Cardiovascular Risk Assessment Based on US Cohort Studies
Findings From a National Heart, Lung, and Blood Institute Workshop

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This report was derived from a workshop on cardiovascular risk assessment sponsored by the National Heart, Lung, and Blood Institute, which addressed whether risk equations developed in the Framingham Heart Study (FHS) for predicting new-onset coronary heart disease (CHD) apply to diverse population groups. Preparation for the workshop included a reanalysis and comparison of prospective studies in several different populations in which risk factors were related to cardiovascular outcomes. Some studies included fatal and nonfatal CHD end points, whereas others contained only CHD mortality. Extensive collaboration provided as much uniformity as possible with respect to both risk factors and CHD end points.

The FHS has led in defining the quantitative impact of risk factors. Many potential risk factors were measured and related to cardiovascular outcomes. Several risk factors proved to be strong, largely independent predictors of cardiovascular disease (CVD). These factors—advancing age, cigarette smoking, blood pressure (particularly systolic), cholesterol in total serum and HDL, and diabetes—served as the basis for the development of risk prediction equations. If FHS risk estimates are to be widely used, they must apply widely in the US population. To document their transportability, they must be compared with prospective studies in other populations. Although the FHS is the longest running prospective study, there are other major studies. The cardiovascular end points of these other studies have varied. Some include cardiovascular morbidity and mortality; others have only cardiovascular mortality. Among the end points, CHD is the most extensively reported; for this reason, CHD was the primary focus of the workshop.

Population Comparisons in Risk Estimation

Multivariate Relative Risk Comparisons

In preparation for the workshop, multivariate regression coefficients for each risk factor were compared in different populations with those of the FHS. Adjusted relative risk estimates make it possible to determine whether each independent risk factor confers a similar or different relative risk among different populations.

Population-Attributable Fraction for the Major Risk Factors

Multivariate relative risk can be distinguished from the contribution of a risk factor to CHD within a particular population. The major risk factors vary in prevalence among different populations; e.g., blacks in the United States have an unusually high prevalence of hypertension, whereas among Native Americans, type 2 diabetes predominates. The population-attributable fraction denotes how much of the population burden of CHD could be eliminated if the specific risk factor were to be removed from the population. Each such fraction can be viewed as adding to the population baseline risk, which is the level of risk one starts with in a given population, before quantifying and adding in the contributions of major CHD risk factors to predicting events.

Receiver-operator characteristic (ROC) analysis is carried out to judge the ability of various risk factors (alone or in combination) to discriminate between those who develop an event from those who do not. The area under the ROC curve (AUC) estimates the probability of the risk function assigning a higher risk probability to those who will develop an event than to those who will not. Essentially, this statistic quantifies the ability to discriminate events from nonevents.

ROC analysis is commonly used to determine whether addition of a new risk factor to risk prediction equations provides incremental independent predictive power. Adding new risk factors gives a new prediction equation and a corresponding increase in the AUC. The level of increase can be used to assess the value of new risk factors for discriminating events from nonevents.

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The ROC AUC ranges from 0.5 to 1.0. An AUC of 0.5 signifies correct classification in only 50% of cases, no better than chance; an AUC of 1.0 indicates perfect classification. In the FHS, age alone raised the AUC to 0.65. Addition of other powerful risk factors, including blood pressure, blood lipids, smoking, and diabetes, raised the AUC to 0.78. This AUC increase of only 0.13 produced by combining major risk factors illustrates the limited power of ROC analysis to reveal an impact of single new risk factors.

Population Baseline Risk
For given levels of a set of risk factors, absolute risk for CHD varies among different populations. This population baseline absolute risk, defined above, is thus independent of the major risk factors. Factors responsible for the population baseline absolute risk are not well understood. Underlying risk factors almost certainly influence baseline risk; these include body fat content, physical activity, diet composition, personal and social behavior, and genetic makeup, including family history. Emerging risk factors [plasma levels of triglycerides, lipoprotein(a), homocysteine, and fibrinogen, as well as markers of inflammation and oxidative stress] likewise may affect population baseline risk. Independent contributions of multiple underlying and emerging risk factors to population baseline risk are largely undetermined. Population baseline risk nonetheless potentially modifies absolute risk estimates of individuals when they derive from populations other than those from which risk equations were developed.

