Summary of
National Heart, Lung, and Blood Institute
Workshop on Cardiovascular Risk Assessment

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Abstract

Background: The National Heart, Lung, and Blood Institute conducted a Workshop in January 1999 to assess the applicability to other U.S. populations of coronary heart disease (CHD) risk prediction algorithms generated from the Framingham Heart Study (FHS). This report presents major findings from the workshop, including consideration of applications of risk assessment in practice.

Methods and Results: Longitudinal cohorts were identified for testing the accuracy of the FHS function. The function--based on age and categories of blood pressure, total cholesterol, HDL cholesterol, smoking and diabetic status--was applied (separately by gender and race) to each of the other cohorts. Accuracy of 5-year predictions of non-fatal myocardial infarction or CHD death were compared to those using functions developed with the study's own data. Other than in the older subjects in one cohort, agreement between FHS-based predictions and observed results for relative risk associated with each risk factor was good, except that hypertension was a somewhat stronger predictor in black subjects, especially women. Discrimination between cases and non-cases based on the FHS function as a whole was also satisfactory, but generally not quite as good as the study's own functions. For three cohorts, the FHS function over-predicted absolute CHD risk and some recalibration of the function would be required for optimal use.

Conclusions: From a quantitative viewpoint, the applicability of the FHS risk algorithm using traditional risk factors appears satisfactory for most populations. The Workshop also identified unresolved issues with regard to 1) further development of risk assessment tools, 2) effects on physician and patient behavior, and 3) the role of global risk assessment in clinical guidelines.

Keywords: coronary disease, epidemiology, prevention, risk factors

Introduction

This report presents the background and summarizes the proceedings of a workshop on cardiovascular risk assessment sponsored by the National Heart, Lung, and Blood Institute and held on January 19-20, 1999. The primary purpose of the workshop was to assess whether risk equations developed in the Framingham Heart Study for predicting new onset coronary heart disease (CHD) are applicable to diverse population groups. A second purpose was to identify the issues concerning clinical use of risk assessment that require clarification and analysis. Most of the data presented in this workshop was the product of a reanalysis and comparison of results from prospective studies in several different populations in which risk factors were related to cardiovascular outcomes. Extensive analyses and collaboration were required to obtain as much uniformity as possible with respect to both risk factors and CHD end-points. The primary end-point in these comparisons was CHD death plus non-fatal myocardial infarction. Additional analyses were derived from studies in which CHD mortality was the only CHD end-point. This report summarizes the major findings of these new analyses and comparisons. Subsequent publications based on these analyses will expand on numerical and statistical data.

One of the foremost advances in the field of cardiovascular medicine has been the discovery that the major forms of cardiovascular disease--coronary heart disease (CHD) and stroke--are preceded by measurable factors called *risk factors*. Persons who carry these risk factors are more likely to develop cardiovascular disease than are persons in whom these factors are absent. Another signal advance was the demonstration through controlled clinical trials that therapies reducing risk factors will decrease risk for cardiovascular-renal disease and stroke. Particularly notable among these clinical trials were those employing drugs that lower serum cholesterol and blood pressure. The ability to substantially reduce risk for cardiovascular disease through a treatment of risk factors has raised the important issue of how to identify patients who are candidates for clinical management of risk factors.

During the past decade the concept has evolved that intensity of management of risk factors should be proportional to a person's absolute risk for cardiovascular disease. This concept was adopted by the National Cholesterol Education Program (NCEP) for adjusting the intensity of cholesterol-lowering therapy (1,2). The concept was reinforced by a Bethesda conference sponsored by the American College of Cardiology (ACC) (3). It has further been emphasized by guidelines adopted by joint European cardiovascular societies (4). This approach also has been increasingly adopted in blood pressure guides, especially the Sixth Report of the Joint National Committee (JNC VI) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (5). Adjusting intensity of risk reduction to a patient's absolute risk is meant to appropriately balance efficacy, safety, and cost effectiveness of drug therapy. This approach has proved to be widely attractive to the cardiovascular community (6). It finds its ultimate expression in risk-reduction therapies for very high-risk patients who have established atherosclerotic cardiovascular disease. Reports that intensive risk-reduction therapies applied to patients with established CHD strikingly reduce subsequent coronary events clearly demonstrate the efficacy, safety, and cost- effectiveness of aggressive risk-factor reduction (7-11). The success of therapies for secondary prevention now opens the door to more aggressive risk

reduction in primary prevention. To favorably balance safety and cost effectiveness with efficacy of therapy in primary prevention, appropriate patient selection is required. A key component of the identification of candidates for aggressive primary prevention is the assessment of global risk.

If the concept of adjusting intensity of risk reduction to absolute risk is to be adopted, a technique must be developed to accurately estimate absolute risk. Absolute risk is the probability of developing a cardiovascular event over a specific period. Earlier studies on the impact of risk factors emphasized relative risk, which is the ratio of the absolute risk in persons with a risk factor compared to the absolute risk in a person without the risk factor. Estimates of relative risk are useful for indicating the power of a risk factor to predict development of disease. Relative risk also is considered the best indication of strength of association for inferring causality. However, according to the developing paradigm of matching intervention to risk (1-5), absolute risk is a critical parameter for selecting patients for risk-reduction therapies.

The Framingham Heart Study has taken the lead in defining the quantitative significance of risk factors (12). This 50-year study made baseline measurements of risk factors in the community of Framingham, MA, and followed this cohort and their adult children for cardiovascular events over a long period. A battery of potential risk factors was measured and correlated with cardiovascular outcomes. Statistical analyses examined the predictive power and independence of each risk factor. These analyses uncovered several risk factors that were strong, largely independent predictors of cardiovascular disease. These factors served as the basis for the development of risk prediction equations. Application of these equations to individuals allows them to be classified into risk categories.

If Framingham risk estimates are to be widely employed, they must be transportable to populations other than Framingham. To determine their ability to perform widely, they must be compared to prospective studies in other populations. Although the Framingham Heart Study is the prospective study of longest duration, it is by no means the only such study. Many prospective studies have been carried out in the United States, but other populations around the world have been investigated as well. The primary question addressed in the current workshop was whether risk prediction equations derived form the Framingham Heart Study apply to other populations. The endpoints of these various studies have varied. Some have included cardiovascular morbidity and mortality; others have examined only cardiovascular mortality. The most extensive findings have been reported for the various manifestations of CHD; thus CHD end-points were the primary focus of this workshop.

Quantitative risk assessment is particularly useful for the identification of patients at high risk who are most likely to benefit from clinical management of risk factors. Global risk assessment however has other purposes. For example, the finding of a high absolute risk in a patient can be used to motivate this patient to modify behavior to reduce risk. It can also reassure patients who are at low risk.

