AHA Scientific Statement

Primary Prevention of Coronary Heart Disease: Guidance From Framingham

A Statement for Healthcare Professionals From the AHA Task Force on Risk Reduction

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The Framingham Heart Study has contributed importantly to understanding of the causes of coronary heart disease (CHD), stroke, and other cardiovascular diseases. Framingham research has helped define the quantitative and additive nature of these causes or, as they are now called, "cardiovascular risk factors."[1] The National Cholesterol Education Program (NCEP)[2,3] has made extensive use of Framingham data in developing its strategy for preventing CHD by controlling high cholesterol levels. The NCEP guidelines[2,3] adjust the intensity of cholesterol-lowering therapy with absolute risk as determined by summation of risk factors. The National High Blood Pressure Education Program (NHBPEP) has set forth a parallel approach for blood pressure control. In contrast to the NCEP,[2] however, earlier NHBPEP reports

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issued through the Joint National Committee[4] did not match the intensity of therapy to absolute risk for CHD. "Normalization" of blood pressure is the essential goal of therapy regardless of risk status. Blood pressure–lowering therapy is carried out as much for prevention of stroke and other cardiovascular complications as for reduction of CHD risk. Nonetheless, risk assessment could be important for making decisions about type and intensity of therapy for hypertension. Thus, the most recent Joint National Committee report[5] gives more attention to risk stratification for adjustment of therapy for hypertension. Although Framingham data have already been influential in the development of national guidelines for risk factor management, the opportunity may exist for both cholesterol and blood pressure programs to draw more extensively from Framingham results when formulating improved risk assessment guidelines and recommending more specific strategies for risk factor modification.

The American Heart Association has previously used Framingham risk factor data to prepare charts for estimating CHD risk. Framingham investigators of the National Heart, Lung, and Blood Institute prepared the original charts and have now revised them using updated Framingham data.[6] The risk factors have been reclassified to be more consistent with NCEP[2,3] and Joint National Committee[4,5] cut points. This statement discusses the new Framingham charts, their essential features, and their appropriate use. In addition, several issues related to CHD prevention raised by these charts are examined. Other issues of risk management not considered in these charts are also addressed.

Concept of Risk Factors

The concept of risk factors constitutes a major advance for developing strategies for preventing CHD. The Framingham Heart Study played a vital role in defining the contribution of risk factors to CHD occurrence in the general population of the United States. The major risk factors studied extensively at Framingham include cigarette smoking,[7–19] hypertension,[11,20–33] high serum cholesterol and various cholesterol fractions,[34–50] low levels of high-density lipoprotein (HDL) cholesterol,[51–57] and diabetes mellitus.[58–70] Advancing age is also included as a risk factor in the Framingham charts because of increased absolute risk with aging.[71–75]

Factors other than those listed as *major* risk factors increase the likelihood for developing CHD. Among these, which have been studied at Framingham or elsewhere, are obesity, physical inactivity, family history of premature CHD, hypertriglyceridemia, small low-density lipoprotein (LDL) particles, increased lipoprotein (a) (Lp[a]), increased serum homocysteine, and abnormalities in several coagulation factors. Despite the potential importance of these other factors, they are not included in the Framingham risk charts for both theoretical and practical reasons. Nonetheless, they deserve some comment and consideration of reasons for omission.

Framingham research reveals that both obesity[76–78] and physical inactivity[79–82] are positively associated with risk for CHD. Even so, Framingham data suggest that obesity and

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physical inactivity exert much of their adverse influence on development of CHD through the major risk factors. Certainly it is possible that some of the increased risk imparted by obesity and physical inactivity results from mechanisms unrelated to the major risk factors. However, these mechanisms are not well understood, and it is difficult to define the risk imparted by these 2 factors independent of their influence on the major risk factors. The NCEP[2,3] and the AHA[83] take the position that obesity and physical inactivity *are* important risk factors for CHD; however, they generally are not used in quantitative risk assessment but rather stand as targets for modification for everyone. Certainly both public health and clinical efforts to promote desirable body weight and regular exercise deserve a high priority in prevention.

Family history undoubtedly gives useful information about an individual's risk status. The NCEP[2,3] considers a positive family history of premature CHD a risk factor and uses it in defining risk status. Framingham data also indicate that a positive family history is a risk correlate.[84] However, the independent effect of a positive family history is difficult to determine. Almost certainly familial influences on risk status are mediated in part through blood pressure and serum lipoprotein levels. Even so, a positive family history of premature CHD cannot be ignored in clinical evaluation. Not only should such a history increase awareness that an individual is at greater risk, but it calls for evaluation of other family members who may carry heritable risk factors.