Results From US Longitudinal Cohort Studies With CHD Morbidity and Mortality as an End Point
To evaluate transportability of FHS risk equations, prospective data on CHD morbidity and mortality from other populations were compared with those of FHS. These other cohort studies enrolled a more diverse sample than provided by FHS. Specific studies (and their special characteristics) are included below.

1. The Atherosclerosis Risk in Communities Study (ARIC), which included a sizable proportion of middle-aged African Americans.
2. The Cardiovascular Health Study (CHS) of older adults.
3. The Strong Heart Study (SHS) of Native Americans.
4. The Honolulu Heart Study (HHHS); its subjects were Asian Americans.
5. The Puerto Rico Heart Study (PRHS) of Hispanic Americans.
6. The Physicians Health Study (PHS), which included subjects with a higher-than-average socioeconomic status.

The end point for the primary analytic comparisons was “hard” CHD (myocardial infarction or CHD death). Before statistical analysis, comparability of variables among different studies was ensured as much as possible. The studies shared several features: They all (1) were prospectively followed cohorts, (2) assessed the major CHD risk factors, (3) implemented active events surveillance, and (4) used physician adjudicators and medical records to validate events.

There also were some differences. The PHS was a randomized trial, whereas all others were solely observational cohort studies. The HHS and PRHS cohorts were enrolled in the 1960s, whereas the ARIC, CHS, SHS, and PHS cohorts were enrolled in the 1980s. (Data for the FHS risk functions were from 1971 to 1986.) There were other variations. Lipoprotein laboratory assessment differed; 1 study used self-reported blood pressure levels; and definition of glucose intolerance varied (ie, glucose tolerance testing, fasting glucose, self-reported diagnosed diabetes).

The workshop also sought to standardize the definition of hard CHD used in the analyses from participating studies. Despite small differences, the global definition of CHD was quite similar to that used in the FHS. To achieve methodological compatibility in the main comparisons, participating investigators used the FHS risk prediction model to assess the applicability of FHS estimates in these more diverse populations. They also generated optimal models for predicting CHD morbidity and mortality in their population (with and without allowing for inclusion of variables not currently included in the FHS prediction equation).

Three fundamental questions were addressed: (1) whether the major risk factors predict similarly in other populations as in the FHS; (2) whether FHS functions discriminate between those who will develop hard CHD (events) from those who will not (nonevents) with the same ability as the best functions developed from the studies themselves; and (3) whether the combined risk factors impart the same estimates for absolute risk as they do in the FHS. If absolute estimates are similar, then it can be said that other groups have a similar population baseline risk as the FHS population; if not, the population baseline risk must differ from that of FHS.

The ARIC Study
The ARIC cohort consisted of men and women, 45 to 64 years of age, without a history of myocardial infarction or stroke at baseline. Follow-up averaged 7.2 years. ARIC included both white and black subjects, whereas the FHS cohort was almost entirely white. In ARIC, CHD included hospitalized myocardial infarction, fatal CHD, cardiac procedures, and ECG evidence of silent myocardial infarction. Besides standard risk factors, subjects were assessed for fibrinogen, lipoprotein(a), ankle-brachial blood pressure index, and carotid wall thickness by B-mode sonography.

Standard risk factors had a similar relative predictive power for major coronary events in ARIC and the FHS. An exception was in the black subgroup in ARIC, in whom CHD outcomes for a given increase in blood pressure were worse for blacks in ARIC than whites in either ARIC or the FHS. The baseline population risk for major coronary events, however, was essentially the same for FHS whites, ARIC whites, and ARIC blacks. Therefore, no adjustment was required for absolute risk estimates in the ARIC population with FHS equations.