Categories of Risk Factors

A background review of the categories of risk factors may help to put the issues under consideration in the workshop into perspective. Without question CHD is a multi-factorial disease. The essential pathological process leading to CHD is coronary atherosclerosis. CHD is the product of a chain of causality beginning relatively early in life. The causes of CHD are multi-layered and overlapping. However, dividing these causes into categories based on their temporal relationship to CHD may be useful. The chain of causality can be visualized as a pyramid of several layers (Figure 1). At base are the *underlying risk factors*; these factors give rise to the next level, the *major atherogenic risk factors*. The latter are factors proven to be direct causes of coronary atherosclerosis. This second layer also contains another set of factors that can be called the *provisionally atherogenic risk factors (or provisional risk factors)*. There is growing evidence that several of the provisional risk factors promote atherogenesis, although the extent of their contribution remains open to question. The top layer contains the contribution of the atherosclerotic plaque itself to the development of CHD. Major advances are being made in understanding how the coronary plaques break down to produce major coronary events. Thus, it is becoming increasingly apparent that the presence of an atherosclerotic plaque per se is a *risk factor* for CHD (13). Finally, there are *undetermined causes* of coronary heart disease. Many investigators hold that the underlying risk factors either promote atherogenesis or precipitate major coronary events in ways other than through the major atherogenic risk factors. The provisional risk factors are good candidates for some of the undetermined causes of CHD. Undoubtedly, still other factors are involved. Much current research is focused on arterial wall factors, yet to be discovered, in the causation of clinical CHD. In the discussion to follow, the known causes of CHD are classified and reviewed.

Underlying (predisposing) risk factors. These factors include adverse nutrition, obesity, physical inactivity, family history of premature cardiovascular disease, male sex, and others (ethnic, behavioral, socioeconomic). Family history is closely linked to many genetic factors that contribute to cardiovascular disease. The major nutritional cause is a high population intake of saturated fat and cholesterol, which raises the serum cholesterol levels (2). Another is a high population intake of salt, which raises blood pressure (5). Other dietary factors (e.g., N-9, N-6, N-3 fatty acids, folic acid, antioxidant vitamins, soluble fiber, potassium, protein quality, and alcohol) appear to influence risk for CHD through yet-to-be-determined mechanisms (2). Caloric imbalance leading to obesity can be listed as another nutritional factor contributing to CHD risk (14). Obesity is known to have an unfavorable effect on several of the major and provisional atherogenic risk factors (14). In addition, it causes insulin resistance that may independently affect risk (15). The adverse effects of obesity on CHD are worsened when fat is distributed predominately to the upper body (abdominal obesity) (14). Physical inactivity is accompanied by increased CHD risk (16). The atherogenic risk factors are worsened by physical inactivity, and the cardiovascular system may be adversely affected in other ways as well (17).

Major, atherogenic risk factors. The Framingham Heart Study early identified certain factors that independently predict development of cardiovascular disease. Most of these risk factors correlated with all forms of atherosclerotic disease, although evidence was strongest for CHD. The current workshop focused primarily on the association of these risk factors with

CHD. This was for two reasons: first, the need for global risk assessment for primary prevention of CHD has become a critical clinical issue; and second, available prospective data are most robust for this end-point. Even so, the workshop also took advantage of the information contained in other prospective studies that had only mortality end-points. Factors identified by Framingham investigations as most strongly and consistently correlated with risk for CHD were cigarette smoking, blood pressure, serum total cholesterol (and LDL cholesterol), serum HDL cholesterol (inversely), and diabetes (18). Abnormalities in these factors are related to CHD risk independently of other putative risk factors, and hence are called *independent risk factors*. A large body of data of several types strongly suggests that each of these risk factors enhance risk for CHD by directly promoting the atherosclerotic process; some may also evoke other pathological mechanisms including cardiac hypertrophy, thrombosis, and arrhythmogenesis. Finally, they have a relatively high prevalence, significantly enhancing the population burden of CHD; hence they are called *major risk factors*. The risk factors in this category are the backbone of global risk assessment to detect higher risk patients for intensive medical intervention. Thus they were the risk factors compared among the different prospective studies.

Provisional (conditional) atherogenic factors. Other factors, which have been associated with increased risk for CHD, are candidates for being atherogenic risk factors. They include some species of triglyceride-rich lipoproteins (TGRLP) (19,20), abnormally small LDL particles (21,22), lipoprotein (a) [Lp(a)] (23,24), homocysteine (25,26), coagulation factors (fibrinogen, plasminogen activator inhibitor-1 [PAI-1]) (27,28), and persistent low-level inflammation or infection (29,30). These measures are not routinely included in Framingham risk equations due to the desire to keep the functions simple and limited to standard risk variables. In both the Framingham data base, and in some of the other studies reported in this workshop, some of these factors do have independent predictive power.

Age and atherosclerotic plaque burden as risk factors. The Framingham Heart Study and all other prospective studies reveal that absolute risk rises with advancing age. At any level or combination of atherogenic risk factors, the absolute risk for cardiovascular events becomes progressively higher as people grow older. This steady rise of risk with aging led Framingham investigators to designate *age* as a major, independent risk factor. The mechanism whereby advancing age increases risk for CHD seemingly is related to the time-dependent progressive accumulation of coronary atherosclerosis. Pathological studies in all populations show that the burden of atherosclerosis rises with age (31). Other investigations indicate that risk for major cardiovascular events is proportional to the total coronary plaque burden. Although major coronary events (unstable angina and myocardial infarction) are initiated mainly by the rupture of vulnerable plaques, the total probability of plaque rupture correlates positively with total plaque burden. It might be noted that although age is a powerful predictor of CHD in populations, amounts of atherosclerosis vary greatly among individuals. For this reason, there is growing interest in using non-invasive methods for assessing plaque burden for individuals. These measurements could provide a better estimate of risk that accompanies plaque burden than does a given patient's age (32).

Although total plaque burden is correlated with risk for major coronary events, it fails to identify vulnerable plaques that are prone to rupture and precipitation of acute coronary thrombosis. Newer inflammatory markers (e.g., high-sensitivity C-reactive protein) appear to reflect a propensity to plaque rupture and may provide incremental predictive power for major coronary events (33,34). This workshop did not evaluate newer inflammatory markers as predictors of CHD, but noted it as a promising area for research.

Cardiovascular indicators of high risk. Finally, several clinical and/or non-invasive indicators point to high risk for future CVD events. A long-recognized indicator is left ventricular hypertrophy (LVH) by electrocardiogram (ECG) (35,36); echocardiographic LVH has a similar impact. Patients with LVH appear to be at increased risk for myocardial infarction, cardiac arrhythmia, and sudden death. Various other ECG abnormalities have been reported to be associated with increased risk (37,38). These include evidence of myocardial ischemia or electrical instability either by resting ECG or exercise ECG. Various other non-invasive methods to detect myocardial ischemia or dysfunction further have been reported to have independent predictive power (39).

Current Approaches to Risk Assessment

National Cholesterol Education Program. The NCEP employs a two-pronged approach to the clinical assessment of risk. The first is an evaluation of the underlying risk factors--nutrition, obesity, physical inactivity, and family history of premature CHD. The NHLBI's Obesity Education Initiative (OEI) (14) provides supplemental information on assessment of obesity and physical activity status. Adverse nutrition, obesity, and physical inactivity constitute direct targets of intervention and advice in all patients, regardless of the status of the major, independent risk factors.