Framingham risk scores do not include serum triglyceride levels. Much research confirms that elevated serum triglycerides are significantly correlated with risk.[85] However, a controversy has raged for many years over whether elevated triglycerides are an independent risk factor.[86] For example, triglyceride levels are inversely correlated with serum HDL-cholesterol levels.[87] Moreover, in multivariate analysis of the type used by Framingham investigators, low HDL-cholesterol levels are a more consistent and reliable predictor of increased CHD rates than are elevated triglyceride concentrations.[51–57] Thus, for simplicity, serum HDL-cholesterol levels are used in Framingham scores[6] and triglyceride levels are ignored. This approach does not necessarily mean that triglyceride-rich lipoproteins are not atherogenic. There is growing evidence that certain species of these lipoproteins are in fact atherogenic[88,89] and probably should be targets of therapy. Even so, for risk assessment, HDL-cholesterol levels reflect a significant portion of the risk imparted by higher serum-triglyceride concentrations. Another lipoprotein abnormality, small LDL particles, is likewise strongly associated with low serum HDL-cholesterol levels.[90] Small LDL particles may promote atherosclerosis,[91,92] but Framingham prediction scores subsume them under the HDL category. Future research will be required to define the independent contributions of the 3 components of the atherogenic lipoprotein phenotype—elevated triglyceride-rich lipoproteins, small LDL particles, and reduced HDL cholesterol—to overall CHD risk.[93] Use of serum HDL-cholesterol levels to define the risk accompanying this complex phenotype is undoubtedly an oversimplification, but this drawback is partially offset by clinical usefulness.

Lp(a) may be still another lipid risk factor. Several reports[94–97] indicate that elevated serum Lp(a) concentrations are associated with high risk for CHD. Although other reports[98,99] fail to document a significant link between Lp(a) levels and CHD rates, the preponderance of the evidence seems to support a significant relationship. However, before measurements of Lp(a) levels can be routinely used in risk prediction, a stronger link between Lp(a) and atherogenesis must be established, and accurate and inexpensive measurements must be widely available.

Another category of candidate risk factors includes abnormalities in several coagulation factors.[100] Among these factors are platelet hyperreactivity,[101] high levels of hemostatic proteins (fibrinogen[102–107] and factor IV[108–111]), defective fibrinolysis,[112–115] and hyperviscosity of the blood.[103] The most extensive epidemiological data link plasma fibrinogen concentrations to CHD risk,[102–107] but other abnormalities may be important as well. In addition, evidence suggests that plasma markers for endothelial cell injury and inflammation may be predictors of acute coronary events.[100] Research on these various factors promises to provide new insights into the pathogenesis of CHD, but their quantitative roles have not been determined sufficiently to include them in risk prediction equations. Moreover, accurate measurements of these coagulation factors are not yet widely available to practicing physicians.

In recent years there has been a growing interest in the possibility that a condition called *insulin resistance* underlies several metabolic risk factors, predisposing the individual to premature CHD.[116] Insulin resistance refers to a generalized metabolic disorder in which various tissues are resistant to normal levels of plasma insulin. Metabolic abnormalities include defective glucose uptake by skeletal muscle, increased release of free fatty acids by adipose tissue, overproduction of glucose by the liver, and hypersecretion of insulin by pancreatic β-cells. The presence of insulin resistance can usually be detected clinically by truncal (or abdominal) obesity[117] and hyperinsulinemia.[116] CHD risk factors often present in patients with insulin resistance include the atherogenic lipoprotein phenotype, hypertension, impaired glucose tolerance, and a prothrombotic state.[116] This clustering of several metabolic risk factors in a single patient has been termed the *metabolic syndrome*.[93] The major Framingham risk factors include some of the components of metabolic syndrome but not all. Thus, the aggregate risk carried by patients with insulin resistance may be underestimated by Framingham scores.

The final risk predictor is serum homocysteine level. Persons with the rare congenital disorder homocysteinuria develop severe arterial disease[118]; this discovery gave rise to the theory that high homocysteine levels may be a cause of CHD. Furthermore, according to several studies,[119–122] moderately elevated serum levels of homocysteine in the general population are positively associated with CHD occurrence. In addition, patients with a genetic defect in an enzyme producing high homocysteine levels also appear to be at increased risk for CHD.[123,124] Whether measurement of plasma homocysteine concentrations is clinically useful in risk stratification is uncertain but worthy of further investigation.

Future research on these additional risk factors, which are not included among the Framingham scores, could provide new insights into mechanisms of atherogenesis. Eventually some of these other factors may be useful additions to risk prediction equations. Even now they may deserve some consideration in therapeutic decisions. Still, an important question should be addressed first: what proportion of CHD events in the general population can be explained by the major risk factors already used in the Framingham risk scores? Some pathological studies[125,126] suggest that only about half of the variation in size of atherosclerotic lesions can be attributed to known risk factors. On the other hand, when the concept of excess coronary risk is used, the major risk factors seemingly account for most of the *premature* CHD in the United States. Excess risk represents risk greater than that present in the absence of any risk factors, eg, no smoking or diabetes, total cholesterol <160 mg/dL, and blood pressure <120/80 mm Hg. Follow-up data from screenees of the Multiple Risk Factor Intervention Trial[127] indicate that about 85% of excess risk for premature CHD can be explained by the major risk factors. Framingham data are generally in accord with this conclusion; persons with a low-risk profile (ie, optimal blood pressure, total cholesterol 160 to 199 mg/dL, HDL cholesterol ≥45 mg/dL for men or ≥55 mg/dL for women, nonsmoking, nondiabetic) are at quite low absolute risk for CHD.[6] Although risk rises with aging even in the absence of these major risk factors, absolute risk remains relatively low, even in older people. Persons with a low-risk profile generally have less than half the risk of the average Framingham participant throughout life. Note that the low-risk profile includes a total cholesterol level in the range of 160 to 199 mg/dL. When the cholesterol level is below 160 mg/dL, risk is markedly attenuated.