Other risk factors [eg, fibrinogen and lipoprotein(a)] only modestly improved the prediction model for ARIC by ROC: altogether they raised the AUC from 0.69 to 0.72. Carotid intimal-medial thickness (IMT) was a relatively strong predictor in otherwise low-risk ARIC subjects; however, predic-
tion based on carotid IMT was attenuated in higher-risk subjects by the inclusion of standard risk factors. Carotid IMT measures raised the AUC of the ROC curve only modestly. In contrast, when carotid IMT was evaluated in multivariate analysis, IMT was a robust independent risk factor after adjustment for other risk factors. This apparently discrepant result raises questions about the power of ROC analysis to define the independent contributions of new risk factors.

The CHS
The CHS enrolled older adults, 65 to 100 years of age at baseline. CHS is important because FHS estimates are limited by relatively small numbers of older subjects. Previous studies have shown a decline in relative risk estimates for some risk factors, especially cholesterol, with advancing age. Of note, the FHS equations based on smaller numbers of elderly subjects did not predict CHD morbidity and mortality well in the CHS cohort. Total cholesterol and HDL cholesterol were particularly weak predictors. Conversely, the coefficient for diabetes was substantially higher in CHS than in the FHS. In the older subjects of CHS, FHS predictors discriminated better in men than in women.

Some factors other than standard risk factors assumed increased predictive power in CHS. In men, systolic blood pressure, HDL, ECG changes, and triglycerides were independent predictors. In CHS women, family history of CHD, diabetes, and ECG abnormalities were more powerful predictors. In both men and women, carotid wall thickness (IMT) was an independent predictor, as previously reported. The strength of predictive power of carotid IMT in elderly in whom conventional risk factors show a declining relative risk suggests that risk for CHD in this age group is increasingly determined by atherosclerotic burden.

The PHS
The PHS was a nested case-control study that by design created similar age and smoking prevalence among cases and controls. The study therefore could not evaluate the effects of these variables. Risk equations including blood pressure and lipids/lipoproteins similarly predicted morbidity and mortality from CHD in PHS and FHS cohorts. In both studies, blood pressure and serum lipoproteins had the same effect on absolute risk. This is important because PHS participants were enrolled across the entire nation, indicating broad transportability.

The SHS
The SHS, a cohort of Native Americans, allows comparisons of risk measures, including how baseline population risk compares with that for US whites. Many coefficients were similar between the SHS and FHS in prediction of CHD morbidity and mortality. Some differences were noted. A high total cholesterol imparted more relative and absolute risk among Native Americans than in the FHS. However, the adverse effects of low HDL on CHD morbidity and mortality were attenuated in Native Americans. Diabetes conferred higher risk among Native Americans than in the FHS. Contrary to common belief, Native Americans do not have a low population baseline risk for CHD; furthermore, standard risk factors carry as much absolute risk for CHD as they do in FHS.

The PRHS
The PRHS enrolled men of Hispanic ethnicity. Multivariate relative risk of various risk factors in PRHS and FHS populations was similar, but the FHS model overestimated absolute risk for CHD among Puerto Ricans. Whether this overprediction from FHS equations extends to other Hispanic populations in the United States is unresolved. In the PRHS, adding body mass index, physical activity, heart rate, and vital capacity enhanced the predictive power of a model generated for the Puerto Rican population. Overall, coefficients generated specifically from PRHS better predicted CHD events than did those of the FHS equations. Nevertheless, when a simple adjustment was made to the FHS equation to account for differences in average CHD incidence between the FHS and PRHS cohorts, the FHS-based predictions became comparable to those produced by the PRHS model. This can be considered a “calibration” adjustment.

The HHS
The HHS consisted of Japanese American men who were 45 to 64 years of age in 1965. FHS equations overpredicted absolute risk for CHD by ~25%, indicative of a lower baseline population risk. Differences additionally were noted in the relative influence of some risk factors in the FHS and HHS populations. Diabetes raised the risk for CHD more in the HHS than in the FHS, whereas HDL was a weaker predictor. When a calibration adjustment was made to the FHS model to account for average CHD incidence differences between these populations, the FHS model performed as well as the best HHS model.

