A Practical Approach to Risk Assessment to Prevent Coronary Artery Disease and Its Complications

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The recent focus on emerging cardiovascular risk factors, such as C-reactive protein, homocysteine, and small, dense low-density lipoprotein (LDL), may give the false impression that the current approach to the assessment of cardiovascular disease risk fails to identify a large section of the high-risk population. On the contrary, the new guidelines of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) propose classifying an enormous number of individuals, including people with any form of atherosclerotic disease, diabetes, and a combination of major risk factors, into the category of high risk (>20% likelihood of a major coronary event or stroke in 10 years). Considering the widespread prevalence of the metabolic syndrome—a high-risk condition characterized by mild hypertension, mild dyslipidemia, hyperglycemia, and visceral obesity—we may be faced with the challenge of implementing aggressive risk reduction therapies in as much as 30% of the adult US population. From the point of view of risk assessment, a practical approach is to follow the NCEP guidelines (ie, place patients with diabetes and those with atherosclerotic complications in the highest risk category), apply the Framingham calculation to determine risk in people with common risk factors, and initiate early intervention in people who have familial hypercholesterolemia (LDL cholesterol >200 mg/dL) or a family history of early cardiovascular disease. The emerging risk factors may be useful for further stratifying risk in individuals with intermediate risk and the presence of risk factors not included in the Framingham calculation.
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Our current approach to the prevention of coronary artery disease (CAD) is predicated on identification of risk factors and the quantitative assessment of short-term cardiovascular risk. The major independent risk factors originally identified in the Framingham Heart Study include (1) elevated serum total cholesterol and low-density lipoprotein (LDL) cholesterol, (2) low levels of high-density lipoprotein (HDL) cholesterol, (3) elevated blood pressure, (4) cigarette smoking, and (5) advancing age.[1,2] The so-called major risk factors are distinguished in Table 1 as modifiable and not modifiable. These factors are defined with remarkable agreement in guidelines and classifications from different medical and governmental agencies in Europe[3,4] and the United States.[5]

Data from the Multiple Risk Factor Intervention Trial[6] (MRFIT) and the Nurses' Health Study[7] indicate that the major risk factors account for >80% of the excess risk for premature CAD. Of note, obesity, physical inactivity, and a high-fat diet are now considered major risk factors in their own right.[5] These factors are usually not used in formulas of risk assessment, however, because their widespread distribution would greatly increase the number of individuals qualifying for pharmacologic treatment.

Several emerging risk factors for CAD have been identified and classified as lipid and nonlipid risk factors (Table 2). The distinction between major and emerging risk factors serves to differentiate between parameters with different levels of experimental, epidemiologic, and clinical validation.

The major modifiable risk factors for CAD are important both for assessment of risk and as targets for intervention. Numerous clinical trials have demonstrated that risk reduction strategies, including cessation of cigarette smoking,[8] lowering high blood pressure in hypertensive patients,[9,10] and low-dose aspirin therapy,[11] can significantly decrease the incidence of cardiovascular events and total mortality. Perhaps most impressive are data from large clinical trials showing that lowering LDL cholesterol with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is effective for both primary and secondary prevention of CAD.[12]

A variety of medical therapies are available for use in the prevention of CAD and of its clinical expression. Preventive efforts should target each major risk factor. Guidelines for the management of individual risk factors are provided by the National High Blood Pressure Education Program,[13] the American Diabetes Association,[14] and by the third Adult Treatment Panel (ATP III) report of the National Cholesterol Education Program (NCEP).[5]

This article focuses on the approach advocated by the NCEP, in which the major target for therapy is LDL cholesterol lowering; risk assessment is used to guide treatment decisions.

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TABLE 1 Major Cardiovascular Risk Factors

Modifiable	Nonmodifiable	Life Habit
Elevated LDL-C	Age	Obesity
Low HDL-C	Male sex	Physical inactivity
Hypertension	Family history	Atherogenic diet
Diabetes		
Cigarette smoking		

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

TABLE 2 Emerging Cardiovascular Risk Factors

Lipid	Nonlipid
Triglycerides	Homocysteine
Lipoprotein remnants	Thrombogenic/hemostatic factors
Small LDL particles	Inflammatory markers
Lipoprotein(a)	Impaired fasting glucose
Metabolic syndrome	Metabolic syndrome

LDL = low-density lipoprotein.