The mechanisms whereby various risk factors enhance risk for CHD constitute a topic of growing interest. According to recent concepts, coronary atherogenesis can be divided into 2 broad phases. The first is coronary plaque development leading to stable, fibrotic lesions. When arterial narrowing by obstructive lesions becomes sufficiently severe, coronary blood flow can be impeded, producing stable angina pectoris. The second phase of atherogenesis is formation of unstable plaques; such plaques are prone to rupture or erosion, which activates the clotting cascade. The result of plaque rupture is an acute thrombotic event: unstable angina or acute myocardial infarction.[128,129] According to the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study,[125,126] each of the major risk factors enhances development of fibrotic plaques. Other lines of evidence point to cigarette smoking and high blood cholesterol levels as important causes of unstable plaques; the most convincing evidence of the role of these 2 factors in producing plaque instability is the marked reduction in acute coronary events (acute myocardial infarction and unstable angina) that follows smoking cessation[130] and cholesterol-lowering therapy[131–133] in patients with advanced atherosclerotic disease. Hypertension possibly promotes enlargement of plaques more than it destabilizes coronary lesions as suggested by the observation that blood pressure lowering does not reduce the occurrence of acute coronary events as much as smoking cessation and serum cholesterol reduction.[134,135] Nonetheless, Framingham data[6] demonstrate that sustained hypertension carries as much long-term risk for myocardial infarction as do smoking and elevated cholesterol. There is no doubt that high blood pressure accelerates atherogenesis[125,126] and lowering of blood pressure reduces CHD risk.[136,137] Thus, blood pressure control is a necessary element in long-term prevention of CHD. The specific role played by diabetes mellitus in plaque growth and rupture remains unclear. Recent autopsy data suggest that hyperglycemia promotes plaque development[138]; the high incidence of myocardial infarction in patients with diabetes raises the possibility that hyperglycemia also predisposes such patients to plaque rupture or erosion.[139] Framingham data cannot delineate the influence of risk factors in the different stages of atherogenesis; instead, they provide a summation of effects. In most Framingham reports, the coronary end points on which risk scores are based include summation of onset of angina pectoris, acute myocardial infarction, coronary insufficiency, and coronary death. In the accompanying report,[6] another end point, *hard CHD*, is added; this end point excludes angina pectoris and may more closely reflect the incidence of thrombotic coronary events.

Relative Versus Absolute Risk

Relative risk is the ratio of the likelihood of CHD developing in persons with and without a given risk factor or at a given intensity of a risk factor. Absolute risk is the probability of developing CHD in a finite period, eg, within the next 10 years. In a sense, relative risk reflects the rate at which a person is accruing absolute risk. Serum cholesterol data provide a good example of the difference between relative and absolute risk. A young adult with a high serum cholesterol level carries a low absolute risk for CHD but has a high relative risk compared with a young adult with a low serum cholesterol level. The hypercholesterolemic young adult is unlikely to develop CHD in the next 10 years, but his or her chances of experiencing premature CHD in the long term (eg, before age 65) are high. Long-term follow-up data from Framingham confirm this concept: cholesterol levels measured in young adulthood are inversely associated with life expectancy.[47] Results from other studies[140–142] further support the concept that a high relative risk in young adulthood is transformed into a high absolute risk in the long run. The goal for reducing elevated serum cholesterol in young adults thus is to retard atherogenesis throughout life, not to prevent myocardial infarction in the next decade. This essential aim does not necessarily justify the use of cholesterol-lowering drugs that are expensive and of uncertain long-term safety in young adulthood; however, it does warrant attempts to modify lifestyle habits and control other risk factors early in adulthood to slow atherogenesis. This aim also justifies efforts to detect elevated serum cholesterol in young adults.[143] There is a current misconception on the part of some investigators that absolute risk for CHD can be almost fully reversed by aggressive cholesterol-lowering therapy initiated after atherosclerosis has become advanced.[144,145] Certainly reduction of serum cholesterol levels in patients with advanced atherosclerotic disease does substantially reduce morbidity and mortality from CHD,[131–133] but the persistently high

rate of coronary events even in those patients who receive cholesterol-lowering drugs reveals that risk cannot be fully reversed.

Framingham risk scores furnish 2 ways to estimate relative risk. One compares a given individual's estimated risk with the absolute risk of an individual at low risk, ie, a person who is largely without risk factors. The other compares a given individual's estimated risk with the risk of an average person of the same age and sex. The latter ratio is commonly used, although it tends to underestimate the preventable component of coronary risk because the average American is developing coronary atherosclerosis at an unnecessarily rapid rate. A better way to assess the full potential for risk reduction, when introduced relatively early in life, is to compare estimated absolute risk with truly low risk. As indicated before, about 85% of excess risk for CHD in the whole US population can be explained by the sum of major risk factors.[127] Total excess risk for an individual patient can be estimated by subtracting that person's absolute risk from the absolute risk of a person of the same age and sex who is at low risk.