The NCEP further introduced the concept that an estimation of absolute risk can be used to modify the intensity of cholesterol-lowering therapy (1,2). For patients without CHD or other clinical forms of atherosclerotic diseases, categories of absolute risk are determined by counting of categorical risk factors. According to NCEP guidelines, the presence of zero or one risk factor warrants an LDL-cholesterol goal of < 160 mg/dL, whereas two or more risk factors calls for an LDL-cholesterol goal of <130 mg/dL (Table 1). The risk factors currently employed to adjust goals for LDL cholesterol in primary prevention also are listed in Table 1. Of note, NCEP included a *family history of premature CHD* as an independent risk factor among others to modify LDL-cholesterol goals. Also, a single cut point for age, which differed between men and women, counted as one risk factor; above this defining age, increasing age did not change an individuals risk category. When previous NCEP guidelines were developed, consideration was given to using Framingham equations with risk factors as continuous variables related to CHD risk. This approach however was rejected in favor of simply counting of categorical risk factors. The latter was thought to simplify clinical application. For patients with established atherosclerotic disease, NCEP guidelines do not use risk factors to modify intensity of cholesterol-lowering therapy; rather, all patients with established CHD or other clinical forms of

atherosclerotic disease are considered to be at high risk and deserving of an LDL-cholesterol target of $\leq$ 100 mg/dL.

National High Blood Pressure Education Program (NHBPEP). The clinical guidelines for this program are presented in Joint National Committee (JNC) reports. Those reports before JNC VI did not formally modify targets for blood pressure-lowering therapy according to the presence or absence of other risk factors. Categorical hypertension is considered to be a dangerous risk factor deserving of clinical intervention. The clinical management of hypertension aims to prevent stroke, chronic renal failure, and heart failure, as well as CHD. JNC reports therefore avoided delay in treatment of categorical hypertension even though short-term absolute risk for CHD may not be high. Less severe forms of hypertension warrant a trial of non-drug therapy; but if this fails to achieve normal blood pressure, drug therapy is recommended. In the JNC VI report (5), lower cutpoints for initiation and targets for blood pressure were set for patients with established cardiovascular disease, end-organ damage, or diabetes mellitus than in those without.

Framingham risk assessment algorithms. The Framingham Heart Study has long furnished an algorithm to assess absolute risks for CHD and stroke based on the major risk factors. In the past, a scoring sheet derived from Framingham equations was published by the American Heart Association. Risk scores were based on the values for causative risk factors plus age. In addition, earlier Framingham/American Heart Association score sheets included left ventricular hypertrophy (LVH) by electrocardiogram as a contributing risk factor. Risk factors were graded according to increasing levels of severity. Recently, Framingham investigators published a new risk-assessment algorithm based on updated analysis (18). This algorithm has dropped LVH as a major risk factor. It graded risk factors according to cut points delineated by NCEP and JNC guidelines. Risk scores for absolute risk were related to two clinical outcomes—total CHD and hard CHD. Total CHD included stable angina pectoris, history of myocardial infarction and unstable angina (coronary insufficiency), electrocardiographic evidence of myocardial infarction, and CHD death. Hard CHD included only myocardial infarction and CHD death. For the current workshop, the Framingham scoring has been re-analyzed to include only hard CHD as an outcome. This analysis allows for comparison of Framingham data with other prospective studies. A scoring table modified for the current workshop and including only myocardial infarction plus CHD death is presented for men and women (Table 2). The Framingham approach to *global risk assessment* not only is useful for defining risk in quantitative terms, but it also can identify patients who are at increased risk on the basis of multiple marginal risk factors. The latter is a potential advantage over tools that employ only categorical factors.

European guidelines. Several organizations in Europe have adopted the Framingham approach of global risk assessment for the development of their guidelines for primary prevention of CHD. These organizations include the following: the joint task force of European and other Societies on Coronary Prevention representing the European Society of Cardiology, European Atherosclerosis Society, European Society of Hypertension, International Society of Behavioural Medicine, European Society of General Practice/Family Medicine, and European

Heart Network (joint European societies); the joint working party to develop recommendations on prevention of coronary heart disease in clinical practice represent the British Cardiac Society, British Hyperlipideaemia Association, British Hypertension Society, and the British Diabetic Association (joint British societies); and the International Task Force for Prevention of Coronary Heart Disease (International Task Force). Key distinguishing features of each of these guidelines can be reviewed briefly.

Guidelines of the joint European societies (4) employ Framingham equations for global risk assessment. The parameters included in the European algorithm include cigarette smoking, blood pressure, serum total cholesterol, and age. From these parameters, 10-year absolute risk is projected for total CHD. Estimates for total CHD, which include stable angina, are higher than those for hard CHD shown in Table 2. European risk scoring is presented in the form of multi-colored diagrams that categorize risk into five levels: very high (>40%), high (20 to 40%), moderate (10-20%), mild (5-10%), and low (under 5%). HDL cholesterol is not used in risk prediction, although it is consistently used in Framingham equations. Also, patients with diabetes are not included in risk predictions, because of the recognition that absolute risk is higher than indicated by standard risk factors when patients have diabetes.

Joint British societies (40) propose a similar approach to global risk assessment, using Framingham scoring for total CHD. The British algorithm (39), however, contains important differences compared to the European algorithm (4). In the former, the total cholesterol/HDL cholesterol ratio is used instead of total cholesterol as the cholesterol predictor. Risk categories are divided into three levels of 10-year absolute risk: > 30%, 15-30%, and < 15%. A separate score sheet is provided for patients with diabetes.

An International Task Force (41) comprised mainly of European investigators have also published guidelines for cardiovascular risk reduction. They identified three levels of absolute risk: small increase, moderate increase, and high risk. This task force favored using an algorithm for estimating global risk based on the Munster Heart Study (the PROCAM algorithm). The latter tool is designed for prediction of first coronary events and takes into account nine independent risk variables: age, smoking history, personal history of angina pectoris, presence or absence of a family history of myocardial infarction, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, and the presence or absence of diabetes. The task force has developed a computer-based method for estimating absolute risk based on these risk factors. It is available in interactive form on the Task Force website at http://www.CHD-taskforce.com.

Population Comparisons in Risk Estimation

Multivariate relative-risk comparisons. One of the essential aims of the workshop was to compare the multivariate regression coefficient for each of the major risk factors among different populations. Prospective data were supplied to Framingham investigators who compared estimated risk-factor coefficients with those obtained in the Framingham population. Coefficients obtained in multivariate analysis allow for estimates of relative risk, i.e.,

multivariate relative risk. Adjusted relative risk estimates make it possible to determine whether each risk factor confers a similar or different relative risk among different populations.

Population attributable fraction for the major risk factors. The prevalence of the major risk factors varies among different populations. For example, blacks in the United States are known to have an unusually high prevalence of hypertension, whereas type 2 diabetes is unusually common among Native Americans. The multivariate relative risk imparted by each risk factor must be distinguished from the contribution of that risk factor to CHD within a particular population. The latter can be called the *population attributable fraction* of CHD for the risk factor. This fraction is a measure of how much of the population burden of CHD could be eliminated if the specific risk factor were to be removed from the population.

Receiver operator characteristic (ROC) analysis. This analysis is carried out to judge the ability of various risk factors (alone or in combination) to discriminate those who develop an event (hard CHD) from those who do not (41,42,43,44). Associated with the ROC is a statistic, called the area under the ROC curve or the "c" statistic, which is an estimate of the probability of the risk function assigning a higher risk probability to those who will develop an event than to those who will not. In other words the statistic quantifies the ability to discriminate events from non-events.

Another useful application of ROC analysis is to determine whether the addition of newer risk factors to risk prediction equation provides significant independent predictive power (18,44,45,46,47). The addition of newer risk factors gives a new prediction equation and a corresponding increase in the ROC c statistic. The increase can be used to judge the practical usefulness of the new risk factors in discriminating events from non-events.