LIFE-HABIT RISK FACTORS

The ATP III defines 3 life-habit risk factors as major and modifiable: (1) obesity, (2) physical inactivity, and (3) a high-fat diet. Obesity is defined as a body mass index >30; overweight is a body mass index between 25 and 29.9.[15] People who are overweight or obese have an increased risk of CAD, stroke, and all-cause mortality. The Framingham Heart Study demonstrated that obesity is strongly predictive of CAD, and that risk for cardiovascular disease is particularly increased when abdominal obesity (waist circumference >102 cm, or 40 inches in men; 88 cm, or 35 inches, in women) is present.[15] Many observational studies have shown that physical activity can reduce the risk for CAD and that lack of exercise is a risk factor for CAD. Consumption of an atherogenic diet with high intake of saturated fatty acids and cholesterol clearly causes an increase in serum LDL cholesterol levels. The ATP III considers these life-habit risk factors as direct targets for clinical intervention through therapeutic lifestyle changes, although they are not used to set lower LDL cholesterol goals.

EMERGING LIPID RISK FACTORS

Triglycerides, remnant lipoproteins, and small, dense LDL: Although many prospective epidemiologic studies show a positive relation between serum triglyceride levels and the incidence of CAD, multivariate analyses have often failed to identify serum triglycerides as an independent risk factor.[16] Recent meta-analyses have found that increased levels of triglycerides are, in fact, an independent risk factor for CAD.[17,18] Elevated serum triglyceride levels are associated with other lipid risk factors, including remnant lipoproteins, small, dense LDL, and low HDL cholesterol levels. Triglycerides are also associated with such nonlipid risk factors as obesity, hypertension, diabetes, cigarette smoking, insulin resistance, and the prothrombotic state.

The atherogenicity of triglycerides is related to the lipoprotein particles with which they associate. There is strong evidence that remnants of very-low-density lipoprotein and chylomicrons are atherogenic. Small, dense LDL particles are formed in large part in response to elevations in triglycerides and have been linked to an increased risk for CAD in several studies,[19–21] but the extent to which they predict CAD independently is still controversial.[22] The ATP III does not recommend measurement of small LDL particles in routine practice, but it gives increased weight to elevated serum triglycerides levels as a marker for atherogenic remnant lipoproteins and as an element of the metabolic syndrome. Non–HDL cholesterol (total cholesterol − HDL cholesterol) is recommended as a secondary target of therapy in persons with high triglyceride levels (≥200 mg/dL), following the assumption that all cholesterol in plasma, except for HDL cholesterol, provokes atherosclerosis.

Beyond the consideration of triglycerides as a risk factor for CAD is the therapeutic dilemma raised in cases of combined hyperlipidemia, where the adjustment of the primary metabolic abnormality would require an intervention on triglycerides, despite the guidelines' focus on LDL cholesterol reduction. Inherent in the ATP III is that the achievement of LDL cholesterol goals in individuals with combined hyperlipidemia often requires combination therapy. Clinical trials are needed to demonstrate that the increased risk of side effects incurred with the use of combination therapy is justified by improved clinical outcomes.

Lipoprotein(a): Elevated plasma levels of lipoprotein(a) have been found to be strongly associated with an increased risk of CAD, especially in the presence of elevated LDL cholesterol levels.[23] A lipoprotein(a)

of 30 mg/dL is commonly accepted as a threshold for coronary disease risk.

Lipoprotein(a) levels are higher in African Americans, but a greater risk for CAD associated with elevated lipoprotein(a) has not been documented in this group.[24] Measuring serum lipoprotein(a) levels can be useful in individuals who have a strong family history of premature atherosclerosis or individuals with inherited causes of hypercholesterolemia, such as familial hypercholesterolemia.[25]

EMERGING NONLIPID RISK FACTORS

Homocysteine: Homocysteine, a sulfur-containing amino acid, is an intermediate in the metabolism of methionine and cysteine. Homocystinuria is a rare genetic disorder associated with 10-fold elevation of plasma homocysteine levels, premature atherosclerosis, and recurrent thrombosis.

Several prospective and case-control studies have shown that elevations of serum homocysteine are positively correlated with risk for CAD.[26–28] In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),[29] a primary prevention trial of lovastatin in the prevention of acute coronary syndromes, elevated homocysteine predicted future coronary events, but it did not identify any subgroups that would respond to statin therapy.

Treatment with folic acid and vitamins B_6 and B_{12} lowers homocysteine levels. Clinical trials to examine whether lowering homocysteine levels prevents CAD are in progress. Given the uncertainty about the relation between homocysteine and CAD, routine homocysteine measurement is not recommended. Measurement of homocysteine may be useful in selected cases, such as for individuals with a strong family history of premature CAD who are otherwise at low risk, and in individuals with premature CAD, stroke, or venous thromboembolism without other predisposing risk factors.[27]

THROMBOGENIC/HEMOSTATIC FACTORS

Platelets and coagulation factors are clearly involved in the thrombotic process, and aspirin and other antiplatelet therapies have been shown to reduce the risk of myocardial infarction.[30] Elevated levels of fibrinogen create an increased risk of CAD independent of serum cholesterol levels.[31] A number of other hemostatic factors have been found to be associated with increased CAD risk, including activated factor VII, plasminogen activator inhibitor–1, tissue plasminogen activator, factor V Leiden, von Willebrand factor, protein C, and antithrombin III.