Estimated absolute risk should provide a guide to intensity of risk factor management. For example, the NCEP[2,3] places increased emphasis on the absolute-risk calculation to guide considerations on when to use cholesterol-lowering drugs. Treatment of other risk factors is mandated to prevent other complications besides CHD (eg, blood pressure control to prevent stroke and smoking cessation to prevent lung cancer and other pulmonary diseases); effective therapies therefore cannot be delayed. In contrast, cholesterol management aims primarily to prevent CHD; consequently, aggressive cholesterol lowering through the use of powerful drugs is best reserved for persons at high absolute risk.[2,3] Recent clinical trials[131–133] have demonstrated the efficacy and safety of cholesterol-lowering drugs for prevention of CHD in patients at high absolute risk; sufficient information to prove the long-term safety of cholesterol-lowering drugs is not available to justify their use in patients at moderate risk.

Primary Versus Secondary Prevention

Primary prevention generally means the effort to modify risk factors or prevent their development with the aim of delaying or preventing new-onset CHD. The term "secondary prevention" denotes therapy to reduce recurrent CHD events and decrease coronary mortality in patients with established CHD. Secondary prevention strategy is aimed at both control of risk factors and direct therapeutic protection of coronary arteries from plaque eruption. This dual approach has led some investigators to view secondary prevention efforts as treatment of coronary artery disease. Although there may be a slim distinction between secondary prevention and high-risk primary prevention, once a patient has exhibited clinical atherosclerotic disease, he or she is unequivocally at very high risk for developing new acute coronary events.[2,3] Aggressive preventive measures are thus justified. For purposes of secondary prevention, manifest atherosclerotic disease includes angina pectoris or a history of documented myocardial infarction, history of coronary artery procedures (bypass graft or angioplasty), peripheral artery disease, aortic aneurysm, and symptomatic coronary artery disease.[2,3] The AHA has published recommendations for risk management in patients with established atherosclerotic disease.[146]

Framingham risk scores in the accompanying publication[6] apply essentially to primary prevention. These scores were obtained in patients without manifest atherosclerotic disease. Risk factors continue to affect outcomes in patients with manifest atherosclerotic disease, but absolute risk predictions based on the current presentation[6] do not apply to patients with established atherosclerotic disease.

Potential Uses of Framingham Risk Charts

The Framingham charts provide a realistic picture of a given individual's true absolute and relative risks. Therefore, they can be helpful in tailoring a plan for risk factor management. The NCEP[2,3] used Framingham data to link recommended intensity of cholesterol management to absolute risk. NCEP risk categories,[2,3] however, were more broadly outlined. The new Framingham scores aim to provide a more precise delineation of absolute risk, which in turn might lead to a more precise selection of appropriate therapy. For example, the new scores might be used in deciding when to initiate drug therapy for risk reduction.

Another potential use of the Framingham charts is patient education and motivation. Patients with low risk scores can be reassured. Those with higher scores should, as a minimum, be counseled to adopt risk-reducing life habits, ie, smoking cessation, dietary change, weight control, and exercise. For the patient, risk scores highlight the cumulative danger of having several risk factors. It must be emphasized, however, that a low absolute risk, particularly in young adults, does not ensure a lifetime of low risk.[143] Not only does absolute risk increase with aging, but the number and severity of metabolic risk factors typically worsen with aging. Serum cholesterol levels rise throughout young adulthood and into middle age. In many people, systolic and diastolic blood pressures rise progressively throughout adulthood, even into older age. Insulin resistance usually worsens with aging, resulting in a progressive increase in the prevalence of noninsulin-dependent diabetes mellitus. All of these changes with aging are accentuated in persons who gain weight and become more sedentary with the passing years. Thus, both the NCEP[2,3] and the Joint National Committee[4,5] recommend periodic retesting for risk factors, even for persons previously found to be at low risk. Total cholesterol and HDL cholesterol should be checked at least once every 5 years and blood pressure measured at least once every 2 years.

The risk charts add perspective by comparing the relative importance of the different risk factors. For example, the charts indicate that high total cholesterol and low HDL-cholesterol levels carry an absolute risk similar to those imparted by smoking, diabetes, and moderate hypertension. These similar influences of different factors on CHD risk are not widely appreciated. It is critical to point out, however, that risk scores presented in the charts are not accurate when risk factors are present in severe form; thus, heavy smoking, marked hypertension, and extremely elevated serum cholesterol confer much greater risk than that suggested by the scores. Furthermore, when young adults manifest severe forms of risk factors, the danger of developing premature

CHD is especially high. For such patients, a major effort should be made to modify risk factors.

Age as a Risk Factor

Absolute risk for CHD increases with age in both men and women[71–75] as the result of progressive accumulation of coronary atherosclerosis with aging. In fact, most new-onset CHD now occurs after age 65; this trend is especially pronounced in women.[147] Because of a high absolute risk in elderly patients, opportunities for primary prevention in this age group should be substantial. The extent to which prevention can be realized in older persons remains somewhat uncertain, however, because of a lack of clinical trials that specifically target this age group. Most investigators[2–5] agree that primary prevention efforts are justified in the "young" elderly, ie, those aged 65 to 75 years. Framingham data afford absolute risk estimates for people in this age range that may assist in selection of candidates for aggressive primary prevention. A growing consensus moreover extends secondary prevention efforts to the "old" elderly, ie, >75 years.[2–5] Primary prevention efforts in older elderly people should be addressed more cautiously but cannot be ruled out. Certainly smoking cessation at any age is prudent. Treatment of systolic hypertension even in very old patients reduces risk for both stroke and CHD.[148] On the other hand, initiation of cholesterol-lowering therapy in persons aged >75 years for the purpose of primary prevention is an issue of some dispute; nonetheless, if therapy was started in the earlier years, it should be continued.