The area under the ROC curve (c statistic) ranges from 0.5 to 1.0. An area of 0.5 signifies correct classification in only 50% of cases, no better than chance. An area of 1.0 indicates perfect classification. The c statistic for the recently published Framingham algorithm was 0.78 (18). Clearly the major risk factors predict better than chance, but as one would expect, their accuracy is not perfect.

Because the relation between age and CHD is very strong, as an independent risk factor may complicate the analysis. Risk increases exponentially with age, and advancing age tends to obscure the influence of other risk factors. Thus, if a broad range of ages is employed in ROC analysis, age alone contributes most of the area under the curve above 0.5. Table 2 shows a series of ROC analyses presented at the workshop by Dr. Richard Cooper that shows a lack of incremental predictive power for CHD mortality when other risk factors are added to age in several populations. Thus, the ROC analysis may well fail to detect a real independent contribution of newer, provisional risk factors. Alternate means of assessing the magnitude of independent prediction may be required. In the Framingham model the use of age only produced an ROC area (c statistic) of 0.65. The increment from this to 0.78 shows substantial additional discrimination from the other risk factors, including blood pressure, blood lipids, smoking, and diabetes.

Population baseline absolute risk. For given levels of a set of risk factors, the absolute risk for CHD may vary among different populations. Moreover, there is a component of risk that is entirely independent of the major risk factors. This component can be called the *population baseline absolute risk* (47). The factors contributing to the population baseline absolute risk are not well understood. However, the underlying predisposing risk factors that vary among populations undoubtedly modify absolute risk. These include body fat content, physical activity, the composition of the diet, personal and social behavior, and the genetic make-up of various ethnic groups. Provisional ("newer") risk factors likewise vary within different populations, and these too could influence population baseline absolute risk. The independent contributions of these multiple predisposing and provisional risk factors to the population baseline absolute risk have not been determined for various populations. Nonetheless, the population baseline risk cannot be ignored when estimating the absolute risk of individuals of a given population by the combining of the major risk factors.

Transportability of Framingham Risk Equations to other Study Populations: Results from US Longitudinal Cohort Studies with CHD Morbidity and Mortality as an End-Point

To evaluate the applicability of Framingham risk equation to other populations, prospective data from other populations were compared to those of Framingham. Detailed results of the analyses have recently been published (48). These additional cohort studies enrolled a more diverse sample than was enrolled in the original Framingham cohort. Specific studies (and a unique characteristic of the cohort) providing data on CHD morbidity and mortality at the workshop included:

1. The Atherosclerosis Risk in Communities Study, which included a sizable proportion of middle-aged African-Americans;
2. The Cardiovascular Health Study of older adults;
3. The Strong Heart Study of Native Americans;
4. The Honolulu Heart Study of Asian Americans;
5. The Puerto Rico Heart Study of Hispanic Americans;
6. The Physicians Health Study, which included subjects with higher-than-average socio-economic status.

For the purposes of this workshop, attempts were made to assure comparability of variables used and analyses performed across the different studies. The cohort studies have the following shared features: 1) all were prospectively followed cohorts; 2) all assessed the major CVD risk factors; 3) all implemented an active events surveillance system; and 4) all used physician adjudicators and medical records to validate events. There were some differences among these studies. The Physicians' Health Study was a randomized trial whereas all the others were prospective observational cohort studies. The data for these studies were collected during different time periods with the Honolulu and Puerto Rico cohorts enrolled in the 1960's, whereas the ARIC, CHS, Strong Heart and Physicians' Health Study cohorts were enrolled in the 1980's. Whereas major CVD risk factor measurements were collected there was some variability in methods between studies. There are several examples of variability: lipoprotein

laboratory assessment methods differed; blood pressure measurement techniques had only subtle differences (although one study used self-reported blood pressure levels); and the definition of glucose intolerance varied (i.e., glucose tolerance testing, fasting glucose, self-reported diabetes).

Because "hard" CHD (myocardial infarction or CHD death) was the end-point for the primary analytic comparisons, the workshop also sought to standardize the definition of hard CHD used in the analyses from participating studies. Whereas some differences were present in the data available for these analyses, the global definition of CHD was quite similar to those used in the Framingham study. To achieve methodological compatibility, participating investigators did the following: (a) used the Framingham risk prediction model to assess the applicability of Framingham estimates in these more diverse populations, and (b) 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 Framingham prediction equation).

Three fundamental questions were addressed in this study. The first was whether the major risk factors carry similar predictive power, relative to one another, in other populations compared to Framingham data. In other words, do the different risk factors have the same relative weights as those shown in the Table 2? The second question was whether the Framingham functions can discriminate those who will develop hard CHD (events) from those who will not (non-events) with the same ability as the best functions developed from the studies themselves. The third question was whether the summed risk factors impart the same estimates for absolute risk, as they do in Framingham. If absolute estimates are similar then it can be said that other groups have a similar population baseline risk as the Framingham population; if not, the population baseline risk will differ from that of Framingham.

The Atherosclerosis Risk in Communities Study (ARIC). The ARIC cohort consisted of men and women, age 45-64 years, who had no history of myocardial infarction or stroke at baseline examination in 1987-1988 (49). ARIC included both white and black subjects in contrast to Framingham, which was almost entirely white. Subjects were assessed for incidence of CHD, hospitalized myocardial infarction, fatal CHD, cardiac procedures, and electrocardiographic (ECG) changes indicative of silent myocardial infarction for a period averaging 7.2 years. In addition to standard Framingham risk factors, the subjects were assessed for fibrinogen, Lp (a), blood pressure medication, ankle-brachial blood pressure index, and carotid wall thickness by B-mode sonography.

The standard risk factors were found to have a relative predictive power for major coronary events similar to that found in Framingham. The only exception was in the black population in which blood pressure conferred a higher relative risk. In other words, the clinical outcomes for a given blood pressure increase were worse for blacks in ARIC than in whites in either ARIC or Framingham. The baseline population risk for major coronary events, however, appeared to be similar for Framingham whites, ARIC whites, and ARIC blacks. Therefore,

when using the Framingham risk algorithm (appendix), no adjustment was required for absolute risk estimates in the ARIC population, either for white or black.

The addition of other risk factors [e.g. fibrinogen and Lp(a)] only slightly improved the prediction model for ARIC, e.g. the area under the ROC curve increased from 0.69 to 0.72. Carotid IMT proved to be a stronger predictor in the otherwise low-risk group and prediction based on this factor was attenuated in the group estimated to be at high risk for CHD by standard risk factors. In ROC analysis, measures of carotid IMT contributed only modestly to the AUC of the ROC curve. In contrast, as shown by a recent publication (50) on the same population, when carotid IMT was evaluated in multivariate analysis, IMT proved to be a robust independent risk factor after adjustment for other risk factors. This apparently discrepant result compared to ROC analysis raises questions about the preferred approach to determine the independent contributions of new risk factors.

The Cardiovascular Health Study (CHS). This cohort consisted of older adults, ages 65 to 100 years at baseline (51). CHS is of interest because Framingham estimates are limited by relatively small numbers of older subjects. Many studies have shown a decline in relative risk estimates for some risk factors, especially lipid risk factors, with advancing age. Consequently, the Framingham risk prediction equations did not predict CHD morbidity and mortality well in the CHS cohort. Particularly weak in predictive power were total cholesterol and HDL cholesterol. On the other hand, the coefficient for diabetes was substantially higher in CHS than in Framingham. In CHS, Framingham predictors tended to be more discriminatory in men than in women.

