S. Negi, M.D.

CORONARY HEART DISEASE RISK STRATIFICATION: PITFALLS AND POSSIBILITIES

Smita Negi, M.D. and Vijay Nambi, M.D.
Baylor College of Medicine, Methodist DeBakey Heart & Vascular Center, Houston, Texas

Introduction

Atherosclerosis of the coronary arteries, or coronary heart disease (CHD), is the most common cause of mortality in U.S. adults.[1] The pathobiology of atherosclerosis and its complications is a continuum. At one end of the spectrum are young individuals without atherosclerotic disease who have not yet been exposed to lifestyle or other risk factors, and at the other end are patients with manifest atherosclerosis — myocardial infarction, stroke, and disabling peripheral arterial disease — where risk of recurrent disease and death is driven by the same factors initially responsible for the emergence of disease. However, it is clear that while risk factors are important in the development of CHD, not everyone with risk factors develops the disease and not everyone with CHD has risk factors. Furthermore, even similar degrees of exposure to a risk factor leads to disease in some individuals and not in others. Risk prediction, which is crucial in predicting and hence preventing disease, therefore becomes very challenging. In this article we review the currently available risk stratification tools for predicting CHD risk and discuss potential ways to improve risk prediction.

Current Risk Stratification Tools

The Framingham Heart Study (FHS) investigators described clinical factors associated with CHD that led to the development of the "Framingham Risk Score" (FRS).[2] The FHS identified older age, male gender, hypertension, diabetes, total cholesterol, high density lipoprotein cholesterol (HDL-c), and smoking as major or "traditional" risk factors (TRF) for CHD and, based on the estimated risk, classified individuals into the low- (0–10% estimated 10-year risk), intermediate- (10–20% estimated 10-year risk) and high-risk (>20% estimated 10-year risk) groups.[2] Over time, the FRS has become the standard clinical risk assessment tool for CHD and forms the basis of the algorithm used in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) guidelines.[3] Several other similar risk scores have been developed and used, such as the Atherosclerosis Risk in Communities (ARIC) CHD risk score[4] and the Systemic Coronary Risk Evaluation (SCORE)[5] that is used in Europe.

Limitations of Current Risk Scores

Although the modified FRS recommended by the NCEP ATP-III guidelines is a good risk prediction tool and forms the cornerstone of our CHD risk prediction efforts, it does have certain limitations. First, it classifies approximately 75% of the population as low or intermediate in risk even though 60% of cardiac events occur in these individuals.[6] Second, although ischemic stroke is an equally important complication of atherosclerosis and shares the same risk factors, stroke risk prediction schemes are different from those of CHD, and stroke is not an endpoint predicted by the FRS CHD risk score.[4, 7, 8] Thus, one may have different estimated risk for stroke and CHD (i.e., high risk for one and low risk for the other, and vice versa), and since preventive strategies are the same for both stroke and CHD, opportunities to initiate early treatment may be missed.[9] Third, the FRS cohort was drawn from a small homogenous population, and its risk assessment ability may have to be interpreted with caution when applied to a larger, more

diverse population group. Thus, there is a need to identify newer risk factors that may be used independently and/or in conjunction with traditional risk assessment tools to better identify both the long- and the near-term CHD risk of an individual.

Concept of Lifetime Risk

All conventional risk assessment tools have been designed to predict the "short term" or 10-year risk of the subject. Individuals may have low short-term risk yet their long-term or "lifetime" risk may be significant.[10] Lifetime risk is likely more important and valuable in young and middle-aged individuals in whom the short-term risk (due to their age) may be "low" despite having suboptimal levels of risk factors. For example, the lifetime risk of CHD by cholesterol levels at 40 years of age was reported to be 31%, 43%, and 57% for men with cholesterol levels <200 mg/dL, 200–239 mg/dL and ≥ 240 mg/dL respectively.[11] In a study that evaluated individuals enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) study and the Multi-Ethnic Study of Atherosclerosis (MESA), the investigators reported that individuals with low short-term risk could be divided into high lifetime risk and low lifetime risk. Not surprisingly, the low short-term/high lifetime risk group had a baseline burden of subclinical atherosclerosis [as evaluated by coronary artery calcium (CAC) score or carotid intima media thickness (CIMT)] that was significantly greater than the low short-term/low lifetime risk group and a rate of coronary artery calcium progression that also was significantly higher than the low short-term/low lifetime risk group.[12] Lifetime risk therefore is an important consideration, especially for young and middle-aged individuals.