Cigarette Smoking

Cigarette smoking is a powerful risk factor that probably predisposes the smoker to CHD in several ways. According to autopsy studies,[126,127,149,150] smoking accelerates coronary plaque development. Framingham data further reveal that smoking is a powerful risk factor for myocardial infarction, even stronger than for angina pectoris.[13] Of great importance is the fact that smoking cessation rapidly and markedly reduces risk for myocardial infarction.[130] These 2 findings taken together imply that cigarette smoking probably destabilizes coronary plaques and promotes plaque rupture and coronary thrombosis. Thus, smoking is especially dangerous in patients with advanced coronary atherosclerosis.

The Framingham scores assign 2 risk points for cigarette smoking. This seems appropriate for patients who smoke about 1 package of cigarettes a day. Those who smoke more are at extremely high risk for premature CHD, much more so than revealed by the risk score. Moreover, the dangers of cigarette smoking to overall health go beyond its effects on risk for CHD. Smoking is the predominant cause of peripheral arterial disease,[151] it is a major risk factor for stroke,[18] it underlies many different forms of cancer, and it causes chronic lung disease. For these reasons, cigarette smoking is the foremost preventable cause of death in the United States[152]; efforts toward smoking cessation deserve high priority in any prevention strategy.

Hypertension

High blood pressure is a potent risk factor. The Framingham risk chart highlights the danger imparted by moderate hypertension.[6] Moderate elevations of blood pressure are a particularly strong risk factor in women. Unfortunately, a substantial portion of the US population with hypertension is inadequately treated.[153] The Joint National Committee reports[4,5] recommend therapy for blood pressure readings consistently >140/90 mm Hg. The Joint National Committee[4] encourages modification of lifestyle to reduce blood pressure but also recognizes that medications are often required to achieve normalization of blood pressure. In previous Joint National Committee reports,[4] absolute risk for CHD was not considered in setting target values for blood pressure lowering because of the other dangers accompanying untreated, moderate hypertension (eg, stroke and renal failure). The normal range for blood pressure (<140/90 mm Hg) thus becomes the target for all persons. Ample clinical trial evidence[134] indicates that many strokes can be prevented by blood pressure control. Certainly another purpose of hypertension management is reduction of CHD risk; recent data from clinical trials indicate that blood pressure lowering does in fact decrease CHD risk.[136,137] The most recent Joint National Committee report[5] recommends different therapeutic regimens, depending on blood pressure range, presence of major risk factors, and evidence of target organ damage or clinical cardiovascular disease. When diabetes is present, risk status is elevated to that associated with target organ damage or clinical cardiovascular disease. For patients at moderate risk, as defined by both blood pressure and other risk correlates, changes in life habits are the recommended therapy; for patients at high risk, antihypertensive drugs are required.

The NCEP[2,3] gives equal weight to untreated and treated hypertension in assessment of risk; both count as 1 risk factor in the NCEP guidelines. The Framingham scores chart hypertension according to degree of severity and use current blood pressure for assessment whether or not specific therapy is being used. This approach is in accord with the way blood pressure data are collected at Framingham and may offer an improved estimation of risk. In clinical practice, of course, several blood pressure measurements are preferable to single readings when deciding on type and intensity of treatment.[4,5]

Serum Cholesterol

Serum total cholesterol levels correlate with CHD risk over a broad range of levels. Although the NCEP[2] defines a total cholesterol level <200 mg/dL as desirable, CHD risk is lower still at levels <160 mg/dL; thus, in the Framingham chart,[6] total cholesterol levels <160 mg/dL are scored with −3 points for men and −2 points for women. Total cholesterol levels between 160 and 199 mg/dL are scored as 0; values of 200 to 239 mg/dL, called "borderline-high" for both men and women,[2,3] receive 1 point. Total cholesterol of 240 to 279 mg/dL is scored as 2 points for both men and women; ≥280 mg/dL, as 3 points for both men and women.

The NCEP[2,3] identifies serum LDL cholesterol, not total cholesterol, as the primary target of cholesterol-lowering therapy. An approximate correspondence between total cho-

Comparable Levels for Serum Total Cholesterol and LDL Cholesterol

Total Cholesterol		LDL Cholesterol	
Level	Category	Level	Category
<200 mg/dL	Desirable	<130 mg/dL	Desirable
200–239 mg/dL	Borderline high	130–159 mg/dL	Borderline high
≥240 mg/dL	High	≥160 mg/dL	High

LDL indicates low-density lipoprotein.

lesterol and LDL cholesterol, as developed by the NCEP,[2,3] is shown in the Table. In deference to the NCEP, Framingham investigators have also provided risk scores based on LDL-cholesterol levels. It should be noted, however, that the Framingham database for total cholesterol is greater than LDL cholesterol, and Framingham scores accompanying different levels of total and LDL cholesterol do not correlate in precisely the same manner as that of the Table. For example, in men, the Framingham scores do not show a gradient of risk between desirable LDL cholesterol (100 to 129 mg/dL) and borderline-high risk LDL cholesterol (130 to 159 mg/dL) as noted for corresponding values for total cholesterol. Moreover, risk scores in men are lower for higher corresponding levels of LDL cholesterol than for total cholesterol. A similar inconsistency is noted for women. Other data sets that include greater numbers of patients than the Framingham study reveal a more continuous relationship between serum cholesterol risk and incidence of CHD.[127] Thus, when using Framingham cholesterol data for risk stratification, it may be preferable to use total cholesterol over LDL cholesterol because of the greater strength of the data set. Alternatively, risk scores for LDL cholesterol could be adjusted to those for total cholesterol using the corresponding values shown in the Table.