In the elderly populations of CHS, factors other than standard Framingham risk factors assumed increased predictive power. In CHS men, systolic blood pressure, HDL, ECG changes, and triglyceride were independent predictors. In CHS women, family history, diabetes, and ECG abnormalities were more powerful predictors. Also, in both men and women of CHS, carotid wall thickness (IMT) was an independent predictor. A recent separate report from CHS indicated that carotid IMT scores are a strong independent risk factor for CHD (52). This finding accords with other reports that carotid IMT is positively correlated with the severity of coronary atherosclerosis. 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 coronary atherosclerotic burden.

The Physicians Health Study (PHS). This nested case-controlled study by definition created similar age and smoking prevalence among cases and controls (53); thus the study's ability to evaluate the effects of these variables was precluded. However, risk prediction equations that include blood pressure and lipid/lipoprotein levels were very comparable in predicting CHD morbidity and mortality between the PHS cohort and the Framingham cohort. In other words, blood pressure and serum lipoproteins appeared to impart a similar absolute risk for the Physicians Health population and the Framingham male population. This is an important finding because physicians were enrolled nationwide, and they were not limited to particular geographic regions.

The Strong Heart Study (SHS) is a cohort of Native Americans (54). The germane questions are whether baseline population risk differs in Native Americans compared to American whites and blacks and whether specific risk factors have a greater or lesser relative impact on risk than do Framingham risk factors. In general, many coefficients were similar in the Strong Heart Study model compared to the Framingham model for prediction of CHD morbidity and mortality. However, some differences were noted. For example, a high level of total cholesterol had a greater influence on absolute risk among Native Americans than in the Framingham population. In contrast, the negative effects of a low HDL on CHD morbidity and mortality were attenuated in Native Americans. Diabetes, which is common among Native Americans, seemingly carries a worse prognosis than observed in Framingham. Macro-albuminuria also was found to be an independent risk factor for CVD in the Strong Heart Model. An important result of the Strong Heart Study is the observation that Native Americans do not carry a low population baseline risk for CHD; moreover, standard Framingham risk factors impart at least as high an absolute risk for CHD as they do in Framingham.

The Puerto Rico Heart Study (PRHS) has enrolled a group of men of Hispanic ethnicity (55). Multivariate relative risk of various risk factors was similar in Puerto Rican and Framingham populations; in contrast, the Framingham model overestimated absolute risk for CHD among Puerto Ricans. Whether this over-prediction in the Framingham population extends to other Hispanic populations in the United States is uncertain and disputed. In the Puerto Rico study, adding body mass index, physical activity, heart rate, and vital capacity enhanced the predictive power of a model generated for the Puerto Rican population; adding alcohol consumption and dietary fat only slightly improved prediction. Overall, coefficients generated specifically from the Puerto Rico Heart Study better predicted CHD events than did those of the Framingham equations. When a simple adjustment was made to the Framingham equation to account for differences in average CHD incidence between the Framingham and Puerto Rican cohorts, the Framingham-based predictions were comparable to those produced by the Puerto Rico model. This could be considered a "calibration" adjustment.

The Honolulu Heart Study (HHS) consists of Japanese American men who were 45-64 years old in 1965 (56). Framingham equations over-predicted absolute risk for CHD by about 25%, indicative of a lower baseline population risk. In addition, differences were noted in the relative influence of different risk factors in Framingham and Honolulu populations. Diabetes raised the risk for CHD more in Honolulu than in Framingham. In contrast, HDL was a weaker predictor of CHD in Honolulu than in Framingham. When a calibration adjustment was made to the Framingham model to account for average CHD incidence differences between these populations, the Framingham model performed as well as the best Honolulu model.

In summary, data from ARIC and the Physicians Health Study, which should encompass the majority of American adults, fit the Framingham equations well both for relative influence of the various standard risk factors (multivariate relative risk) and baseline population risk. The population baseline risk of Native Americans likewise was similar to the Framingham population. For other populations (Puerto Rico and Honolulu) calibration adjustments to the Framingham 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 to Framingham equations, even if only slightly. Further, in the elderly population of the CHS, Framingham 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 was frequently employed, but the limitations of this analysis point to the need for newer methods to discriminate independent prediction.

Risk Predictors in Prospective Studies With CHD/CVD Mortality as the Major Outcome

Several prospective studies have collected data relating risk factors to CVD and CHD mortality and were reviewed in this workshop. The applicability of Framingham risk equations in the populations of these studies could not be assessed because of a lack of data on CHD morbidity. They nonetheless may provide perspective on the quantitative relationship of cardiovascular risk factors to mortality from CVD and CHD. They included:

1. The Chicago Heart Association Detection Project (11,016 men ages 18-39 years),
2. The Chicago Western Electric Company (2,107 men ages 40-50 years plus over 1,600 men with serial data),
3. The Multiple Risk Factor Intervention Trial (MRFIT) screenees (361,662 men ages 35-57 years),
4. The first and second National Health and Nutrition Examination Survey (2,753 men and 3,858 women from NHANES I and 2,655 men and 3,050 women from NHANES II, and a pooled sample of 940 black men and 1,463 black women),
5. The Women's Pooling Project (25,978 women ages 30-97).

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. Despite wide variations in study designs, procedures for risk factor measurement and ascertainment of outcomes, the results of risk prediction were remarkably consistent between the studies. Some of the salient outcomes of these analyses can be reviewed.

Age was a strong predictor of CVD and CHD mortality in all of the studies. In addition, other risk factors often differed in their predictive power according to age group. Much of the prior data about risk assessment and prediction derives from middle age populations. Several cohorts displayed broad age categories and allowed for generation of risk prediction models. The Chicago Heart Association study revealed that standard risk assessment is remarkably efficacious and durable in young men. In this study the Cox model coefficient for cholesterol was two-fold higher in young adults compared with middle-aged subjects. In younger men, serum cholesterol and cigarette smoking contributed more to CHD risk than did systolic blood pressure. 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 were more powerful predictors of CHD/CVD death in younger than in older women. For example, the relative risk for CVD for cholesterol $\geq$ 280 mg/dL (compared to < 200 mg/dL) was 6.1 among women aged 30-44 years, but fell to 0.9 in those $\geq$ 65 years.

Ethnicity has been implicated as one factor affecting population baseline risk for morbidity and mortality of CHD and CVD. Nevertheless, the influence of ethnicity may be confounded by socioeconomic status. MRFIT (whites, blacks, Asians and Hispanics), NHANES (whites and blacks), and the Women's Pooling Project (whites, blacks and Hispanics) all revealed that multivariate relative risk for CVD mortality was similar for the various risk factors across ethnic groups. MRFIT investigators were able to examine the data according to median income of zip code of residence and found no systematic differences in multivariate relative risk 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; nonetheless, the prediction of absolute risk for total CVD was improved by the application of ethnic-specific models. In the Women's Pooling project, prediction models generated from whites appeared to under-predict risk for CVD mortality in black women. However, models developed for whites of NHANES over-predicted CVD mortality in black men. These data suggest that assessment of the relative risk of a given factor using a single algorithm for CVD mortality is appropriate for most ethnic and socioeconomic groups. On the other hand, if the goal is prediction of actual deaths, ethnic-specific models provide improvement of 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. These discrepancies for total CVD mortality seem at variance with the comparable estimates of relative and absolute risk for non-fatal and fatal myocardial infarction in whites and blacks of Framingham and ARIC. This difference raises the interesting possibility that absolute risk for CHD morbidity may not parallel precisely absolute risk for CVD mortality among different populations.

