Assessing risk for coronary heart disease: Beyond Framingham

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Abstract: The Framingham Heart Study, initiated over 50 years ago, introduced the concept of risk factors for coro- nary heart disease (CHD) and has served as the stan- dard for risk assessment over the years.1-4 Major risk factors identified by the Framingham Heart Study, in- cluding age, sex, total cholesterol, high-density li- poprotein (HDL) cholesterol, smoking, and systolic blood pressure, have been incorporated into a scoring system that identifies subjects at high (>20%), interme- diate (10%–20%), and low (<10%) risk for developing CHD over the next 10 years.5 These major or tradi- tional risk factors account for approximately 50% of the variability in risk in high-risk populations and ex- plain >80% of the excess population risk for CHD.6-8 Recent clinical trials in high-risk subjects demonstrate dramatic reductions in risk (approximately 33%–50% in 5 y) with risk reduction therapies.9 This provides strong support for the concept that CHD and its se- quela can be prevented by aggressive medical therapy and therapeutic lifestyle changes. Recent American Heart Association (AHA) guidelines (2002)4 for primary prevention of cardiovascular disease and stroke recom- mend that risk-factor screening in adults should begin at age 20 and should be repeated at least every 5 years in the absence of risk factors and every 2 years if risk factors are present. This panel recommends that global risk should be estimated in all adults >40 years of age. In this issue of the Journal, Cohn et al10 have pro- posed a method for risk assessment that focuses on measurements of early vascular dysfunction and dis- ease markers rather than standard risk factors. Studies are ongoing in their outpatient cardiovascular disease prevention clinic to validate the model by relating risk assessments to disease outcomes over time.

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The Framingham Heart Study, initiated over 50 years ago, introduced the concept of risk factors for coronary heart disease (CHD) and has served as the standard for risk assessment over the years.[1-4] Major risk factors identified by the Framingham Heart Study, including age, sex, total cholesterol, high-density lipoprotein (HDL) cholesterol, smoking, and systolic blood pressure, have been incorporated into a scoring system that identifies subjects at high (>20%), intermediate (10%–20%), and low (<10%) risk for developing CHD over the next 10 years.[5] These major or traditional risk factors account for approximately 50% of the variability in risk in high-risk populations and explain >80% of the excess population risk for CHD.[6-8] Recent clinical trials in high-risk subjects demonstrate dramatic reductions in risk (approximately 33%–50% in 5 y) with risk reduction therapies.[9] This provides strong support for the concept that CHD and its sequela can be prevented by aggressive medical therapy and therapeutic lifestyle changes. Recent American Heart Association (AHA) guidelines (2002)[4] for primary prevention of cardiovascular disease and stroke recommend that risk-factor screening in adults should begin at age 20 and should be repeated at least every 5 years in the absence of risk factors and every 2 years if risk factors are present. This panel recommends that global risk should be estimated in all adults >40 years of age. In this issue of the Journal, Cohn et al[10] have proposed a method for risk assessment that focuses on measurements of early vascular dysfunction and disease markers rather than standard risk factors. Studies are ongoing in their outpatient cardiovascular disease prevention clinic to validate the model by relating risk assessments to disease outcomes over time.

A guiding principle of primary prevention therapy is that the intensity of risk reduction therapies should be tailored to the level of individual risk.[2,3,6,9] Although the AHA/ACC Scientific Statement on assessment of cardiovascular risk,[9] the AHA sponsored Prevention Conference V,[6] and the National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III)[3] recommend risk factor assessment and Framingham score as first steps to guide therapeutic strategies, each panel recognized that factors other than the traditional Framingham risk factors contribute significantly to global risk for CHD. Table I lists the traditional Framingham risk factors and additional potential categories that may contribute to risk. The list is a modification of categories described by the AHA/ACC Scientific Statement[9] and Prevention Conference V.[6] The following discussion provides (1) an overview of these non-Framingham risk categories, (2) a potential algorithm for incorporating parameters from these risk categories into risk assessment beyond that provided by a Framingham score, and (3) a potential approach to estimating global absolute risk based on analyses that combines Framingham risk factor and risk variables from multiple data sets.

