2 protein expression in the natural progression of human coronary atherosclerosis. Arterioscler Thromb Vasc Biol. 2006;26:2523–9.
22. Corson MA, Jones PH, Davidson MH. Review of the evidence for the clinical utility of lipoprotein-associated phospholipase A2 as a cardiovascular risk marker. Am J Cardiol. 2008;101:41F–50.
23. Thompson A, Gao P, Orfei L, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet. 2010;375:1536–44.

24. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA. 2007;297:611–9.
25. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity c-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2004;109:837–42.
26. Nambi V, Hoogeveen RC, Chambless L, et al. Lipoprotein-associated phospholipase A2 and high-sensitivity c-reactive protein improve the stratification of ischemic stroke risk in the Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2009;40:376–81.
27.• White HD, Held C, Stewart R, et al. Darapladib for preventing ischemic events in stable coronary heart disease. N Engl J Med. 2014;370:1702–11.

Randomized Clinical Trial showing darapladib, a selective oral inhibitor of lipoprotein-associated phospholipase A2, did not reduce the risk of the end points of cardiovascular death, myocardial infarction, or stroke.

28. Munzel T, Gori T. Lipoprotein-associated phospholipase A(2), a marker of vascular inflammation and systemic vulnerability. Eur Heart J. 2009;30:2829–31.
29.• Garg PK, McClelland RL, Jenny NS, et al. Lipoprotein-associated phospholipase A2 and risk of incident cardiovascular disease in a multi-ethnic cohort: the multi ethnic study of atherosclerosis. Atherosclerosis. 2015;241:176–82.

A study using a large population based multi-ethnic cohort that showed lipoprotein-associated phospholipase A2 remained positively associated with CVD risk despite the presence of other CVD.

30. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009;361:2518–28.
31. Erqou S, Kaptoge S, Perry PL, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302:412–23.
32. Lee S, Birukov KG, Romanoski CE, Springstead JR, Lusis AJ, Berliner JA. Role of phospholipid oxidation products in atherosclerosis. Circ Res. 2012;111:778–99.
33. Di Angelantonio E, Gao P, Pennells L, et al. Lipid-related markers and cardiovascular disease prediction. JAMA. 2012;307:2499–506.
34.• Willeit P, Kiechl S, Kronenberg F, et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. J Am Coll Cardiol. 2014;64:851–60.

Study showing that Lp(a) predicts 15-year CVD outcomes and improves CVR risk prediction particularly in those previously identified to be in the intermediate-risk group for CVD events.

35. Cao JJ, Biggs ML, Barzilay J, et al. Cardiovascular and mortality risk prediction and stratification using urinary albumin excretion in older adults ages 68–102: the Cardiovascular Health Study. Atherosclerosis. 2008;197:806–13.
36. Hillege HL, Fidler V, Diercks GF, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002;106:1777–82.
37. Yuyun MF, Khaw KT, Luben R, et al. A prospective study of microalbuminuria and incident coronary heart disease and its prognostic significance in a British population: the EPIC-Norfolk study. Am J Epidemiol. 2004;159:284–93.
38. Ko GT, So WY, Chan NN, et al. Prediction of cardiovascular and total mortality in Chinese type 2 diabetic patients by the WHO definition for the metabolic syndrome. Diabetes Obes Metab. 2006;8:94–104.
39. Jassal SK, Langenberg C, von Muhlen D, Bergstrom J, Barrett-Connor E. Usefulness of microalbuminuria versus the metabolic syndrome as a predictor of cardiovascular disease in women and men >40 years of age (from the Rancho Bernardo Study). Am J Cardiol. 2008;101:1275–80.
40. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001;286:421–6.
41. Thanikachalam M, Swaminathan A, Sunderarajan J, Harivanzan V, Thanikachalam S. Abstract 15897: microalbuminuria is associated with subclinical cardiovascular disease parameters independent of traditional risk factors in a large population based study. American Heart Association Scientific Sessions. Dallas, Texas: Circulation, 2013.
42. Wachtell K, Ibsen H, Olsen MH, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Ann Intern Med. 2003;139:901–6.
43. Rozanski A, Gransar H, Hayes SW, et al. Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. J Am Coll Cardiol. 2013;61:1054–65.
44. Ziadi MC, Dekemp RA, Williams KA, et al. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. J Am Coll Cardiol. 2011;58:740–8.
45. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation. 2011;124:2215–24.
46. Young LH, Wackers FJ, Chyun DA, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA. 2009;301:1547–55.
47. Bourque JM, Patel CA, Ali MM, Perez M, Watson DD, Beller GA. Prevalence and predictors of ischemia and outcomes in outpatients with diabetes mellitus referred for single-photon emission computed tomography myocardial perfusion imaging. Circ Cardiovasc Imaging. 2013;6:466–77.

48. Murthy VL, Naya M, Foster CR, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation. 2012;126:1858–68.
49. Schroeder S, Kopp AF, Baumbach A, et al. Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. J Am Coll Cardiol. 2001;37:1430–5.
50. Hoffmann U, Moselewski F, Nieman K, et al. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. J Am Coll Cardiol. 2006;47:1655–62.
51. Cordeiro MA, Lima JA. Atherosclerotic plaque characterization by multidetector row computed tomography angiography. J Am Coll Cardiol. 2006;47:C40–7.
52. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol. 2007;50:319–26.
53. Motoyama S, Kondo T, Anno H, et al. Atherosclerotic plaque characterization by 0.5-mm-slice multislice computed tomographic imaging. Circ J. 2007;71:363–6.
54. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol. 2009;54:49–57.
55. Kamimura M, Moroi M, Isobe M, Hiroe M. Role of coronary CT angiography in asymptomatic patients with type 2 diabetes mellitus. Int Heart J. 2012;53:23–8.
56.• Min JK, Labounty TM, Gomez MJ, et al. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. Atherosclerosis. 2014;232:298–304.
Study showing that among asymptomatic patients with diabetes, coronary computed tomographic angiography was able to add incremental risk prediction and reclassification after adjustment for standard CAD risk factors including coronary artery calcium.
57. Zellweger MJ, Hachamovitch R, Kang X, et al. Prognostic relevance of symptoms versus objective evidence of coronary artery disease in diabetic patients. Eur Heart J. 2004;25:543–50.
58. Choi EK, Koo BK, Kim HS, et al. Prognostic significance of asymptomatic coronary artery disease in patients with diabetes and need for early revascularization therapy. Diabet Med. 2007;24:1003–11.
59. Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro A. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. J Am Coll Cardiol. 2006;47:65–71.
60. Wackers FJ, Young LH, Inzucchi SE, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care. 2004;27:1954–61.
61.• Muhlestein JB, Lappe DL, Lima JA, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. JAMA. 2014;312:2234–43.
Study showing that among asymptomatic patients with diabetes, use of coronary computed tomographic angiography did not reduce rates of all-cause mortality, nonfatal myocardial infarction, or unstable angina.
62. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33:1635–701.
63. Den Ruijter HM, Peters SA, Anderson TJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. 2012;308:796–803.
64. Nambi V, Chambless L, Folsom AR, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk in Communities) study. J Am Coll Cardiol. 2010;55:1600–7.
65.• Polak JF, Szklo M, Kronmal RA, et al. The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis. J Am Heart Assoc. 2013;2, e000087.
A study using a large population based multi-ethnic cohort that showed ultrasound-derived plaque metrics independently predicted CVD events and improved net reclassification when added to Framingham risk factors.
66. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA. 2003;290:898–904.
67. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA. 2003;290:891–7.