There has been considerable interest in the role of plasminogen activator inhibitor–1 in the pathogenesis of atherothrombosis and as a risk factor predictive for CAD. Decreased fibrinolytic activity and elevated levels of plasminogen activator inhibitor–1 have been linked with an increased risk of myocardial infarction in prospective studies.[32] Recent data from a nested case-control study of the Stockholm Heart Epidemiology Program[33] have shown that elevated levels of tissue plasminogen activator/plasminogen activator inhibitor–1 complexes correlated with risk for recurrent myocardial infarction, supporting the hypothesis that associations between tissue plasminogen activator and cardiovascular risk are caused by elevated levels of tissue plasminogen activator/plasminogen activator inhibitor–1 complexes and reflect impaired fibrinolysis, rather than increased tissue plasminogen activator activity.

Interestingly, elevated plasminogen activator inhibitor–1 levels are also associated with features of the metabolic syndrome, including insulin resistance and hypertriglyceridemia.[32] Although measurement of various markers of thrombosis/hemostasis may be indicated in certain individuals with a history of thrombotic events, measurement of prothrombotic factors is not currently recommended as part of routine assessment of CAD risk.

INFLAMMATORY MARKERS

Atherosclerosis has features of an inflammatory disease, and there has been tremendous interest in the ability of inflammatory markers, particularly C-reactive protein, to predict CAD risk. C-reactive protein is an acute-phase protein produced by the liver in response to various cytokines during inflammation, tissue injury, or infection. The new high-sensitivity tests detect levels of C-reactive protein that, although within the normal range, may be indicative of low-level inflammation.

Data from both the Physicians' Health Study and the Women's Health Study indicate that a high-sensitivity C-reactive protein level in the highest quartile is associated with an increased risk of cardiovascular events.[34,35] Analysis of data from the Cholesterol and Recurrent Events (CARE) study—a secondary prevention trial in which patients with known CAD were treated with pravastatin or placebo—has shown not only that the elevated levels of high-sensitivity C-reactive protein predicted events, but also that individuals with an elevated high-sensitivity C-reactive protein appeared to receive the greatest benefit from treatment with pravastatin.[36,37] In the AFCAPS/TexCAPS,[38] high-sensitivity C-reactive protein appeared to identify individuals with low plasma lipid levels who responded to lovastatin. Lovastatin was effective in those participants who had a ratio of total cholesterol to HDL cholesterol that was lower than the median and a C-reactive protein level higher than the median. However, lovastatin was ineffective in participants with a ratio of total cholesterol to HDL cholesterol and a C-reactive protein level that were both lower than the median.[38] Thus, high-sensitivity C-reactive protein appears to hold promise as an independent risk factor with some predictive power beyond the lipid risk factors.[5]

The Writing Group, from a workshop on inflammatory markers in cardiovascular disease sponsored by the Centers for Disease Control and Prevention and by the American Heart Association, recently issued recommendations on the use of high-sensitivity C-reactive protein as a marker for cardiovascular risk in

clinical practice.[39] The Writing Group endorsed the optional use of high-sensitivity C-reactive protein to identify patients without known cardiovascular disease who may be at higher absolute risk than estimated by major risk factors. Measurement of high-sensitivity C-reactive protein may be useful in patients at intermediate risk (10% to 20% risk of CAD in 10 years). The assay should be performed in a metabolically stable person without obvious inflammatory or infectious conditions. To provide a more stable estimate of the high-sensitivity C-reactive protein level, the average value of 2 high-sensitivity C-reactive protein assays performed 2 weeks apart should be used. If a level of >10 mg/L is identified, there should be a search initiated for an obvious source of infection or inflammation, and the result of >10 mg/L should then be discarded and the high-sensitivity C-reactive protein measured again in 2 weeks. The high-sensitivity C-reactive protein cut points for low risk (<1.0 mg/L), average risk (1.0 to 3.0 mg/L), and high risk (>3.0 mg/L) correspond to approximate tertiles of high-sensitivity C-reactive protein in the adult population. Because the high-risk tertile has approximately a 2-fold increase in relative risk compared with the low-risk tertile, the finding of high-sensitivity C-reactive protein >3.0 mg/L may prompt the start or intensification of medical therapy or be used to motivate patients to improve their lifestyle or comply with medications. The utility of high-sensitivity C-reactive protein in secondary prevention appears to be more limited because individuals at high risk (>20% risk in 10 years) or with established atherosclerotic disease should be treated intensively, even if they have no signs of inflammatory response.