Coronary disease equivalents

Subjects with diagnosed CHD have a >20% 10-year risk for developing future cardiac events including acute myocardial infarction and cardiac death and thus are at high risk. Noncardiac conditions with similar risk are referred to as coronary disease equivalents. The Prevention Conference V[6] and ATP III[3] recognized that patients with diabetes mellitus, symptomatic carotid artery disease, and peripheral vascular disease have a >20% 10-year risk for developing cardiac events, placing them in the high-risk population and requiring aggressive risk-factor reduction through med ical therapies and therapeutic lifestyle changes.

Predisposing risk factors

Predisposing risk factors for coronary heart disease, defined as those that worsen independent risk fac tors,[6,9] include (1) family history of premature CHD, occurring in a first degree male relative <55 years of age, or first degree female relative, <65 years of age, (2) metabolic or insulin resistance syndrome (defined

as >3 of the following: abdominal obesity [male >102 cm waist, female > 88 cm], fasting glucose >110 mg/dL, systolic pressure >130 mm Hg, diastolic >85 mm Hg, triglycerides >150 mg/dL, HDL cholesterol <40 mg/dL in males and <50 mg/dL in females), (3) obesity (body mass index >30 kg/m^2) and, (4) physical inactivity. Obesity and physical inactivity are considered major risk factors by the AHA.[11,12] ATP III[3] recognized metabolic syndrome as a secondary target for risk reduction therapy after the primary target, low-density lipoprotein (LDL) cholesterol. Significant depression also has been recognized to be associated with increased coronary heart disease events.[13]

Conditional or emerging risk factors

Conditional risk factors are defined as those associated with increased risk for CHD but whose causative, independent, and quantitative contribution to CHD need additional documentation.[6,9] These include the inflammatory marker, high sensitivity C-reactive protein (hs-CRP),[14,15] homocysteine, lipoprotein(a), small dense LDL particles, which appear to be atherogenic, and prothrombotic factors (ie, plasminogen activator inhibitor [PAI-1] and fibrinogen). These parameters have been identified in certain studies to provide a graded independent risk for developing coronary heart disease.[16,20] With time, one or more may be accepted not only as a major risk factor but also a target for therapy. For example, a recent panel convened by the AHA and Center for Disease Control and Prevention[21] reviewed the data relating hs-CRP to risk for CHD, sudden death, and preclinical vascular disease. An hs-CRP level of 1 to 3.0 mg/L was associated with an average risk, whereas a level >3.0 mg/L was associated with a >2 relative risk or high risk. They recommended limited use of hs-CRP as an independent marker for further risk stratification in people at intermediate risk. ATP III noted that although the emerging risk factors should not be used to modify LDL cholesterol goals, they may be used to guide intensity of risk reduction therapy.

Assessment of atherosclerotic plaque burden: preclinical vascular disease

Current thinking about the pathogenesis of coronary heart disease[15,22] holds that atherosclerosis begins in early adult life when LDL particles from the circulating blood become attached to the arterial endothelial layer and migrate to the intima, where they become trapped in macrophages to form foam cells. As the foam cells accumulate, they form fatty streaks on the vessel lining. The fatty streaks gradually enlarge to form raised fibrous plaques. The fibrous plaques contain a variety of inflammatory cells and subsequently develop a fibrous cap and a central lipid core. Calcium becomes deposited in the core of the plaque. Influenced by multiple risk factors, the process of plaque development and growth progresses at a variable rate over years. When certain plaques narrow the artery approximately >75%, pain symptoms may occur during physical activities, and exercise stress test may become positive. It is thus apparent that symptoms first occur at a late stage when the disease is far advanced, often involving not only multiple coronary arteries but also multiple organ systems. Cardiac events including unstable angina, acute myocardial infarction, and sudden death may occur earlier without warning due to rupture of the fibrous cap resulting in acute thrombosis and interruption of blood flow. Studies have demonstrated that plaque rupture, in many cases, occurs from plaques that are not severe enough to limit blood flow or cause symptoms or abnormal functional test.[23] The atherosclerotic process is thus present and ac