Summary of Studies
In summary, data from ARIC and the PHS, which should encompass most American adults, fit the FHS equations well both for relative influence of the various standard risk factors (multivariate relative risk) and population baseline risk. The population baseline risk of Native Americans likewise was similar to the FHS population. For other populations (PRHS and HHS), calibration adjustments to the FHS equations improved their performance greatly. Nonetheless, for each specific cohort, the use of study-specific risk equations improved the ability to predict CHD morbidity and mortality compared with FHS equations, even if only slightly. Furthermore, in the elderly population of the CHS, FHS scoring failed to provide accurate predictions of risk. Addition of newer risk factors and subclinical disease measures somewhat improved the prediction of CHD events in several populations. Nonetheless, there was not a consensus on how best to evaluate the independent contributions of newer risk factors. ROC analysis is frequently used, but the limitations of this analysis point to the need for newer methods to discriminate independent prediction.

Risk Predictors in Prospective Studies in Which CHD/CVD Mortality Was the Major Outcome
Several prospective studies collected data relating risk factors to CVD and CHD mortality. The applicability of the usual
FHS risk equations to the populations of these studies could not be assessed because of a lack of data on CHD morbidity. They nonetheless provide additional perspective on the quantitative effects of cardiovascular risk factors. Five studies were included: (1) the Chicago Heart Association Detection Project (11,016 men 18 to 39 years of age), (2) Chicago Western Electric Company study (2,107 men 40 to 50 years of age plus >1,600 men with serial data), (3) the Multiple Risk Factor Intervention Trial (MRFIT) screenee (361,662 men 35 to 57 years of age), (4) the first and second National Health and Nutrition Examination Survey (NHANES; 2,753 men and 3,858 women from NHANES I and 2,655 men and 3,050 women from NHANES II, plus a pooled sample of 940 black men and 1,463 black women), and (5) the Women’s Pooling Project (25,978 women 30 to 97 years of age drawn from FHS original and offspring cohorts and ARIC, NHANES I, and 5 smaller cohorts). These cohorts are characterized by diversity in the age and ethnic composition of the populations, varying lengths of follow-up, differences in risk factor information collected, and distinct approaches to subgroup analyses. Several studies provided the advantages of broad age ranges and of long follow-up. Despite considerable variations in study designs, procedures for risk factor measurement, and ascertainment of outcomes, the results of risk prediction were remarkably consistent among studies. Several of the salient outcomes of these analyses can be summarized.

Age predicted CVD and CHD mortality strongly in all studies. Other risk factors, however, often differed in their predictive power by age. For example, the Cox model coefficients for cholesterol were 2-fold higher in young adults than for middle-aged subjects. In MRFIT, multivariate Cox coefficients for the relation between CHD/CVD mortality and each of the major risk factors (total cholesterol, cigarette use, and systolic blood pressure) became successively smaller with each 5- or 3-year age stratum from 35 to 57 years. The Women’s Pooling Project likewise noted that several major CVD risk factors carried higher relative risk for CHD/CVD death in younger than in older women. In this study, the relative risk for CVD morality for cholesterol ≥280 mg/dL (compared with <200 mg/dL) was 6.1 among women 30 to 44 years of age but fell to 0.9 in those ≥65 years of age. Likewise, relative risk from diabetes and stage 3 hypertension varied, depending on the length of follow-up, but both decreased over time from baseline measurement.

Diabetes is a major cause of cardiovascular events and CHD/CVD death. MRFIT related risk factors to CHD mortality in a 16-year follow-up of >5,000 men having diabetes at baseline. All other risk factors added to CHD/CVD mortality in patients with diabetes. When other risk factors were controlled for, absolute risk for CHD/CVD and all-cause mortality was 5- to 7-fold higher in diabetic than in nondiabetic subjects. Cox coefficients for other risk factors were somewhat smaller in patients with diabetes, showing that diabetes appears to be a particularly strong risk factor for mortality from CVD/CHD. In the Chicago Heart Association study, symptomatic hyperglycemia in white and black men was found to increase in relative risk over time, being greatest after 12 years.