The Writing Group recommended against widespread screening of the entire adult population for high-sensitivity C-reactive protein and indicated that serial testing of high-sensitivity C-reactive protein should not be used to monitor effects of treatment. The need for further research to help define the most effective and efficient use of inflammatory markers for prediction of cardiovascular disease risk was stressed.

THE METABOLIC SYNDROME

The metabolic syndrome is characterized by a constellation of metabolic risk factors, including abdominal obesity, atherogenic dyslipidemia (elevated triglycerides, small, dense LDL, low HDL cholesterol levels), elevated blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. The ATP III provided criteria for the diagnosis of the metabolic syndrome, which is made when ≥3 of the risk determinants are present.

The prevalence of the metabolic syndrome, as defined by the ATP III, is approximately 22%, based on analysis of data on 8,814 US men and women ≥20 years of age from the National Health and Nutrition Examination Survey (NHANES) (1988 to 1994).[40] When applied to the entire adult US population, this translates into approximately 47,000,000 people who have the metabolic syndrome. A recent prospective study of 4,483 men and women participating in a family study of type 2 diabetes in Finland and Sweden reported that the risk for CAD and stroke was increased 3-fold in subjects with the metabolic syndrome. Cardiovascular mortality was markedly increased as well, with microalbuminuria being its strongest predictor.[41]

The relevance given by the new guidelines to the diagnosis of the metabolic syndrome suggests that many of these patients may be in or near the high-risk category. When evaluated according to the Framingham formula, however, patients who have the features of the metabolic syndrome, but have no other risk factors, are unlikely to be identified as high-risk subjects. This is because 3 elements (triglycerides, abdominal obesity, and glucose levels) that characterize the metabolic syndrome are not included in the Framingham formula. The ATP III recognizes the metabolic syndrome as a secondary target of risk reduction therapy after the primary target of LDL cholesterol.

The first line of therapy for the metabolic syndrome is therapeutic lifestyle changes, including weight reduction and increased physical activity. The importance of lifestyle changes is demonstrated by the results of a recent diabetes prevention trial involving 3,234 individuals without diabetes with elevated fasting and postload plasma glucose levels who were randomly assigned to placebo, metformin, or a lifestyle modification program (with goals of ≥7% weight loss and ≥150 minutes of physical activity per week).[42] Compared with placebo, lifestyle intervention reduced the incidence of diabetes by 58%, and treatment with metformin reduced it by 31%.[41] Perhaps the best advice we can give to our obese, hypertensive, mildly dyslipidemic patients is "eat less and exercise more."

CALCULATION OF ABSOLUTE RISK

Data from the Framingham Heart Study and the Multiple Risk Factor Intervention Trial have demonstrated that risk factors are additive, and the data support an approach that encompasses all the major risk factors.[1,43] This concept of synergism among risk factors was exploited by the NCEP recommendations issued by the ATP I and ATP II, in which all major independent risk factors are used to stratify individuals according to risk. Although the ATP II emphasized intensive management of LDL cholesterol in persons with established CAD (secondary prevention), the major new feature of the ATP III is a focus on primary prevention in persons with multiple risk factors. Counting categorical risk factors has the appeal of simplicity, but it is not as accurate as using graded risk factors for global risk assessment[2,44] to reach the ultimate objective of identifying people with a high likelihood of a cardiovascular event in the near future.

In recent years, professional societies and governmental agencies in both Europe and North America have encouraged physicians to make the transition from risk factor counting to quantitative assessment of a patient's absolute risk of a cardiovascular event. Absolute risk is defined as the probability of develop-

ing a "hard outcome," such as a heart attack or sudden coronary death, over a defined period. Because placement of any patient in the highest risk category determines initiation of aggressive therapeutic measures, including the use of multiple medications, the definition of high risk is a particularly hot topic in the field of cardiovascular disease.

In Europe, different medical societies have proposed numbers between 1.5% and 2% per year as the threshold above which the patient is considered at the highest risk.[3] Assuming linearity of risk over time, these values are similar to those proposed by the ATP III guidelines of cholesterol control, which define the highest risk category as those patients having a likelihood of a cardiovascular event >20% in 10 years (2% per year).[5] In England, the Standing Medical Advisory Committee defines high-risk status as an indication for statin use in prevention of CAD as an absolute risk of ≥30% in 10 years.[45] These guidelines are controversial because using them means that significantly fewer patients will qualify for medical therapy than would qualify using the European or US guidelines.[46,47] Given the cost to society of prescribing an expensive and not risk-free medication to larger strata of the population, the definition of high risk will continue to be finessed within the range of 15% to 30% in 10 years. The focus on using a short-term (≤10 years) assessment of absolute risk is also guided largely by cost considerations.