Table I. Risk factor categories for coronary heart disease

Framingham risk factors
Age
Total cholesterol (LDL cholesterol)
Smoking
HDL cholesterol
Systolic blood pressure
LVH
Coronary disease equivalents
Diabetes mellitus
Symptomatic carotid disease
Peripheral vascular disease
Predisposing risk factor
Family history of premature coronary heart disease
Metabolic syndrome—insulin resistance
Obesity
Physical inactivity
Psychosocial factors
Ethnic characteristics
Conditional risk factors
Inflammatory markers (ie, elevated hs-CRP)
Increased homocysteine
Increased lipoprotein (a) Increased
small dense LDL particle
Increased prothrombotic factors, ie, fibrinogen PAI-1
Noninvasive assessment of atherosclerotic plaque burden and/or
preclinical vascular disease
Ankle/brachial blood pressure index (ABI)
Coronary calcium score—EBCT, helical CT
Carotid intima media thickening (CIMT), B-mode Echo
Endothelial function-brachial artery flow mediated dilation (BAFMD)
Plaque characterization-MRI, CT
Arterial elasticity (compliance)
Micro albuminuria
Assessment of silent ischemia
Exercise ECG testing
Exercise and pharmacologic stress echo
Exercise and pharmacologic perfusion imaging

tively progressing many years before symptoms, acute cardiac events, and exercise or stress-inducible ischemia. It is also apparent that measurements of the presence and activity of the preclinical atherosclerotic process, representing the vascular expression of multiple interacting risk factors, is essential to not only enhance risk assessment,[24] but may also provide new targets for risk reduction therapy. Endothelial dysfunction, a potential measure of disease activity, is present very early in the atherosclerotic process,[25-28] even in arteries that do not demonstrate significant plaque development. A variety of new technologies are now available to assess preclinical vascular disease, atherosclerotic plaque burdens, and endothelial function before the onset of symptoms.[24] The following provides an overview of these technologies.

Ankle/brachial blood pressure index (ABI)

The ABI measurement requires only a blood pressure cuff and hand held Doppler, and thus is a very simple and inexpensive office-based diagnostic test for peripheral arterial disease of the lower extremities. An ABI :S0.90 in 1 leg confirms the diagnosis of preclinical vascular disease and has an approximately 90% sensitivity and 95% specificity for >50% stenosis in the lower extremities.[29,30]

Coronary calcification score

The amount of calcium localized in the atherosclerotic plaques within the coronary arteries can be quantitated with electronic beam computed tomography (EBCT) or helical computed tomography.[31-33] Although the calcium score provides an index of plaque burden,[33] it does not define severity of stenosis or identify unstable plaques. Certain studies support the independent prognostic value of the coronary calcification score (CCS).[34-36] Other studies have reported that the CCS does not provide risk assessment beyond that provided by Framingham risk factor analysis.[37] Because CCS increases progressively with age and is influenced by sex, the CCS should be interpreted as a function of age and sex. A CCS in the 75th percentile for age or greater indicates excess plaque formation and increased risk for future events. Grundy et al[38] has suggested that the CCS as a measure of plaque burden may be considered as a substitute for age as a risk factor in the Framingham risk equation. Because coronary calcifications tend to lag behind plaque formation, the presence of a low CCS in subjects with significant risk factors should not be used to exclude therapy, especially at an early age. Although CCS is currently being used throughout the United States to assess asymptomatic atherosclerosis and risk, Prevention Conference V 2000,[24] convened in 1998, felt that its greatest potential was in the detection of advanced atherosclerosis in patients who are at intermediate risk. A low score may be used to place the patient in a lower risk category. A higher score (ie, greater than the 75th percentile for age) may place the patient in a higher risk group.