Obesity is a factor that may influence population baseline risk. The Chicago Heart Association study determined that elevated body mass index was not a consistent and significant predictor of CHD mortality in the first 12 years of follow-up; beyond 12 years, however, after adjustment for other risk factors, body mass index emerged as an independent and graded risk factor in both men and women.

Race and ethnicity also have been implicated as factors affecting population baseline risk for morbidity and mortality of CHD and CVD. Their influence, however, may be confounded by socioeconomic status. Analyses from MRFIT (whites, blacks, Asians, and Hispanics), NHANES (whites and blacks), and the Women’s Pooling Project (whites, blacks, and Hispanics) revealed that multivariate relative risk for CVD mortality was similar for the various risk factors across ethnic groups. MRFIT investigators examined the data according to median income of zip code of residence and found no systematic differences in multivariate relative risk across strata defined by socioeconomic status or geography. For NHANES and the Women’s Pooling Project, the magnitude of the Cox coefficients for individual risk factors did not vary by ethnic group; prediction of absolute risk for total CVD nonetheless improved by application of ethnic-specific models. In the Women’s Pooling Project, prediction models generated from whites underpredicted risk for CVD mortality in black women. Conversely, models for whites from NHANES overpredicted CVD mortality in black men. These data suggest that assessment of the relative risk of a given factor with a single algorithm for CVD mortality is appropriate for most ethnic and socioeconomic groups. Nonetheless, if the goal is prediction of absolute mortality risk, ethnic-specific models are needed to improve prediction. Alternatively, an adjustment for differences in population baseline risk of CHD/CVD mortality between ethnic groups can be made while maintaining similar Cox coefficients for standard risk factors in a single model. Discrepancies for total CVD mortality seem at variance with the comparable estimates of relative and absolute risk for nonfatal and fatal CHD in whites and blacks from ARIC and the FHS. This difference raises the interesting possibility that absolute risk for CHD morbidity may not correlate strongly with absolute risk for CVD mortality in some populations.

An important question is whether additional variables improve the ability to predict CVD/CHD mortality beyond the major risk factors and age. For instance, in the Chicago cohort, resting ECG findings, such as ST-T abnormalities, conveyed independent prediction. Many of the older cohorts that have enough power to examine mortality, however, have not evaluated the role of other risk factors.

Application of FHS Risk Equations to Specific Populations

White Populations Other Than FHS

Congruence of FHS predictions for hard CHD between white populations of the FHS and ARIC must be considered a major conclusion of the workshop. FHS equations seemingly can be applied broadly to white populations in the United States. This conclusion is strengthened by the similarities between...
multivariate relative risk and population baseline absolute risk in FHS men and the PHS.

**Black Populations**
In broad terms, FHS equations for hard CHD apply similarly in white and black populations in the United States. The influence of blood pressure is an exception. FHS equations underpredicted blood pressure–associated risk in ARIC black men and women. Use of FHS equations in blacks probably should give extra weight to blood pressure. In the Women’s Pooling Project and NHANES, equations for the white populations were not highly predictive of deaths resulting from CHD/CVD in the black populations. Thus, factors operating subsequent to the onset of CHD may affect CVD mortality in black persons.

**Other Ethnic Groups**
Workshop comparisons confirmed previous observations that absolute baseline risk differs among populations. Variation in population baseline risk can be distinguished from differences in the population-attributable fraction for the major risk factors. Differences in population baseline risk may extend to various ethnic groups and will require adjustment of absolute risk estimates based on ethnicity. Ethnic differences in CVD risk could be explained by variability in underlying or emerging risk factors not included in FHS equations. In Asian men from Honolulu and Hispanics in Puerto Rico, FHS coefficients overpredicted risk for CHD. Simple calibration adjustment to the FHS functions to adjust for baseline average CHD incidence rates greatly improved the performance of the FHS functions in these populations. No data were available on the predictive power of FHS equations in Americans of South Asian origin, a population known to have a high baseline risk.