The ATP III guidelines recommend using a modification of the Framingham equation to calculate 10-year risk of hard CAD events for individuals with ≥2 major risk factors. As all major risk factors can lead to the development of atherosclerosis and premature CAD over time, each major risk factor may deserve clinical intervention regardless of the short-term risk. The major thrust for long-term risk reduction is the implementation of therapeutic lifestyle changes.

RISK ASSESSMENT

The ATP III guidelines recommend a 2-step process for risk assessment. The first step involves counting major risk factors that modify LDL goals (Table 3). A very important change in the ATP III was raising the level at which low HDL cholesterol levels are considered a major risk factor from <35 mg/dL to <40 mg/dL. This change will dramatically increase the number of individuals with risk factors for CAD who qualify for treatment. A guiding principle of the ATP III is that intensity of LDL-lowering therapy should be adjusted according to the patient's risk for developing CAD. There are 3 categories of risk that modify LDL goals (Table 4). A CAD "risk equivalent" (10-year risk for CAD >20%) means that the patient's risk of a major coronary event is the same as that of a patient with established CAD.

An important feature of the ATP III is that individuals with diabetes mellitus who do not have evidence of CAD are raised to the level of a CAD risk equivalent. The diagnosis of diabetes, therefore, is not part of the calculation to assess risk. The presence of other clinical forms of atherosclerotic disease, including peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease, also confers the level of CAD risk equivalent.

The use of noninvasive tests to diagnose subclinical atherosclerosis was recently reviewed[48] and was addressed in the report from the American Heart Association's Prevention Conference V.[49] In general, several of these approaches are promising, but their widespread use in screening is not currently recommended. The exception is the use of the ankle-brachial index to screen individuals for detection of peripheral vascular disease; this may be a cost-effective approach to elevating the asymptomatic individual with multiple risk factors into the category of CAD risk equivalent.[48]

The ATP III incorporates global risk assessment in individuals who have ≥2 major risk factors. The 10-year risk assessment is conducted with Framingham scoring to identify individuals whose 10-year risk warrants consideration for intensive treatment. Individuals with a 10-year risk for CAD >20% are considered CAD risk equivalents, and the LDL cholesterol goal is set at <100 mg/dL. This calculation of 10-year risk for individuals with ≥2 risk factors also determines the level of LDL cholesterol at which to consider drug therapy.[5]

The risk calculation, based on assumptions taken from the Framingham database, considers 7 factors: sex, age, total cholesterol, HDL cholesterol, blood pressure, use of blood pressure medications, and cigarette smoking. The ATP III Executive Summary and the Framingham formula can be downloaded from the Internet.[50,51]

The time needed to assess risk averages <15 seconds; the identification of 10-year risk may lead to the decision to start therapy and to improved compliance by the patient. The formula is accurate for use in daily practice and has been validated in clinical trials. For example, the placebo cohort of the West of Scotland trial[52] showed a 5-year event rate that exactly matched that predicted by the Framingham formula, based on the distribution of risk factors at baseline in that population.

LIMITATIONS OF THE FRAMINGHAM CALCULATION

There are uncommon, but definitely not rare, circumstances when the patient's presentation and risk profile may be predominantly or exclusively caused by risk factors that are not given relevance in the Framingham formula. These are outlined below.

Family history of early atherosclerotic disease: The formula does not account for this most important of risk factors. For this reason, clinicians should use their judgment in deciding whether to place a patient with an impressive family history in the high-risk category, regardless of the results of the Framingham calculation (or avoid calculating risk in these patients). Prospective studies have demonstrated that a family history of premature CAD is an independent risk factor even when other risk factors are taken into consideration.[53] Estimates of the relative risk conferred by a

TABLE 3 Major Risk Factors (Exclusive of Low-Density Lipoprotein Cholesterol [LDL-C]) that Modify LDL-C Goals

- Cigarette smoking
- Hypertension (BP ≥140/90 mm Hg or on antihypertensive medication)
- Low HDL-C (<40 mg/dL)
- Family history of premature CAD (male first-degree relative <55 yr, female first-degree relative <65 yr)
- Age (men ≥45 yr, women ≥55 yr)

BP = blood pressure; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol.
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TABLE 4 Low-Density Lipoprotein (LDL) Cholesterol Goals and Cut Points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate TLC (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CAD or CAD risk equivalents (10-yr risk >20%)	<100	≥100	≥130 (100–129: LDL-lowering drug optional)
≥2 risk factors (10-yr risk ≤20%)	<130	≥130	10-yr risk 10%–20%: ≥130 10-yr risk <10%: ≥160
0–1 risk factor	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

CAD = coronary artery disease; LDL-C = low-density lipoprotein cholesterol.
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history of CAD in a first-degree relative range from 2 to 12 times that of the general population.[54–56] The risk for CAD increases with the number of first-degree relatives affected and the younger the age of onset in the affected family member (clinical problems in first-degree relatives occurring at relatively young age [ie, <55 for men and <65 for women]). In general, the clustering of CAD risk in families follows a polygenic rather than a mendelian pattern.[57] Family history is also a consideration in individuals with inherited disorders of lipoprotein metabolism, such as familial hypercholesterolemia. Family history may lead to more aggressive LDL cholesterol–lowering goals in primary prevention than would be obtained by using the Framingham risk calculation.