Carotid intima-medial thickening [24]

Prevention Conference V, 2000, summarized the role of B-mode ultrasound measurements of carotid intima-media thickening (IMT) in assessing CHD risk. The panel noted that carotid IMT was related to cardiovascular risk factors and was an independent predictor of atherosclerosis and CHD events and stroke.[39-41] In the Cardiovascular Health Study[41] that included patients >65 years of age without clinical CHD, the relative risk for MI or stroke increased linearly with IMT, with a relative risk in the highest versus lowest quintile of 3.87. The association was significant after adjustment for traditional risk factors. The panel concluded that in asymptomatic subjects >45 years of age, carotid IMT measurements in an experienced laboratory provide incremental information to traditional risk factor assessment. Serial measurements of carotid IMT may provide a measure of disease progression and thus an additional way to monitor.

Endothelial function: Brachial artery flow mediated dilation

Through its unique location and functions, the endothelium plays a key role in the development of atherosclerosis and its thrombotic consequences. A healthy endothelium produces a variety of anti-atherogenic substances, including nitric oxide, which promotes vasodilation in addition to its multiple anti-atherogenic properties, which include inhibition of monocyte, leukocyte, and platelet adhesion to the vessel wall, inhibition of platelet aggregation, antioxidant properties and inhibition of smooth muscle proliferation.[42] Studies have demonstrated that endothelial mediated vasodilation is reduced early in the atherosclerotic process, even before angiographic morphologic changes.[25,26] It is also reduced in animal models and patients with hypercholesterolemia before the appearance of atherosclerosis,[27,28] and progressively worsens as the severity of atherosclerosis increases.[43,44] An increase in blood flow increases shear stress and stimulates release of nitric oxide by a healthy endothelium resulting in vessel dilation. This physiologic observation and the close association between vasoreactivity in the brachial and coronary arteries[45] has led to widespread use of brachial artery vasoreactivity to evaluate endothelial function. This technique involves a 5minute forearm cuff occlusion and subsequent release to produce a reactive hyperemic increase in blood flow, and high-resolution ultrasound to quantitate changes in brachial artery diameter (BAFMD). Most of the Framingham risk fac

tors and many of the emerging risk factors are associated with endothelial dysfunction.[4652] Risk factor modification may improve endothelial function and BAFMD.[52-55] More importantly, studies have shown that BAFMD may provide independent predictive data regarding future cardiovascular events.[57,58] Endothelial dysfunction demonstrated by BAFMD, thus, may not only provide additional information regarding risk but also may provide a measure of atherogenic activity, a potential new therapeutic target. The panel for Prevention Conference V[24] concluded that although assessments of endothelial function by BAFMD is a promising technique that may provide independent measures of CHD risk, additional prospective research and greater standardization of the measurement technique is needed before this modality can be included in routine clinical assessment of risk.

Plaque characterization (MRI or CT imaging)

Prevention Conference V[24] briefly reviewed the utility of MRI in evaluating plaque size and composition in the carotid arteries and aorta. Although it was noted that this technology had the potential for identifying unstable plaques, predicting future events, and evaluating responses to therapy, the panel felt that additional studies were needed to further clarify the potential of the new technology.