**Young Adults**
Although absolute risk in young adults is low, relative risk imparted by risk factors is high. The latter translates into long-term, high absolute risk. For example, in the FHS, high serum cholesterol levels in young adulthood indicate a high lifetime risk of developing CHD.

**Older Adults**
Both diabetes and hypertension remain strong predictors of CHD in older persons, but elevated serum cholesterol declines in relative risk. Attributable risk accompanying high serum cholesterol increases with advancing age, but it is difficult to differentiate higher and lower risk in patients >65 years of age on the basis of serum cholesterol levels alone. In the CHS, FHS equations were poor predictors of risk after 65 years of age. In contrast, noninvasive assessments of coronary plaque burden, such as carotid IMT, assumed increasing power to predict risk.

**Women**
FHS equations indicate that absolute risk for CHD is much lower in women than in men, even into advanced age. Still, multivariate relative risk was similar for the different risk factors between men and women, except that diabetes has a disproportionate impact on CHD risk in women. Apparently, diabetes removes some of the protection against CHD normally afforded to women. In CHS, standard risk factors were poor predictors of CHD/CVD mortality in women. There is a widely held view that risk in women increases more steeply after menopause; however, in the Women’s Pooling Project, menopause was not found to alter the AUC of the ROC curve when added to the standard risk factors.

**Research Recommendations**
One goal of the workshop was to define research needs. The following needs were identified.

- To improve the predictive power of FHS data for white and black middle-aged populations in the United States by pooling the databases of the FHS and ARIC.
- To develop adjustments in the FHS risk equations for the various ethnic groups that carry different absolute baseline population risks and to characterize the absolute population baseline risk of other subgroups of the US population, including other Hispanic groups, subgroups of European origins in geographic regions with high rates of CVD, and the subgroup of Americans of South Asian origin.
- To better define the baseline risk of high-risk groups in the United States, including patients with both type 1 and 2 diabetes, those with noncoronary forms of atherosclerotic disease, and those with left ventricular hypertrophy.
- To evaluate risk assessment for predictions of outcome in patients with established CVD.
- To extend risk assessment to CVD end points beyond fatal and nonfatal myocardial infarction, eg, stable angina, unstable angina, stroke, and heart failure.
- To better integrate underlying risk factors (adverse nutrition, obesity, physical inactivity, psychosocial factors, and family history of premature CHD) into global risk assessment. This approach might include developing “primordial scores,” ie, the risk of developing major atherogenic risk factors (hypertension, lipid disorders, and diabetes).
- To improve methods for clinical assessment of underlying risk factors. Improved and simplified nutrition assessment tools are needed. Better techniques for estimating levels of physical inactivity would also be helpful. Methods to readily measure total body fat and abdominal fat in the clinical setting are needed.
- To determine the independent predictive power of emerging risk factors, eg, triglycerides, lipoprotein(a), homocysteine, coagulation factors (fibrinogen, plasminogen activator inhibitor-1), and C-reactive protein.
- To determine the independent predictive power of measures of abnormal cardiovascular function, eg, left ventricular hypertrophy, abnormal resting ECG, abnormal pulmonary function tests, and exercise tolerance.
- To determine the independent predictive power of measures of myocardial ischemia, eg, exercise ECG, exercise and pharmacological (stress) echocardiogram, exercise and pharmacological myocardial perfusion imaging, and PET.
• To determine the independent predictive power of measures of subclinical atherosclerosis, eg, ankle/brachial blood pressure index, carotid IMT, and coronary calcium scores.
• To develop and evaluate tools for application of risk assessment in patient care. The information that is conveyed to patients needs to incorporate both absolute and relative risk. The reference point should be the low-risk patient, not average risk. Risk assessment tools should be developed that will be “user friendly.” Computer-based tools may help. New methods of entering data without direct physician involvement are needed.
• To extend risk prediction algorithms to long-term (and lifetime) risk.

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References

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