Diabetes mellitus is known to be a major cause of cardiovascular events and CHD/CVD death. The largest available data set relating risk factors to CHD mortality is the 16-year follow-up of over 5000 screened men of MRFIT with a diagnosis of diabetes mellitus at baseline. For subjects with diabetes, the absolute risk for CHD-CVD and all cause mortality was five-to-seven fold higher than in non-diabetic subjects. At the same time, the Cox coefficients for each major risk factor (total cholesterol, systolic blood pressure, and cigarette use) were smaller in subjects with diabetes.

An important question for global risk assessment is whether additional variables improve the ability to predict CVD/CHD mortality beyond the major, atherogenic risk factors and age. A recent publication of the Chicago cohort indeed reported the predictive power of abnormal resting ECG findings, such as ST-T abnormalities. Many of the older cohorts that have enough power to examine mortality, however, have not evaluated the role of other risk factors.

The advantage of many of the participating cohorts was that they had long term follow-up of participants. This permitted an evaluation of the impact of varying lengths of follow-up on risk prediction. The Chicago Heart Association study determined that elevated body mass index (BMI) 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, BMI emerged as an independent and graded risk factor in both men and women. Similar findings were observed for asymptomatic hyperglycemia in white and black men in the same cohort. In the Women's Pooling Project, risk ratios were found to be similar for some risk factors over time but risk associated with diabetes and stage III hypertension was found to vary depending on the length of follow-up; the relative risk of both tended to decrease over time.

Overall, several conclusions can be drawn from the studies that examined risk for CHD and CVD mortality. Most important, there was considerable evidence that relative risks were consistent across cohorts and ethnic groups for all major risk factors. Traditional risk factors are more powerful predictors in the young, i.e., relative risk declines with advancing age. Inconsistencies in published data may be the result of variable lengths of follow-up and age distributions of the populations studied. Absolute risk in subgroups may be over- or under-predicted depending on the baseline population risk for CVD in the population upon which the model was generated.

An important issue for estimating relative risk concerns the population stratum employed as the reference. Several previous reports have used the average risk of a population as the denominator. This approach is open to question for "high-risk" populations, where it may underestimate the impact of different risk factors. A better approach may be to use a low-risk group, which is largely devoid of risk factors, as the reference group. When this approach is taken almost all of the *excess risk* in a "high-risk" population can be attributed to the standard risk factors (cigarette smoking, blood pressure, total cholesterol, and HDL cholesterol). Such has been observed for CHD incidence in the Framingham cohort (17); in the MRFIT cohort cigarette smoking and elevations of blood pressure and total cholesterol accounted for most of the excess risk for CHD mortality (57,58).

Application of Framingham Risk Equations to Specific Populations

The data reviewed in this workshop allow for some generalizations to be drawn about application of Framingham risk equations to specific populations. Groups under consideration include different ethnic groups, different age groups, women as well as men, and patients having specific diseases (especially diabetes mellitus). The following summarizes some of the major findings of the workshop.

White populations other than Framingham. The congruence of Framingham predictions for hard CHD between white populations of Framingham and ARIC must be considered a major outcome of the workshop. This finding indicates that Framingham equations can be applied broadly to the white population in the United States. This conclusion is strengthened by the

similarities between multivariate relative risk and population baseline absolute risk in Framingham men and the Physicians Health Study.

Black populations. In broad terms, Framingham equations for hard CHD seemingly apply similarly in white and black populations in the United States. One exception appears to be for blood pressure. For a given level of blood pressure, the Framingham equation under-predicts the risk associated with elevated blood pressure in the black population of ARIC. Therefore, when using the Framingham risk algorithm in blacks, it may be appropriate to give added weight to the blood pressure measure. In the Women's Pooling Project and NHANES, equations for the white population were not highly predictive of CHD/CVD mortality in the black population. This finding could suggest that factors operating subsequent to onset of CHD may affect CVD mortality in the black population.

Other ethnic groups. The comparisons carried out in this workshop confirmed previous observations that absolute baseline risk for developing CHD differs among populations. This variation in population baseline risk must be distinguished from differences in the population attributable fraction for the major risk factor. Along the same lines, differences in population baseline risk may extend to various ethnic groups and will require adjustment of absolute risk estimates based on ethnicity. The possibility also exists that ethnic differences in CVD risk may be explained by variability in underlying or provisional risk factors which are not considered in Framingham equations. Nutrition, body weight, and physical activity are powerful underlying risk determinants. These are not explicitly included in Framingham equations, although they might act through the major atherogenic risk factors. Population habits may vary greatly with respect to these determinants and thereby influence absolute population baseline risk. Other behavioral and social factors typical of populations likewise could affect population baseline risk. Finally, the intriguing possibility remains that genetic factors among different ethnic groups influence the absolute baseline risk of the group.

In two populations, Asian men in Honolulu and Hispanics in Puerto Rico, Framingham coefficients over-predicted risk for CHD. In these two groups, absolute baseline rates for CHD were lower than white and black populations in the United States, and this lower population baseline risk may require an adjustment of projected absolute risk downwards to correspond to the lower baseline risk of the population. Simple calibration adjustment to the Framingham functions to adjust for baseline average CHD incidence rates greatly improved the performance of the Framingham functions in these populations. Whether the Hispanic population living in the contiguous United States has a lower baseline risk is uncertain; a few published studies suggest this to be the case, whereas others claim no such lower baseline risk. Although data were not presented for the predictive power of Framingham equations in Americans of South Asian origin, other studies in migrant South Asians suggest that standard risk equations under-predict absolute risk (59,60). In Native Americans, Framingham equations appeared to be acceptable predictors of absolute risk. In this population, the population attributable fraction for the major risk factors was greatest for diabetes.

Young adults. Although absolute risk in young adults is low, even in those with one or two risk factors, relative risk is high. When risk is estimated for 10 years, relative risk imparted by the presence of risk factors is the highest for any age group. This finding suggests that long-term risk in young adults with risk factors is high. For example, in the Framingham Heart Study, serum cholesterol levels in young adulthood are powerful predictors of life-time risk of developing CHD.

Older adults. Prospective studies consistently show that relative risk accompanying several risk factors declines with advancing age. Both diabetes and hypertension remain strong predictors of CHD in older persons, but an elevated serum cholesterol declines in relative risk. Attributable risk accompanying a high serum cholesterol increases with advancing age, but it is difficult to differentiate higher and lower risk in patients over age 65 on the basis of serum cholesterol levels. As shown in the CHS, Framingham equations were poor predictors of risk after age 65. In contrast, non-invasive assessments of coronary plaque burden such as carotid IMT assume increasing power to predict risk.

Women. Framingham equations indicate that absolute risk for CHD is much lower in women than in men, even into advanced age. At identical levels of risk factors, absolute risk differed markedly between men and women (Table 2). However, in Framingham, 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. These findings along with similar results in other studies, suggest that the presence of diabetes removes the protection against CHD normally afforded to women. In CHS, the 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 the 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.