Improving CHD Risk Assessment

Several new markers (biomarkers, imaging markers, and genetic markers) are constantly being identified and reported. In general, when a new marker is evaluated for its ability to improve risk prediction, it is added and compared to the model based on TRFs. For the marker to be helpful in risk prediction, it must have the ability to discriminate between those with and without disease and furthermore have improved "calibration" when observed and expected events are compared. These are normally evaluated through several statistical tests[13] that include describing improvements in the area under the receiver operator characteristics curve (AUC) and describing the number of individuals that are reclassified, the correctness of reclassification (net reclassification index), and the goodness of fit (i.e., comparing observed events with expected events). The improvement in risk prediction provided by the marker has to be weighed against the risk of the test and the associated costs. In general, there is no value in performing testing beyond the traditional risk scores when an individual is high risk. It is the intermediate-risk group and perhaps sometimes the low-risk group that will likely benefit the most from additional testing for further risk stratification.

Biomarkers

The biomarker that has been best evaluated for CHD risk prediction is high-sensitivity C-reactive protein (hs-CRP). Other markers that appear promising include lipoprotein-associated phospholipase A2 (Lp-PLA2) and amino-terminal pro-B-type (or brain) natriuretic peptide (NT-proBNP). Table 1 summarizes the characteristics of the newer risk-prediction biomarkers in CHD.

C-reactive protein is an acute phase reactant that increases in the setting of injury and inflammation and has been extensively studied as a risk predictor for CHD.[14–17] Small increments in CRP are highly predictive of future vascular events in asymptomatic individuals.[15] CRP has also been shown to be associated with stroke and peripheral arterial disease,[16, 17] indicating a potential role for CRP in the assessment of global vascular risk. The Reynolds Risk Score (www.reynoldsriskscore.org) is a recently developed risk prediction score that includes hs-CRP and a parental history of myocardial infarction in addition to TRFs.[18, 19] It was observed that approximately 30% of initially healthy women estimated to be at "intermediate risk" could be reclassified into higher- or lower-risk categories with greatly improved accuracy using this algorithm. The authors more recently described the Reynolds Risk Score for men and noted that incorporating hs-CRP and parental history into existing risk prediction models again significantly improved global cardiovascular risk prediction.[20]

LpPLA2 is another biomarker that has consistently been associated with both CHD and stroke.[21–23] It is predominantly associated with LDL in the circulation and thought to mediate its inflammatory effects through its action on oxidized phospholipids, releasing lysophosphatidylcholine and oxidized nonesterified fatty acids, both of which are capable of attracting monocytes to an atherosclerotic lesion and further induce the expression of adhesion molecules.[22] LpPLA2 has been evaluated for improvement of stroke risk prediction in the ARIC study.[24] Addition of LpPLA2 to TRF's improved stroke

risk prediction when compared to TRFs alone or CRP and TRFs, while adding LpPLA2 along with CRP to TRFs was shown to best improve risk prediction for ischemic stroke. The improvement was again most significant in a group that was classified initially as intermediate in risk by TRFs.[9] However, LpPLA2 has not been as well studied as hs-CRP, especially with respect to improving CHD risk prediction. Available data suggest that its ability to improve CHD risk prediction may be modest, while its ability to improve ischemic stroke risk prediction may be better.

Brain natriuretic peptide (BNP) is synthesized by cleavage of a precursor protein, proBNP, into an active 32 amino acid hormone and a biologically inactive 76 amino acid peptide, N-terminal pro-BNP. It is secreted by cardiomyocytes in response to stretch and ventricular volume overload and has traditionally been thought of as a marker for congestive heart failure;[25] however, it has been increasingly associated with both CHD and stroke risk.[26] The contribution of NT-proBNP in risk stratification was examined in the Rotterdam study, in which NT-proBNP was added to TRFs to investigate its ability to predict 10-year risk of cardiovascular disease (CVD).[27] It was found that in an asymptomatic older population, NT-proBNP improved risk prediction of CVD beyond TRFs, resulting in a substantial reclassification of participants to a lower- or higher-risk category. However, another study that looked at a combination of BNP and CRP for predicting CHD risk found that, when added to conventional risk factors, only modest improvement in risk prediction was seen in the intermediate risk group.[28]