Arterial elasticity

Oliver and Webb[59] recently reviewed methods for noninvasive assessment of arterial stiffness and their relationship to risk for atherosclerotic events. Measurements of arterial stiffness were related not only to age but also to cardiovascular risk factors and to endothelial function. Although the prognostic value of certain measurements, especially pulse wave velocity, seemed promising, these authors noted that these studies have generally been performed in small groups and with a limited number of at-risk subjects. As described in the current issue of the Journal, Cohn et al[10] have measured arterial elasticity by pulse counter analysis in a group of asymptomatic subjects as part of a screen for detection of early cardiovascular disease (preclinical diseases). Studies by this group have demonstrated that small and large arterial elasticity decreases with age, that small artery elasticity is significantly decreased in patients with cardiovascular disease, and that small arterial elasticity correlates with risk factors for coronary artery disease.[60] Cohn et al[10] hypothesized that a risk screen based on detection of early cardiovascular disease as measured by arterial elasticity and other disease markers rather than on standard risk factors will provide new information regarding risk and new targets for therapy. The proposed risk screen is to be validated by collecting data prospectively in a large group of subjects and relating the measurements to subsequent disease outcomes.

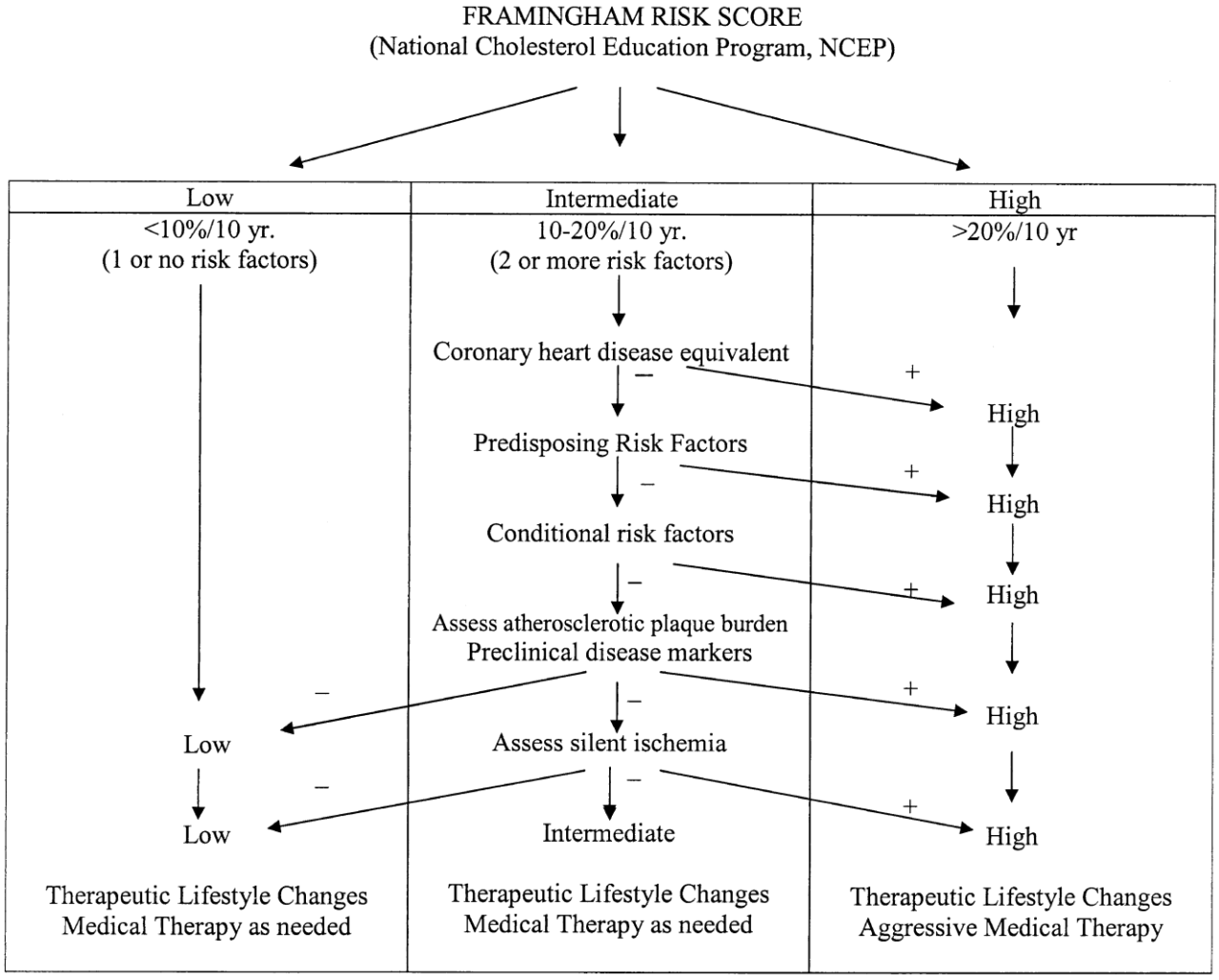
Microalbuminuria

A recent publication from the HOPE study[61] evaluated the relationship between albuminuria and cardiovascular events in individuals with and without diabetes. Microalbuminuria (defined as an albumin/creatinine ratio [ACR] of >2 mg/umoL) occurred in 32.6% of patients with diabetes and 14.8% of patients without. It was observed that any degree of albuminuria was a risk factor for cardiovascular events in individuals with and without diabetes. This risk increased progressively with increasing microalbuminuria. In fact, compared to the lowest quartile of microalbuminuria, the relative risk for cardiovascular events in the fourth quartile was 1.97. Other studies have also documented increased cardiovascular events associated with microalbuminuria.[62]

Assessment of silent ischemia