Diabetes mellitus. Type 2 diabetes is a powerful independent risk factor and has become an increasingly important risk factor in the United States. This is because of increasing obesity, the "aging" of the population, and the expansion of ethnic populations that are particularly susceptible to the development of type 2 diabetes. Framingham equations identify diabetes, defined by categorical hyperglycemia, as a risk equivalent to other categorical risk factors. However, there is a growing view that patients with type 2 diabetes deserve to be evaluated separately in global risk assessment. There are several reasons for this view. First, patients with type 2 diabetes often have insulin resistance and multiple atherogenic risk factors of long duration and thus carry a high risk. This observation is confirmed by recent prospective studies which indicate that middle-aged patients with type 2 diabetes have an absolute risk for major coronary events equivalent to that of non-diabetic patients with established CHD. Second, once patients with diabetes develop CHD, their prognosis for survival is much worse than that of non-diabetic patients with CHD. The unusually high cardiovascular mortality in patients with diabetes was shown clearly in the MRFIT screenee follow-up study.

Other Issues for Applications of Framingham Equations for Global Risk Assessment

Other cardiovascular outcomes. The risk-assessment workshop focused mainly on prediction of CHD morbidity and mortality. The need to predict other cardiovascular outcomes (e.g. stroke, heart failure, renal failure) was recognized however. In the clinical setting, consideration must be given to primary prevention of all forms of chronic cardiovascular disease, and algorithms are needed that incorporate other outcomes besides CHD.

Qualitative categories of risk. There is a need to convert quantitative estimates of risk into qualitative categories so that patients can be easily classified for specific treatment guidelines. One example is the need to distinguish between *high-risk* and *intermediate-risk* categories. Such distinctions are arbitrary, and must derive from an appropriate balancing of efficacy, safety, and cost-effectiveness of available therapies. These definitions therefore cannot be made *a priori* and must evolve out of deliberations of guideline committees. Thus, NCEP and JNC panels will have the responsibility to categorize levels of risk, as they relate to the management of particular risk factors.

Long-term vs. short-term risk. The concept of matching intensity of intervention to absolute risk generally emphasizes risk over the short term, e.g. risk in the next 10 years. Primary prevention however is also for the long term, or even for a lifetime (61). The notion that only patients who are at high risk in the short term deserve clinical management of risk factors goes counter to the basic tenets of NCEP and JNC guidelines. These guidelines indicate the need to reduce risk factors in the clinical setting for patients at intermediate risk as well. In many cases, non-drug therapies can be employed to achieve risk reduction, but patients at intermediate risk should not be ignored. Moreover, a basic principle of primary prevention is that every categorical risk factor must be treated in the clinical setting. Without modification, any single risk factor can lead to serious cardiovascular consequences in the long term. This is particularly so when the risk factor is severe, e.g. heavy cigarette smoking, severe hypertension, familial hypercholesterolemia. But even moderate levels of risk factors can produce clinical complications if left untreated for many years. Although cost-effectiveness of clinical management of moderate risk factors remains an issue, the dangers of ignoring risk factors must be weighed against the costs.

Provisional risk factors. The workshop reports did not indicate that any of the provisional risk factors should be routinely considered in practice as independent, atherogenic risk factor. On the other hand, presentations did not rule out the possibility that some of these risk factors may independently promote atherosclerosis or predispose to CHD. Interest in these risk factors remains high, and in the future, studies must be designed to determine more specifically whether some of the provisional risk factors are truly causative. Participants in the workshop raised the question of whether traditional ROC analysis is sufficient to quantify the independent predictive power of newer risk factors. Of particular importance is whether an elevations of triglyceride-rich lipoproteins, abnormally small LDL, Lp(a), and homocysteine are independently atherogenic. Resolution of these questions is important because each of these factors is a potential therapeutic target.

Underlying risk factors. Among these factors, adverse nutrition, obesity, and physical inactivity are of special interest. Considerable evidence suggests that these factors predispose to the development of cardiovascular disease independently of major atherogenic factors (62,63). However, *independence* of prediction could not be identified in the Framingham Heart Study, or in several other prospective studies (64,65). Nonetheless, it is generally acknowledged that all three are underlying causes of CHD. Thus, they are important targets for clinical intervention to reduce risk for cardiovascular disease. Another risk correlate is a family history of premature CHD; in the development of future treatment guidelines, the issue of whether a positive family history is truly an independent risk factor must be re-examined.

In spite of the unquestioned importance of underlying risk factors, there are two impediments to the use in office-risk assessment of an individual's risk. The first is that they are major causes of the standard atherogenic risk factors which are used in the Framingham algorithm. This overlap makes it difficult to identify the truly independent component of the underlying risk factor. Second, a quantitative assessment of the risk factor is difficult to obtain in the office setting. Nutritional assessment would be required before entering nutritional history into a risk-assessment algorithm, but short of a detailed dietary diary, nutritional assessment is at best qualitative. Clinical measures of obesity are more readily available, but the correlation between these measures and risk are not defined with the precision available for the standard risk factors. Physical inactivity also is a risk factor, but quantitative measures of a person's activity history or state of fitness are not readily available. Because of these limitations, the best approach in the clinical setting appears to make a qualitative assessment of each of the underlying risk factors and to make each a target for direct intervention, i.e., modifying diet composition in a favorable direction, assisting in weight reduction in overweight or obese persons, and encouraging increased physical activity in sedentary individuals.

Non-invasive assessment of subclinical atherosclerosis. In spite of the power of independent risk factors to define risk for CHD, it is generally acknowledged that risk will be underestimated in many patients who fall into the category of intermediate-risk. This is particularly the case for older patients in whom the predictive power of risk factors declines. Thus, there is growing interest in the possibility of refining risk estimates by use of non-invasive procedures for evaluating the extent of subclinical atherosclerosis. Among these tests are the ankle/brachial blood pressure index, resting and exercise ECG, sonography of carotid arteries, and determination of coronary calcium by computerized tomography. The American Heart Association recently held a symposium, called Prevention V, to evaluate the role of non-invasive testing in global risk assessment. The Prevention V report indicated that some of the non-invasive tests may have immediate utility, whereas others require more investigation but are promising. The current workshop did not assess the utility of non-invasive testing, but largely restricted its attention to the risk factors that can be measured in the medical office.

"User-friendly" risk-assessment tools. One of the perceived limitations of the recent Framingham risk-assessment tool is its complexity for clinical usage. European cardiovascular societies have attempted to simplify the application of Framingham risk equations by development of multi-colored charts showing different levels of risk. The American Heart

Association has followed this lead and also has published multi-colored risk assessment charts. Nevertheless, many participants in the current workshop held the view that these charts still are not "user-friendly". Perhaps application could be simplified further by the development of a hand-held calculator in which numbers for different risk factors could be easily added. Some of the participants questioned whether the use of risk assessment algorithms that incorporate continuous variables are inherently more valuable than the current methods of NCEP and JNC that count categorical risk factors. There was a broad impression that more investigation on the optimal presentation of a "risk-assessment tool" is required.

Research Recommendations

During the presentations on available data related to risk assessment, a number of important and unanswered questions arose. These questions point to the need for new research and development of improved risk-assessment techniques. The following areas requiring additional work were identified.