Since most biomarkers only improve risk prediction marginally, studies have looked at the combination of several biomarkers to evaluate the value of a multimarker approach.[28, 29] Recently, Kim et al. investigated whether multiple biomarkers contribute to improved CHD risk prediction in post-menopausal women compared to traditional risk factors only.[30] The authors found only modest improvement in CHD risk prediction when 18 biomarkers were evaluated individually and in multi-marker predictive models along with traditional cardiovascular risk factors for CHD. Overall, biomarkers seem to have modest additive value in improving CHD risk prediction.

Imaging

Coronary artery calcium (CAC) scores have been shown to be associated with prevalent and incident CHD events in multiple observational studies and have also been shown to be additive to Framingham Risk Scores.[31, 32] Higher calcium scores have consistently shown a relationship with increased incidence of CHD events.[33] Recently, Polonsky et al. examined the Multi-Ethnic Study of Atherosclerosis (MESA) and showed that addition of CAC scores to the TRFs significantly improved the prediction of CHD risk in asymptomatic individuals and reclassified more individuals to the extreme-risk categories.[34] With the addition of CACS to the TRF model, 23% of those who experienced events were reclassified as high risk and 13% of those who did not experience events were reclassified to a lower-risk group. Among intermediate-risk individuals, 16% were reclassified as high risk while 39% were reclassified as low risk. Thus, addition of CAC scores to traditional risk models may improve CHD risk prediction and reclassification, especially in intermediate-risk groups. Concerns have been raised about the safety and cost-effectiveness of widespread use of CAC scoring solely for primary prevention. The estimated effective radiation dose of a single CAC screening ranges from 0.8 to 10.5 millisievert (mSv) with a mean and median of 2.3 mSv and 3.1 mSv, respectively, which is minimal.[35] However, if this results in follow-up testing such as CT angiogram or stress testing, the radiation exposure may significantly increase. Hence, CAC scores may help in improving CHD risk prediction but may have to be used prudently.

Carotid intima media thickness (CIMT) is a well-validated imaging surrogate that has been associated with both prevalent and incident CHD and stroke.[36, 37] Further, CIMT has been used to track the progression/regression of atherosclerosis.[38] The NCEP ATP-III identifies the measurement of CIMT as an option to identify individuals at higher risk than that identified by major risk factors alone.[3] A recent large study examined the utility of CIMT ± plaque in risk prediction in a healthy, middle-aged population enrolled in the ARIC study.[39] The study showed that addition of CIMT and the presence or absence of plaque to the TRFs significantly improved CHD risk prediction. Adding CIMT to traditional risk factors reclassified ~23% of the individuals and was associated with improvement in the area under the receiver operator characteristics curve, a better model fit when expected events were compared to observed events, and an NRI of 9.9% and clinical NRI of 21.7% in the overall population. Hence, the addition of CIMT and plaque information, like CAC scoring, seems to improve the ability to predict incident CHD.

Genomics

Although environment plays a significant role in the emergence of conventional risk factors, genetics also has an important contribution. Furthermore, despite having

Table 1. Selected newer markers and their performance in CHD risk prediction.

New Risk Marker	Type	Population	AUC (TRF alone)	AUC (TRF +New Marker)	CNRI (%) (TRF+ New Marker)	Intermediate Risk Group (5-20%) Reclassified (%)
CRP (+ parental history of CHD) Plasma biomarker		Healthy nondiabetic women§ with no CHD[18, 47, 48] *(Ridker et al.)**	0.787	0.808	12	30
		Healthy nondiabetic men with no CHD[20] *(Ridker et al.)**	0.689	0.7	14.2	22
CAC-score	Computed tomography imaging	Healthy nondiabetics with no CHD[34] *(Polonsky et al.)**	0.76	0.81	55	54
CIMT and presence of plaque	Ultrasound imaging	Healthy with no CHD/CVD[39] *(Nambi et al.)**	0.742	0.755	21.7	38

CRP=C-reactive protein; CHD=Coronary Heart Disease; CAC-score=Coronary Artery Calcium Score; CIMT=Carotid Intima Media Thickness; AUC=Receiver-Operating Characteristic Curve; TRF=Traditional Risk Factors; CNRI=Clinical Net Reclassification Index

**Incident CHD events included:*

Ridker et al.: Myocardial infarction (MI), ischemic stroke, coronary revascularization, and cardiovascular deaths.