A panel of Prevention Conference V[63] reviewed the role of exercise electrocardiogram (ECG) testing, stress echo, exercise and pharmacological myocardial perfusion imaging, and positive emission tomography (PET) in assessing silent ischemia. It was noted that in the Multiple Risk Factor Interactive Trial (MRFIT),[64] performed in middle-aged men, and in the Lipid Research Clinic Coronary Primary Prevention Trial,[65] performed in asymptomatic men with hypercholesterolemia, there was a 4-fold increase in 7-year mortality and a 5.7-fold increase in 7.4-year mortality, respectively, in subjects with abnormal exercise ECGs. The panel recommended that exercise ECGs not be routinely used in unselected asymptomatic populations before office screening. They concluded, however, that exercise ECG testing may provide useful risk information to guide aggressive therapies in asymptomatic men >40 years of age with one or more risk factors (intermediate risk subjects). It was also felt that there was insufficient data in women and in the elderly age group (age >75 years) to make recommendations regarding exercise ECG testing in these populations. Although a stress echo and myocardial perfusion imaging are commonly used (with PET less commonly used) to evaluate chest pain symptoms or ischemia, the panel felt that these modalities did not significantly add to exercise ECG testing in the middleaged, asymptomatic male population. It was felt these technologies may, however, provide additional information in women and in the elderly. The panel acknowledged the lack of general availability and high expense of the PET technology.

Figure 1



Assessing risk for coronary heart disease potential algorithm.

Potential algorithm for incorporating predisposing and conditional risk factors and assessments of preclinical vascular disease and atherosclerotic plaque burden into a risk assessment model

It is certainly not appropriate or cost effective to utilize all of the potential factors listed in Table I for risk stratification in each patient. Figure 1 provides a potential algorithm to be considered for global risk assessment. This is modified from recommendations by AHA/ACC Scientific Statement[9] and Prevention Conference V.[6] As outlined in the algorithm, the initial step in risk assessment is to screen for traditional Framingham risk factors and to calculate a 10-year Framingham risk score. A 10-year risk of $<10\%$ is classified as low risk, 10% to 20% intermediate risk, and $>20\%$ as high risk.