According to the NCEP guidelines,[2,3] total cholesterol levels can be used in initial detection of high serum cholesterol; however, serum LDL-cholesterol values should be used in risk assessment and evaluation of response to therapy. For long-term monitoring of most patients on therapy, the serum total cholesterol value will suffice. For individual patients with a high total cholesterol level based on high serum HDL cholesterol, total cholesterol will overestimate risk. This misclassification of risk occurs more often in women than men because women tend to have high HDL concentrations. The NCEP[2,3] recommends estimation of serum LDL cholesterol in any patient whose total cholesterol is ≥240 mg/dL or 200 to 239 mg/dL in the presence of 2 or more CHD risk factors.

Framingham scores for total cholesterol (and LDL cholesterol) *underestimate* risk in patients with severely high cholesterol levels, eg, those with familial hypercholesterolemia,[154] or in some other genetic forms of hyperlipidemia.[2,3] The NCEP[2,3] provides guidelines for treatment of these patients. The NCEP further recommends that young adults with moderate hypercholesterolemia (LDL cholesterol 160 to 219 mg/dL) should *not* receive cholesterol-lowering drugs when they have no other risk factors. This recommendation is justified by the Framingham risk scores; projected 10-year risks in young adults with LDL-cholesterol levels in this range are low. Nonetheless, because of a high relative risk accompanying high-risk LDL-cholesterol levels, efforts to safely and inexpensively reduce cholesterol levels with nondrug therapy should be used to slow the development of coronary atherosclerosis in young adults. According to the NCEP,[2,3] most young adults with still higher LDL-cholesterol levels (≥220 mg/dL) generally deserve drug therapy to retard atherogenesis.

Middle-aged men (aged 45 to 65 years) with high serum cholesterol levels (>240 mg/dL; LDL-cholesterol levels >160 mg/dL) carry an increased risk for CHD. The NCEP[2,3] recommends that physicians counsel such patients on diet modification, weight control, and increased physical activity. An important question is when to initiate cholesterol-lowering drugs in middle-aged men. According to the NCEP guidelines, cholesterol-lowering drugs can be considered for middle-aged men with LDL-cholesterol levels >190 mg/dL or ≥160 mg/dL in the presence of ≥2 CHD risk factors. The recent West of Scotland Coronary Prevention Study (WOSCOPS)[132] confirms that cholesterol-lowering drugs will safely and effectively reduce CHD rates in middle-aged men at high risk. A critical question is whether Framingham risk scores provide incremental assistance in selection of patients for initiation of drug therapy beyond the cut points proposed in the NCEP guidelines.[3] At present it is not possible to define a precise increment of risk above the Framingham average risk that justifies starting a cholesterol-lowering drug. The average 10-year risk for older age groups looks relatively high, even higher than that of the placebo group of WOSCOPS[132]; however, it must be noted that Framingham scores use "softer" CHD end points, including new-onset angina pectoris, whereas the WOSCOPS trial included only "harder" CHD end points. The inclusion of hard CHD in Framingham scores helps redress the balance somewhat.

According to the NCEP,[2,3] if a middle-aged man has an LDL-cholesterol level ≥160 mg/dL and 2 other major CHD risk factors, the use of cholesterol-lowering drugs should be considered. Using the Framingham scores,[6] this combination of risk factors produces a threefold increase in risk for CHD compared with the patient at low risk. In other words, cholesterol-lowering drug therapy probably should be considered for a middle-aged man with a high-risk LDL-cholesterol level and 3 times the absolute baseline risk. Framingham data thus appear to be consistent with current NCEP guidelines. However, a word of caution must be added about using absolute Framingham risk scores as a trigger for starting cholesterol-lowering drug therapy. The decision-making process for cholesterol-lowering drugs must be viewed as "shooting at a moving target." Absolute risk scores may be dramatically altered by institution of other risk-reducing efforts. For example, the increment in risk accompanying cigarette smoking can be erased in 2 to 3 years by smoking cessation. In addition, blood pressure reduction in a hypertensive patient may significantly decrease risk for CHD. Finally, in the Physicians' Health Study,[155] it was reported that risk for acute coronary events can be markedly decreased by the use of low-dose aspirin; many middle-aged men ingest aspirin on a regular basis. Therefore, starting a cholesterol-

lowering drug should not become a therapeutic reflex when a patient crosses a certain risk threshold. A patient's absolute risk must be reassessed in light of other therapeutic strategies being used simultaneously. In addition, the benefits of maximum nondrug therapy (dietary change, weight reduction, increased physical activity) should be added to the risk equation before starting cholesterol-lowering drugs in middle-aged men with moderately elevated serum cholesterol levels.