Polonsky et al.: MI, death due to CHD, resuscitated cardiac arrest, definite or probable angina followed by coronary revascularization, and definite angina not followed by coronary revascularization.

Nambi et al.: Definite or probable MI, silent MI between examinations indicated by electrocardiograms, definite CHD death, or coronary revascularization.

"normal" or "optimal" TRFs, several individuals still develop CHD, which suggests that there are yet unrecognized factors including genetic influences. Human genetics studies are now identifying genomic sites or loci associated with these TRFs and CHD.[40] The association of single nucleotide polymorphism within the chromosome 9p21 locus with CHD was first established by genome-wide studies.[41] In the ARIC study cohort, it was shown that adding the 9p21 genotype to traditional risk factors significantly improved CHD risk prediction, with 12–13% of individuals reclassified in the intermediate low- and intermediate high-risk categories of traditional risk models.[42] However, in the Women's Genome Health Study, Paynter et al.[43] reported that the knowledge of variation at 9p21.3 did not improve the discrimination or classification of predicted risk achieved with traditional risk factors, high-sensitivity C-reactive protein, and family history of premature myocardial infarction. In a more recent analysis of healthy women with no CHD in the Women's Genome Health Study, a total of 101 single nucleotide polymorphisms reported to be associated with cardiovascular disease were identified and a genetic risk score was created. The genetic risk score was not associated with cardiovascular disease risk. In contrast, self-reported family history remained significantly associated with cardiovascular disease in multivariable models.[44] However, most of the single nucleotide polymorphisms that were included in this genetic risk score were associated with traditional risk factors, thereby potentially limiting its ability to predict CHD risk. Novel genotypes associated with various risk factors and CHD will continue to be identified. In the future, it is likely that we will identify genetic risk scores that can significantly improve CHD risk prediction.

Summary

Traditional CHD risk stratification tools are very useful in clinical practice but have significant limitations. It is possible to improve CHD risk prediction using biomarkers, imaging, and genetic markers, but overall the improvements have been modest. Among biomarkers, hs-CRP has been the best studied; among the imaging markers, both coronary calcium score and CIMT have been found to be useful (Table 1). Of the various markers, the coronary calcium score seems to have the most improvement in risk prediction. However, none of these risk prediction strategies have been tested in clinical trials to determine if treatment based on a particular strategy will decrease incident CHD events. The only marker that has been studied in clinical trials as a basis for risk factor modification is hs-CRP, which was evaluated in the JUPITER trial.[45] The JUPITER study showed significant improvement in major cardiovascular events when individuals with average LDL-c

levels (<130 mg/dL) and high hs-CRP (>2 mg/L) were treated with statins.

A recent report by the United States Preventive Task Force (USPTF), however, found that most of the markers discussed here did not have sufficient evidence to merit recommendation for routine use.[46] After evaluating markers that included ankle–brachial index, leukocyte count, fasting blood glucose level, periodontal disease, CIMT, CAC score as measured by electron-beam computed tomography, serum homocysteine level, lipoprotein(a) level, and CRP level, they concluded that while CRP had good data on reclassification, evidence that changes in CRP levels would reduce incident CHD was lacking. The USPTF also concluded that the other markers had insufficient or inconsistent evidence with regard to risk reclassification. However, more evidence of their utility is becoming available — for example, recent publications on CAC score[34] and CIMT[39] in risk prediction have been published since the USPTF report — and it is likely that certain novel markers will have a potential role in improving our CHD risk prediction abilities in the future. In the meantime, clinicians should continue with traditional risk factor assessment and selectively consider using additional markers in CHD risk stratification. Clinicians should also consider an individual's stroke risk and lifetime risk in their risk stratification schema.

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