Patients at low risk may require no further risk assessment, with the primary treatment being therapeutic lifestyle changes and medical therapies for selective risk factors that exceed guidelines (LDL, HTN). Patients at high risk require aggressive medical and therapeutic lifestyle changes without requiring additional risk stratification. Additional assessment may be considered in the high-risk patient (ie, measurement of homocysteine and/or small, dense LDL particles to iden-

tify an additional therapeutic target). Patients who are at an intermediate risk are candidates for further risk stratification as outlined in the algorithm.

The AHA/ACC Scientific Statement on assessment of cardiovascular risk[9] emphasized several factors to be considered in utilizing the Framingham score. The panel noted that although Framingham scoring does not directly measure long-term risk (>10 years), long-term risk could be approximated by summing risk score over successive age categories so that a 20-year risk may be twice the 10-year risk. Because the objective or primary prevention is to reduce long-term as well as short-term risk, a patient in the 50 to 55 years age range who has a 15% 10-year risk may have a >30% risk for developing CHD before age 75 and thus has a high long-term risk requiring more aggressive therapy. The panel emphasized that all major risk factors should be treated regardless of short-term risk because they may cause premature CHD over a period of many years. The panel emphasized that modification of lifestyle habits was the centerpiece of long-term risk reduction therapy, with the use of medical therapies as needed for hypertension and lipid disorders. As previously discussed, patients with diabetes mellitus, symptomatic carotid artery disease, or peripheral vascular disease have CHD-equivalent risk and thus should be placed in the high-risk category as outlined in the algorithm. They do not require additional risk stratification to initiate aggressive medical therapy and therapeutic lifestyle changes. In subjects who continue in intermediate risk, the presence of a strong family history of premature CHD, criteria for metabolic syndrome or insulin resistance, sedentary lifestyle or significant depression support moving the patient to the high-risk group. In subjects who then remain in the intermediate group, one or more conditional or emerging risk factors may be evaluated for further risk stratification. As noted previously, each of these emerging risk factors has been identified in certain studies to provide independent relative risk for developing symptomatic coronary heart disease. We suggest that a patient at intermediate risk may be moved to the high-risk category when the relative risk of a given emerging risk factor exceeds 2. As noted previously,[20] an hs-CRP >3.0 mg/L is associated with a relative risk >2 and thus may be sufficient to increase the patient from intermediate to high risk. On the other hand, it may be reasonable to consider a cumulative relative risk provided by multiple risk factors that are moderately increased (ie, hs-CRP, homocysteine, lipoprotein (a), and fibrinogen to achieve a high-risk status).

In the absence of predisposing or conditional risk factors, the subject at intermediate risk may be further risk stratified by measuring atherosclerotic plaque burden or other markers of preclinical disease. The most frequently used analyses at this time include coronary calcification score by EBCT or helical CT and measurement of the carotid IMT by B-mode echocardiography. As summarized previously, subjects who have coronary calcification scores placing them in the 75th percentile or above for age may be considered patients who have accelerated plaque formation and may be considered at higher risk for future events. A coronary calcium scan of >400 places patients at any age above the 75th percentile, indicating extensive plaque burden and the need for further functional testing for ischemia. Carotid IMT measures in the higher quartiles have been demonstrated to increase risk and may be used for further risk stratification.[41] At the present time it is unclear whether certain noninvasive assessments of preclinical disease should be moved higher in the assessment algorithm. For example, a measurement of ABI should be a part of the baseline office physical exam in patients at intermediate or high risk. The presence of an ABI <0.90 confirms the diagnosis of peripheral vascular disease, a coronary disease equivalent.[29,30] As suggested in the algorithm, the absence of CHD equivalents, predisposing and conditional risk factor and preclinical disease markers, with a low plaque burden may justify movement of a subject from intermediate to low risk. Although exercise studies and functional tests for silent ischemia may provide significant predictive information in the intermediate patient,[63,65] it has been placed last in the algorithm since positive tests are late manifestations of CHD occurring with hemodynamically significant coronary stenosis. A low coronary calcium score may preclude the need for further testing for silent ischemia.