Benefit from the use of cholesterol-lowering drugs for primary prevention in elderly men (>65 years) with high cholesterol levels remains to be demonstrated through clinical trials. Framingham risk scores warn that risk increases progressively with aging. The chart further notes that risk in the elderly is further increased by high cholesterol levels. The total number of older men in the United States with relatively high cholesterol levels is large and growing, and the potential for reducing CHD rates in older men with cholesterol-lowering drugs may therefore be considerable. However, the lack of specific clinical trials that document the degree of benefit from drug therapy leads some authorities to urge caution when resorting to cholesterol-reducing agents for primary prevention in elderly men. The same note of caution mentioned for use of cholesterol-lowering drugs in middle-aged men is needed for elderly men. Without question, use of drugs in older patients should be individualized. In contrast, for *secondary* prevention in older men, a more aggressive approach, in which drugs are used when needed to reach target LDL goals, can be recommended.

A substantial proportion of postmenopausal women have elevated cholesterol levels.[3] However, according to Framingham scores, their 10-year risk for CHD is considerably lower than that for men. The difference between men and women is particularly pronounced for hard CHD end points. In other words, the diagnosis of angina in women contributes a sizable fraction of all CHD end points in the Framingham cohort. The virtual lack of rise in risk for total CHD after age 55 in women is misleading, as shown by the progressive rise in risk for women with hard CHD. These findings are consistent with population studies that show most CHD morbidity and mortality in women occurs after age 70.[147] Regardless, the lower absolute risk in women compared with men up to age 75 alludes to the need for more caution when considering aggressive cholesterol-lowering therapy for primary prevention in postmenopausal women. Framingham data, however, do not speak against the use of cholesterol-lowering drugs in postmenopausal women with severe hypercholesterolemia or those with moderately high cholesterol levels combined with a high score from other risk factors.

Low HDL Cholesterol

The Framingham Heart Study has been a strong proponent of the concept that a low serum HDL-cholesterol level is a major risk factor for CHD.[51–57] Framingham reports advise that the inverse association between HDL-cholesterol levels and CHD risk at least equals the positive association between CHD risk and serum LDL-cholesterol levels. Data from Framingham were influential in the NCEP decision to classify a low HDL level as a major risk factor for CHD.[2,3] Despite a strong epidemiological association, the mechanisms underlying the HDL-CHD link remain poorly understood. Some researchers propose that HDL attenuates the atherogenicity of LDL; if so, a low HDL level may directly promote atherogenesis. Results of the PDAY study[125,126] as well as some animal research[156,157] are consistent with this concept. On the other hand, a low HDL level often signifies the presence of an excess of atherogenic lipoproteins (very low-density lipoprotein [VLDL] remnants and small LDL particles) that typically are not measured[158]; these too may independently raise risk in persons with a low HDL level. In addition, a low HDL concentration commonly coexists with an insulin-resistance state,[159] which may be another unmeasured risk factor. These multiple associations possibly explain why a low serum HDL-cholesterol concentration emerges as such a powerful risk factor[158]; not only may it directly promote atherogenesis, but it is a marker for other risk factors.

The inverse relationship between HDL level and CHD risk extends over a broad range of HDL levels. The NCEP[2,3] defines 3 categories of HDL cholesterol: low (<35 mg/dL), normal (35 to 60 mg/dL), and high (>60 mg/dL). The NCEP classifies low HDL cholesterol as a major risk factor; conversely, a high level is called a "negative" (protective) factor. Framingham scoring creates 5 categories of HDL cholesterol consistent with the finding of a continuous relationship between levels and risk. In accord with the NCEP,[2,3] negative scores are assigned to HDL-cholesterol levels ≥60 mg/dL. On the basis of the score, low HDL-cholesterol levels appear to impart a greater risk for CHD in women compared with men[6]; this appearance is misleading, however, because each point carries more absolute risk in men.

The potential uses of HDL measurements are threefold: risk assessment, adjusting intensity of LDL-cholesterol–lowering therapy, and direct target of therapy. Specific therapies to raise HDL concentrations are not highly effective or practical. Evidence from clinical trials that documents benefit from specific HDL-raising therapies is thus lacking. Certainly smoking cessation, weight control, and regular exercise should be encouraged because of their tendency to raise HDL levels and, importantly, because they have beneficial effects on other risk factors. Nicotinic acid is an effective HDL-raising agent,[160,161] but unfortunately it is not well tolerated by many patients. Thus, at present the principal usefulness of HDL-cholesterol measurement is for risk assessment and guidance on intensity of management of other risk factors, especially elevated serum LDL cholesterol.