Severe hypercholesterolemia: The value of serum cholesterol concentrations as a predictor of clinical events in the Framingham database is not consistent and is limited to the distribution of values up to a total cholesterol of 280 mg/dL. For this reason, patients with more severe problems, including familial hypercholesterolemia, should not be evaluated for risk assessment using the Framingham formula. Familial hypercholesterolemia should be considered as a metabolic disturbance carrying the highest degree of risk in adult patients. Therefore, it should be treated from the moment of diagnosis, sometimes even in early childhood, depending on severity and family history of CAD.

Hypertriglyceridemia: Recent advances have been achieved in understanding the role of triglycerides in CAD. However, triglycerides have not been given any relevance in the Framingham calculation, despite being (1) predictors of heart disease, (2) participators in the pathogenesis of atherosclerosis, and (3) mediators of the therapeutic benefits of lipid-lowering approaches. For this reason, patients with the features of the metabolic syndrome should be evaluated according to another set of criteria, considering that their main lipid problem can only be estimated if the HDL cholesterol is very low. Although low HDL cholesterol commonly accompanies hypertriglyceridemia, it is not clear whether the HDL cholesterol information provides the entire predictability of cardiovascular risk because of atherogenic dyslipidemia.

Abdominal obesity: Although many organizations, including the American Heart Association, have "rehabilitated" obesity as a major risk factor for CAD, the Framingham formula does not assign a value to indices of adiposity. Abdominal obesity is the central element of the metabolic syndrome (or dysmetabolic syndrome X), a clinical phenotype that was highlighted by the NCEP ATP III expert committee as a common presentation carrying a high risk of cardiovascular disease.

Women at higher risk: An issue that quickly becomes apparent when using the Framingham risk assessment tool of the ATP III is that, for a given risk score, the 10-year risk for a woman is lower than that for a man. Consider, for example, a 55-year-old man who has a total cholesterol level of 250 mg/dL and an HDL cholesterol level of 40 mg/dL, is a nonsmoker, has a systolic blood pressure measurement of 160 mm Hg, and is on no medications. Using the ATP III tables, his point count is 15 for a 10-year CAD risk of 20%, elevating him to a CAD risk equivalent. In contrast, a woman with exactly the same numbers would receive a higher point count of 18, but her 10-year CAD risk would only be 6%. Although the difference is because men are at risk 10 years earlier than women, this feature of the ATP III tool has met with criticism.

In the face of national efforts to promote recognition of the importance of CAD risk assessment in

women, it seems contradictory to say that a woman with the same risk factors as a man should not be treated as aggressively. This is an area where physicians must exercise their clinical judgment. If the woman described above had a strong family history of premature CAD, a case could be made either to look at emerging risk factors or to elevate her risk status based on the family history.

Emerginig risk factors: The clinical utility of additional testing is limited to particular patients, such as those with only 1 prominent risk factor, who may otherwise be placed in a low-to-moderate risk category. The main objective in the approach to a patient with undefined CAD risk is to reach an accurate assessment of the 10-year likelihood of having a cardiovascular event. In all patients in whom this can be done with the classic risk factors—which comprises the vast majority of those seen in a primary care practice—there is no a need for additional tests, such as high-sensitivity C-reactive protein, lipoprotein(a), or the density distribution of LDL. Furthermore, there is no need to further upgrade the calculated risk of a patient who is already in the high-risk category. The use of additional tests cannot be advocated with the objective of possibly downgrading risk in patients otherwise identified with conditions that are CAD risk equivalent. For example, in a patient with diabetes and low concentrations of HDL cholesterol, the knowledge that the LDL is predominantly "fluffy," lipoprotein(a) is undetectable, and high-sensitivity C-reactive protein is in the lowest quartile does not allow a reduction in the assessed risk for that patient.

The use of additional tests may have practical relevance in healthy individuals who have only 1 prominent and severe risk factor, such as family history, extreme hypercholesterolemia, severe hypertension, or heavy long-standing cigarette smoking. In dealing with a healthy patient who comes to the office simply because of the knowledge of a family history of CAD, it is possible to reach a point where the patient presentation per se does not justify recommendation for any treatment. In these cases, it is important to explore all avenues to determine if any biochemical parameters of risk track in the family, together with the clinical events, or to determine whether any of the predictors of cardiovascular disease may be elevated in that patient. Likewise, in a patient with just 1 risk factor, the identification of a mostly dense LDL subclass, the presence of very high lipoprotein(a) value, or the presence of high-sensitivity C-reactive protein in the highest quartile may be used as a tool to set the goal to a more aggressive LDL lowering and to improve patient compliance with medical therapy.