Development of a comprehensive global risk assessment model

A goal at this time is to develop a comprehensive and cost effective risk stratification model that incorporates Framingham risk factors with predisposing and emerging risk factors and noninvasive assessment of preclinical atherosclerosis. As noted, many of the non-Framingham risk factors provide relative risk information independent of the Framingham risk score. The Framingham risk score was derived from analysis of a single data set, whereas the enclosed list of non-Framingham risk factors was obtained from multiple data sets (Table I). The challenge at this time is to develop global models that combine multiple risk factor variables from multiple data sets. This model may then be used not only to define risk beyond that provided by the Framingham scoring system, but may also characterize risk that is modifiable by medical and lifestyle therapies and allow the efficacy of these therapies on risk and clinical outcomes to be determined. Validation of global risk stratification models requires the collection of a large data set and documentation of disease

outcomes over time. Additionally, these models will need to be validated and refined as sufficient outcomes accumulate and cost effectiveness is considered.

Hu and Root[66,67] have attempted to address this issue using an analysis that combines information from multiple data sources to create multivariable risk models. This new approach involves building multivariable predictive models one variable at a time and adjusting for the colinearity and concordance between variables from different databases. A multivariable risk model has been developed by this group for CHD starting with the Framingham risk model, and then adding in a stepwise fashion a limited number of well-documented predisposing and conditional risk factors (Table I). These include family history, hs-CRP, lipoprotein (a), physical activity, homocysteine, fibrinogen, and others.[66,67] Univariate relative risks are determined from a comprehensive review of prior epidemiologic studies for each of these new factors. Colinearity between the factors is estimated and adjusted for by using a large cross-sectional database of Americans (the NHANES III database). This model has the flexibility to be updated as new reports are published and variables can be added from the other risk factor categories, including coronary disease equivalents, emerging risk factors, and noninvasive assessment of atherosclerotic plaque burden, as appropriate.

This technique is a first attempt to meet the need for an evidence-based, flexible, statistical method for risk assessment that can be used in the clinical environment. Validation of this method has been difficult, given the constantly evolving list of potential biomarkers and functional tests. To date, these investigators have used 2 initial approaches to validation. The mechanics of the method have been evaluated using a single data set for creating and testing the model. A comparison of this new model with an empirical data driven method demonstrated a high correlation, R^2, of approximately 99%. The more rigorous challenge for any model is to create it using one data set and validate it in another. This has been done in a limited scenario by adding these relatively weak variables available from NHANESIII to the Framingham risk model and testing mortality outcomes in NHANES I. With these limited additions, the area under the ROC curve increased by a marginally statistical amount. More complete validations of this second type are ongoing. This kind of model also provides the flexibility for tracking the response to therapy (ie, risk reduction). For example, a therapeutic target for a specific modifiable risk factor (eg, LDL <130 mg/dL) can be entered into the risk equation and the alterable risk calculated and subsequently monitored. A patient may have a 23% risk of heart disease in the next 10 years, but by lowering total cholesterol to <180 mg/dL, blood pressure to <120/80 mm Hg, and homocysteine to <7 μmol/L, the patient's risk could be lowered to 5% risk in 10 years.

The information gathered in Table I and used in the proposed algorithm described in Figure 1 attempts to answer essentially 2 questions: (1) what is the patient's risk of CHD and (2) what are the therapeutic targets? There is a pressing need for a uniform and integrated risk stratification framework to guide the intensity and focus of risk reduction therapies in an evolving assessment process.

The algorithm that we have proposed, based on recommendations from the AHA/ACC Scientific Statement,[9] the AHA sponsored Prevention Conference V,[6] the analyses by Hu and Root,[66,67] and the risk models proposed by Cohn et al,[10] will attempt to address this need. These methods for risk assessment and stratification will need further validation by acquisition of a large data set, cost-effectiveness considerations, and relating new risk models to disease outcomes over time.

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