- To improve the predictive power of Framingham data for white and black middle-aged populations in the United States by pooling the databases of Framingham and ARIC.
- To develop adjustments in Framingham risk equations for the various ethnic groups that carry different absolute baseline population risks. Examples are Puerto Rican Hispanics and Honolulu Japanese Americans. Also, to characterize the absolute baseline population risk of other subgroups of the U.S. 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 diabetes of both Types 1 and 2, patients with non-coronary forms of atherosclerotic disease, and patients 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 other than fatal and non-fatal myocardial infarction, e.g. 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"—risk for developing the major atherogenic risk factors (hypertension, lipid disorders, and diabetes).
- To develop improved 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 new, provisional risk factors, e.g. triglycerides, Lp(a), homocysteine, coagulation factors (fibrinogen, PAI-1), C-reactive protein.
- To determine the independent predictive power of measures of abnormal cardiovascular function, e.g. left ventricular hypertrophy, abnormal resting electrocardiogram, abnormal pulmonary function tests, exercise tolerance.

- To determine the independent predictive power of measures of myocardial ischemia, e.g. exercise ECG, exercise and pharmacological (stress) echocardiogram, exercise and pharmacological myocardial perfusion imaging, and positron emission tomography.
- To determine the independent predictive power of measures of subclinical atherosclerosis, e.g. 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. Perhaps several different versions of score sheets should be developed and tested in physician's offices. New methods of entering data outside of direct physician involvement are needed.
- To extend risk prediction algorithms to long-term (and life-time) risk.

Summary

The primary purpose of this workshop was to determine whether risk equations developed in the Framingham Heart Study are applicable to other population groups. The major finding was that the Framingham equations appear to have broad applicability in middle-aged white, black, and Native American populations in the United States. Although hypertension appears to be a more powerful risk factor for cardiovascular disease in the black population than revealed in Framingham equations, they otherwise are generally applicable. Certain ethnic groups, notably Japanese men and Puerto Rican Hispanics, appear to carry a lower baseline risk for CHD, and in these populations, Framingham equations tend to overestimate absolute risk. The equations can, however, be adjusted to improve predictions.

The deliberations of the workshop revealed that global risk assessment requires many considerations beyond the simple application of a "risk-assessment tool" for estimating absolute risk. The issue of clinical management of risk factors for patients with single categorical risk factors is of considerable importance. This issue bears on the question of long-term risk that cannot be overlooked in the enthusiasm for global risk assessment for absolute, short-term risk. Further, the use of causal risk factors in the assessment of risk should not detract from the need to pay attention in the clinical setting to other types of risk factors discussed above (underlying, provisional, and plaque burden). Three underlying risk factors—adverse nutrition, obesity, and physical inactivity—deserve particular attention in clinical practice. Whether to treat provisional risk factors is an unresolved issue that requires further investigation. Likewise, expansion of the risk-assessment paradigm though non-invasive methods for estimating subclinical atherosclerosis is promising and may have utility for refining risk estimates in *intermediate-risk* patients and in elderly patients.

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Table 1

Treatment Decisions Based on LDL-Cholesterol

In Patients without Established CHD

Risk Factors*	LDL-Cholesterol Goal
Fewer than two risk factors	< 160 mg/dL
Two or more risk factors	< 130 mg/dL

*** Risk Factors**

Positive Risk Factors

- **Age (male ≥ 45 years; female ≥ 55 years)**
- **Family history of premature CHD**
- **Current cigarette smoking**
- **Hypertension (≥ 140/90 mmHg or on antihypertensive medication)**
- **Low HDL cholesterol (<35 mg/dL)**
- **Diabetes mellitus**

Negative Risk Factor

- **High HDL cholesterol (≥ 60 mg/dL) (offsets one risk factor)**

Table 2

Framingham Scores for Hard CHD

(Non-Fatal Myocardial Infarction and CHD Death)

Risk Factor	Points Male	Points Female
Age		
30-34	-1	-6
35-39	0	-3
40-44	1	0
45-49	2	2
50-54	3	5
55-59	4	6
60-64	5	8
65-69	6	9
70-74	7	10
Total Cholesterol		
< 160	-1	-1
160-199	0	0
200-239	1	3
240-279	3	4
>= 280	4	5
HDL Cholesterol		
< 35	2	6
35-44	1	5
45-49	0	4
50-59	0	0
>= 60	-2	-3
Blood Pressure		
Optimal	0	-4
Normal	0	0
Hi Normal	1	1
Stage I Hyper	2	2
Stage II-IV Hyper	3	4
Diabetes		
No	0	0
Yes	2	5
Smoker		
No	0	0
Yes	3	6

Point Total	10 Year Hard CHD Risk Male	Female
-1	1%	<1%
0	1%	<1%
1	1%	1%
2	2%	1%
3	2%	1%
4	3%	1%
5	3%	1%
6	4%	1%
7	6%	2%
8	7%	2%
9	10%	2%
10	12%	2%
11	16%	3%
12	20%	3%
13	25%	4%
14	32%	5%
15	39%	6%
16	48%	7%
17	57%	8%
18	67%	9%
19	77%	10%
20	85%	12%
21		14%
22		17%
23		19%
24		22%
25		26%
26		30%
27		34%
28		39%
29		44%
30		49%

Table 3

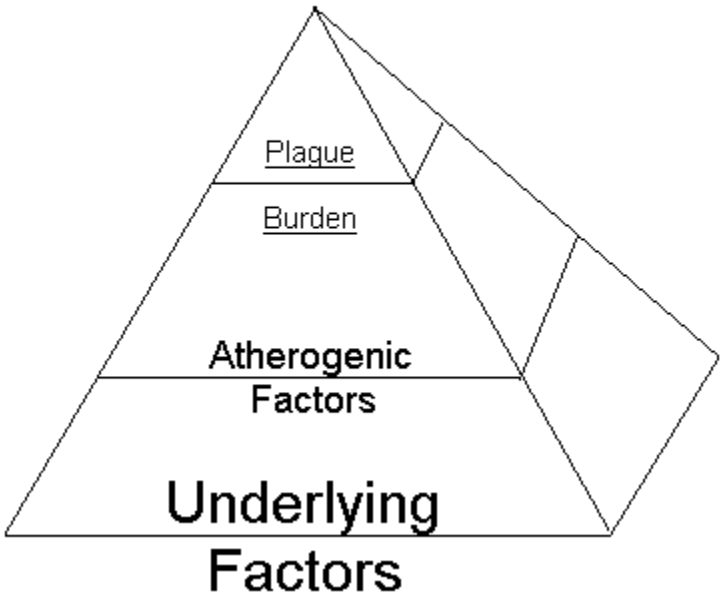
Receiver Operator Characteristics Analyses

Of CHD Mortality From Several Prospective Studies

Study	Sex	Race	Area Under the Curve Receiver Operator Characteristics Analysis: Age Only	Age +SBP	Age +SBP +Chol	Age +SBP + Chol + Curr Smok
NHANES II	M	W	0.81	0.81	0.80	0.82
NHANES II	F	W	0.78	0.78	0.78	0.82
NHANES II	M	B	0.73	0.74	0.72	0.73
NHANES II	F	B	0.76	0.77	0.78	0.78
MRFIT	SI-M	W	0.61	0.61	0.61	0.64
MRFIT	UC-M	W	0.61	0.61	0.60	0.65
LRC-CPPT	RX-M	-	0.60	0.59	0.59	0.65
LRC-CPPT	PL-M	-	0.58	0.56	0.56	0.65

Abbreviations: SBP = systolic blood pressure; chol = total serum cholesterol; curr smok = current cigarette smoking

Figure 1: A schematic of the "pyramid" of coronary heart disease risk factors



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