CONCLUSION

The practice of preventive cardiology is moving toward a need to identify the high-risk patients who have most cardiovascular events at all ages. No individual risk factor is a good predictor of cardiovascular events when analyzed alone, but the combination of information provides an accurate tool for risk assessment in the patient with moderate dyslipidemia and hypertension, while taking into consideration aging and cigarette smoking. The best approach to risk assessment in patients seen most frequently in internal medicine practices combines the use of the Framingham formula with the use of additional testing and clinical judgment in patients with the metabolic syndrome, familial hypercholesterolemia, or family history of premature atherosclerotic disease.

Familial hypercholesterolemia patients should be positioned in the highest risk category and receive aggressive medical treatment. Patients with a strong family history of premature CAD without major risk factors are candidates for assessment of emerging risk factors. The vast number of patients with the metabolic syndrome warrant a concerted effort at lifestyle changes to intervene on the major factor that contributes to the development of this clinical syndrome (ie, central obesity). Only the patients who fail to modify their lifestyles or to attain the necessary decrease in body weight will need to be considered high risk, especially if there are concomitant risk factors.

1. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293–298.

2. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of CHD using risk factor categories. *Circulation* 1998;97:1837–1847.

3. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorala K. Prevention of CHD in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. *Atherosclerosis* 1998;140:199–270.

4. Wood D, Joint European Societies Task Force. Established and emerging cardiovascular risk factors. *Am Heart J* 2001;141:S49–S57.

5. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497.

6. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from CHD continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256:2823–2828.

7. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of CHD in women through diet and lifestyle. *N Engl J Med* 2000;343:16–22.

8. Ockene JK, Kuller LH, Svendsen KH, Meilahn E. The relationship of smoking cessation to CHD and lung cancer in the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Public Health* 1990;80:954–958.

9. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and CHD. Part 2. Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;335:827–838.

10. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: the Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–153.

11. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;321:129–135.

12. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation* 2000;101:207–213.

13. National Institutes of Health, National Heart, Lung, and Blood Institute. *The Sixth Report of the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute; 1997. NIH Publication 98-4080.

14. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. American Diabetes Association: clinical practice recommendations 2002. *Diabetes Care* 2002;25:S1–S147.

15. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. National Institutes of Health. *Obes Res* 1998;6(suppl 2):51S–209S.

16. Hulley SB, Rosenman RH, Bawol RD, Brand RJ. Epidemiology as a guide to clinical decisions: the association between triglyceride and CHD. *N Engl J Med* 1980;302:1383–1389.

17. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol* 1998;81(suppl):7B–12B.