Diabetes Mellitus

Patients with diabetes mellitus carry an increased risk for CHD. Framingham data suggest that hyperglycemia as such is an independent risk factor.[58–70] The mechanisms for this effect are not well understood. Whether improved control of hyperglycemia in diabetic patients reduces risk for CHD remains uncertain. Nonetheless, improved glycemic control apparently does reduce the microvascular complications of diabetes[162]; control of hyperglycemia is thus indicated regardless of its effects on macrovascular disease, ie, atherosclerotic disease. In addition to the independent risk factor hypergly-

cemia, patients with diabetes commonly have other risk factors (eg, hypertension, low serum HDL cholesterol, and hypertriglyceridemia); these additional risk factors accentuate the danger of CHD developing in many diabetic patients.[163] To make matters worse, once a patient with diabetes develops clinical CHD, cardiac complications occur with increased frequency[164]; diabetic patients with CHD experience more morbidity and mortality than do nondiabetic patients with CHD. Control of other risk factors to reduce the likelihood of initially developing CHD consequently becomes a critical need for diabetic patients. Recent clinical trials[131–133] document a significant reduction in recurrent coronary events accompanying cholesterol-lowering therapy in diabetic patients with established CHD. This result demonstrates the efficacy of control of other risk factors in patients with diabetes.

Role of Risk Factors in Women

Prediction scores illustrate the marked difference in CHD risk between men and women before age 70. Onset of CHD in women lags behind that in men by 10 to 15 years. Nonetheless, the data clearly document that the major risk factors have a substantial impact on absolute CHD risk in women. For the US population as a whole, as many women as men eventually die of CHD.[147] Therefore, risk factors in women cannot be ignored. Cigarette smoking should be strongly discouraged. Hypertension requires effective therapy. Maturity-onset diabetes mellitus should be delayed or prevented if possible by weight control and regular exercise. On the other hand, moderately elevated LDL-cholesterol levels in women need not be treated as aggressively in primary prevention as is necessary in men, partly because of overall lower risk and normally higher HDL-cholesterol levels in women.

Clustering of Risk Factors

The Framingham charts clearly show the additive nature of risk factors. There is growing recognition that many persons suffer from multiple risk factors. The tendency of risk factors to cluster in a single individual is being increasingly recognized.[165,166] Obesity and physical inactivity contribute importantly to the development of multiple risk factors in the American population; this clustering of multiple metabolic risk factors is called the *metabolic syndrome*.[93] The increased risk associated with this syndrome is reflected by the Framingham scores for HDL cholesterol, blood pressure, and, in some persons, diabetes mellitus. Risk will be further accentuated in smokers with several metabolic risk factors. There is an increasing need to identify persons with multiple risk factors and, because of their high risk, to initiate management directed at all risk factors.

Limitations of the Framingham Risk Scores

Participants in the Framingham Heart Study are not necessarily representative of the total US population. Various geographic and ethnic groups are underrepresented. The impact of specific risk factors may vary in different populations. Even so, many separate studies document that the major risk factors investigated in the Framingham cohort hold up as risk factors in other populations.[167–175] Although potential differences among various populations must be kept in mind when applying the Framingham scores, quantitative differences in risk predictions are likely to be small among most populations.

Another limitation of Framingham risk scoring is that it does not take into account all risk factors for CHD. Not included are triglycerides, small LDL particles, Lp(a), coagulation factors, and homocysteine. All of these risk factors may not be totally independent of the major risk factors, and the measurements of some are not readily available in clinical practice. Their quantitative impact on CHD risk is not as well defined as for the major risk factors; hence, assigning specific scores is difficult. Nonetheless, each of these factors probably makes some independent contribution to CHD risk, and in the future, risk assessment may be improved by incorporating them into predictive equations.

Conclusions

New Framingham risk scores constitute a step toward integrating Framingham data into national recommendations for blood pressure and cholesterol control. A new classification of risk factor intensity in these latest Framingham scores is largely in accord with classifications developed by the Joint National Committee and the NCEP. Framingham categories for blood pressure are similar to those used by the Joint National Committee.[4,5] For total and HDL cholesterol levels, Framingham charts subcategorize various cholesterol levels to a greater extent than the NCEP,[2,3] although a similar scheme of cut points is used. The Framingham scores particularly highlight the fact that aging progressively enhances risk. Moreover, the difference in CHD risk between men and women up to the age of 70 to 74 years is striking.

The Framingham scores offer both general and specific applications. They suggest priorities for instituting primary prevention strategies and point to factors deserving increased emphasis and those needing less attention. They provide useful estimates of both relative and absolute risk associated with the various risk factors. The authors of future revisions of guidelines and recommendations for control of blood pressure, cholesterol, diabetes, and smoking would do well to pay close attention to the concepts contained in these updated Framingham risk scores.

The revised charts should prove useful to healthcare professionals managing risk factor reduction in individual patients. Risk scores can both motivate and reassure. They also may assist in selection of specific therapies. Of critical importance is the fact that risk factors compound one another. Treating hypertension or lowering serum cholesterol levels in a diabetic patient reduces risk for future CHD just as effectively as controlling hyperglycemia. The Framingham scores admonish healthcare professionals to look at the *whole* patient and to recognize the cumulative nature of risk factors. A multifactorial approach to risk reduction offers the best opportunity for (1) saving patients at high risk and (2) preventing development of high-risk status in the first place.

Of special note, the Framingham data reveal the potential for primary prevention of CHD. Recent dramatic results from secondary prevention trials of cholesterol-lowering therapy highlight the urgency of risk factor management in patients

with established CHD. Nonetheless, if the burden of CHD in American society is to be substantially reduced, primary prevention must be improved. Framingham research points the direction for these efforts. Risk factor modification in the general public and persons at high risk offers the best opportunity for effectively reducing the prevalence of CHD in the United States.

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