18. Assmann G, Cullen P, Schulte H. The Munster Heart Study (PROCAM): results of follow-up at 8 years. *Eur Heart J* 1998;19:A2–A11.
19. Austin MA, King M-C, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype: a proposed genetic marker for CHD risk. *Circulation* 1990;82:495–506.
20. Miller BD, Alderman EL, Haskell WL, Fair JM, Krauss RM. Predominance of dense low-density lipoprotein particles predicts angiographic benefit of therapy in the Stanford Coronary Risk Intervention Project. *Circulation* 1996;94:2146–2153.
21. Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of CAD in men and women. *JAMA* 1996;276:875–881.
22. Mykkanen L, Kuusisto J, Haffner SM, Laakso M, Austin MA. LDL size and risk of CHD in elderly men and women. *Arterioscler Thromb Vasc Biol* 1999; 19:2742–2748.
23. Moliterno DJ, Lange RA, Meidell RS, Willard JE, Leffert CC, Gerard RD, Boerwinkle E, Hobbs HH, Hillis LD. Relation of plasma lipoprotein(a) to infarct artery patency in survivors of MI. *Circulation* 1993;88:935–940.
24. Moliterno DJ, Jokinen EV, Miserez AR, Lange RA, Willard JE, Boerwinkle E, Hillis LD, Hobbs HH. No association between plasma lipoprotein(a) concentrations and the presence or absence of coronary atherosclerosis in African-Americans. *Arterioscler Thromb Vasc Biol* 1995;15:850–855.
25. Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for CAD. *Am J Cardiol* 1998;82(suppl):57U–66U; discussion 86U.
26. Kang SS, Wong PW, Malinow MR. Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease. *Annu Rev Nutr* 1992;12:279–298.
27. Refsum H, Ueland PM, Nygard O, Vollset SE. Homocysteine and cardiovascular disease. *Annu Rev Med* 1998;49:31–62.
28. Giles WH, Croft JB, Greenlund KJ, Ford ES, Kittner SJ. Association between total homocyst(e)ine and the likelihood for a history of acute MI by race and ethnicity: results from the Third National Health and Nutrition Examination Survey. *Am Heart J* 2000;139:446–453.
29. Ridker PM, Shih J, Cook TJ, Clearfield M, Downs JR, Pradhan AD, Weis SE, Gotto AM Jr. Air Force/Texas Coronary Atherosclerosis Prevention Study I: plasma homocysteine concentration, statin therapy, and the risk of first acute coronary events. *Circulation* 2002;105:1776–1779.
30. Hennekens CH, Dyken ML, Fuster V. Aspirin as a therapeutic agent in cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1997;96:2751–2753.
31. Lowe GD, Rumley A. Fibrinogen and its degradation products as thrombotic risk factors. *Ann N Y Acad Sci* 2001;936:560–565.
32. Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and CAD. *N Engl J Med* 2000;342:1792–1801.
33. Wiman B, Andersson T, Hallqvist J, Reuterwall C, Ahlbom A, deFaire U. Plasma levels of tissue plasminogen activator/plasminogen activator inhibitor-1 complex and von Willebrand factor are significant risk markers for recurrent MI in the Stockholm Heart Epidemiology Program (SHEEP) study. *Arterioscler Thromb Vasc Biol* 2000;20:2019–2023.
34. Ridker PM, Cushman M, Stampfer MJ, Tracy RT, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973–979.
35. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, Flaker GC, Braunwald E, for the Cholesterol and Recurrent Events (CARE) Investigators. Inflammation, pravastatin, and the risk of coronary events after MI in patients with average cholesterol levels. *Circulation* 1998;98:839–844.
36. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E, for the Cholesterol and Recurrent Events (CARE) Investigators. Long-term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation* 1999;100:230–235.
37. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836–843.
38. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM Jr, for the Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;344:1959–1965.
39. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107:499–511.
40. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356–359.
41. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683–689.
42. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Diabetes Prevention Program Research: reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403.
43. Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group. Serum cholesterol, blood pressure, cigarette smoking, and death from CHD: overall findings and differences by age for 316,099 white men. *Arch Intern Med* 1992;152:56–64.
44. Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 1999;100:1481–1492.
45. Ramsay LE, Haq IU, Jackson PR, Yeo WW, Pickin DM, Payne JN. Targeting lipid-lowering drug therapy for primary prevention of coronary disease: an updated Sheffield table. *Lancet* 1996;348:387–388.
46. Durrington PN, Prais H, Bhatnagar D, France M, Crowley V, Khan J, Morgan J. Indications for cholesterol-lowering medication: comparison of risk-assessment methods. *Lancet* 1999;353:278–281.
47. Betteridge J, Shepherd J, Thompson G. Use of statins: Sheffield tables have shortcomings [letter]. *BMJ* 1997;315:1619.
48. Pearson TA. New tools for coronary risk assessment: what are their advantages and limitations? *Circulation* 2002;105:886–892.
49. Greenland P, Abrams J, Aurigemma GP, Bond MG, Clark LT, Criqui MH, Crouse JR 3rd, Friedman L, Fuster V, Herrington DM, et al, for the Writing Group III. Prevention Conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention. Noninvasive tests of atherosclerotic burden. *Circulation* 2000;101:E16–E22.
50. The National Insitutes of Health. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Executive Summary. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm. Accessed May 22, 2003.
51. The National Institutes of Health. Risk assessment tool for estimating 10-year risk of developing hard CHD (myocardial infarction and coronary death). Available at: http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof. Accessed May 22, 2003.
52. The West of Scotland Coronary Prevention Study Group. Baseline risk factors and their association with outcome in the West of Scotland Coronary Prevention Study. *Am J Cardiol* 1997;79:756–762.
53. Barrett-Connor E, Khaw K. Family history of heart attack as an independent predictor of death due to cardiovascular disease. *Circulation* 1984;69:1065–1069.
54. Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. *Lancet* 1969;2:1380–1382.
55. Phillips RL, Lilienfeld AM, Diamond EL, Kagan A. Frequency of CHD and cerebrovascular accidents in parents and sons of CHD index cases and controls. *Am J Epidemiol* 1974;100:87–100.
56. Rissanen AM. Familial aggregation of CHD in a high incidence area (North Karelia, Finland). *Br Heart J* 1979;42:294–303.
57. Siegmund KD, Province MA, Higgins M, Williams RR, Keller J, Todorov AA. Modeling disease incidence rates in families. *Epidemiology* 1998;9:557–562.