Primary Prevention of Coronary Heart Disease
Integrating Risk Assessment With Intervention

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The concept that coronary heart disease (CHD) can be prevented has increasingly become a driving force in cardiovascular medicine. For many years, the field gave lip service to prevention but neglected to take it seriously. The possibility of effective prevention was met with skepticism from many quarters. Gradually, however, the tide has turned, and prevention is getting the upper hand. Widespread acceptance of the benefits of prevention came first in the area of secondary prevention, ie, preventing recurrent coronary events in patients with established CHD.[1] Secondary prevention stands at the boundary between prevention and treatment. Many cardiologists consider secondary prevention to be treatment of coronary artery disease; others see it as prevention of recurrent coronary events. There is a more uniform agreement that prevention of new-onset CHD should be called primary prevention. This article examines some of the major issues currently under scrutiny for primary prevention of CHD. Without question, the area of primary prevention is complex and contentious; some of the issues will not be easily resolved. However, if the burden of CHD in industrialized and developing societies is to be substantially reduced, effective strategies for primary prevention must be put in place.

Medical Prevention of Acute Coronary Syndromes

Major advances have recently been made in understanding the pathogenesis of acute coronary syndromes (unstable angina, myocardial infarction, and coronary death). Of great importance was the recognition that rupture of vulnerable plaques leading to coronary thrombosis accounts for most acute coronary syndromes.[2,3] Equally important was the discovery that the risk of plaque rupture and its consequences can be substantially reduced by medical intervention. For example, cigarette smoking almost certainly predisposes to plaque rupture, and smoking cessation rapidly lowers risk for coronary thrombosis.[4] Meta-analysis confirms that lowering blood pressure in hypertensive patients will reduce acute myocardial infarctions.[5] Low-dose aspirin therapy likewise lowers the danger of acute coronary events.[6,7] Finally, recent clinical trials[8–12] demonstrate that cholesterol-lowering therapy will reduce risk for major coronary events beyond previous expectations. Thus, preventive medical therapies are now available to intervene on coronary atherosclerotic disease before it becomes clinically manifest. Appropriate selection of patients for aggressive primary prevention thus emerges as a critical issue.

Concept and Categories of Risk

At the core of primary prevention lies the concept of risk. The general notion has evolved that the intensity of preventive efforts should be adjusted to a patient's risk for developing CHD, ie, the higher the risk, the more aggressive the intervention should be.[13] This strategy seeks to achieve a reasonable balance among 3 factors: efficacy, safety, and costs of intervention. The need for this balance pertains especially in the clinical setting, where professional and financial resources are constrained. The place of clinical management in primary prevention, in contrast to secondary prevention, remains to be clearly defined. Two functions of clinical involvement nonetheless can be visualized. First, by promoting healthier life habits, clinicians link the public health strategy to individuals; and second, by instituting specific risk-reducing therapies, clinicians move secondary-prevention strategies across the boundary into high-risk primary prevention. The first step in primary prevention in the clinical setting is to estimate a patient's risk. Appropriate application of measures to reduce risk in primary prevention requires a full understanding of the categories of risk. Among these categories, 3 can be distinguished: absolute risk, relative risk, and attributable risk. Each deserves brief mention to introduce both risk assessment and treatment strategy.

Absolute risk defines the probability of developing CHD over a finite period. According to probability of CHD, risk can be qualified as high or low. According to period, it can be either short-term (eg, ≤10 years) or long-term. Thus, high risk can be divided between high short-term risk and high long-term risk. Treatment regimens in the 2 high-risk categories may differ by intensity, but both categories need attention by clinicians.[14] Exactly what probability of developing CHD qualifies a patient for being at high short-term risk has been a matter of some dispute.[14,15] One standard could be the patient's likelihood of suffering a major coronary event that is similar to that of patients known to be at high risk, ie, those with established CHD. The projected 10-year risk in the placebo groups of the major cholesterol-

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lowering trials provides 1 example. Patients on placebo of the Cholesterol and Recurrent Events (CARE) study[9] and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study,[10] who should be representative of American patients with CHD, had a projected 10-year risk for major coronary events of ≈26%. A related standard could be the patient with stable angina pectoris; recent analyses[16,17] project an average risk of fatal or nonfatal myocardial infarction in patients with stable angina to be ≈20% in 10 years. Thus, for primary prevention, a high short-term risk might be defined as a probability of developing a fatal or nonfatal myocardial infarction of ≥20% in the next 10 years. High risk for CHD in the short term can be identified by the presence of clinical atherosclerotic disease in other arterial beds, by the presence of subclinical atherosclerosis, or by multiple risk factors.

High risk in the long term can be defined by an elevated risk for CHD over a longer period (>10 years) or even over a lifetime.[18] Several risk factors may contribute to a high long-term risk, but even single risk factors, if left untreated for many years, can hasten the onset of CHD. Thus, patients with single or multiple categorical risk factors should not be ignored by their physicians; primary prevention is for the long term as well as the short term. Patients at high risk in the long term deserve risk reduction under medical supervision.

Finally, a lower risk can be ascribed to patients who are largely devoid of risk factors. For instance, investigators of the Framingham Heart Study[19] recently defined low-risk individuals as being nonsmoking, nondiabetic persons who have a desirable level of LDL cholesterol (100 to 129 mg/dL), an optimal blood pressure (<120/<80 mm Hg), and a relatively high HDL cholesterol (≥45 mg/dL for men and ≥55 mg/dL for women). Even persons who are at low risk by these criteria deserve some attention by physicians. Periodic monitoring is needed to assess whether risk status has changed. Also, because absolute risk rises with advancing age, risk-reduction messages should be conveyed to low-risk persons in accord with the public health effort to reduce risk in the general population.

Relative risk is the ratio of 2 levels of absolute risk. The numerator is the absolute risk of the individual under consideration; the denominator is the average absolute risk of a baseline population, ie, either a low-risk group or an average-risk group. The low-risk state, as defined by Framingham investigators,[19] makes an attractive denominator for evaluating the impact of risk factors in given individuals. Estimates of relative risk carry certain advantages in risk assessment. For instance, a high relative risk in a young adult signifies a high level of absolute risk over the long term; such may call for early, intensified risk reduction. Moreover, because of a rising absolute risk with advancing age, a high relative risk after age 65 signifies a particularly high absolute risk and suggests the need for more aggressive intervention on risk factors.

Attributable risk is the difference in absolute risk between an individual under consideration and that of a control group. Attributable risk typically is low in young adulthood and rises with age. This rise illustrates the continuing importance of risk factors in older age groups, even though relative risk declines with aging.

TABLE 1. Categorical Levels of Major, Causal Risk Factors

Risk Factor	Categorical Level
Cigarette smoking	Any current
Blood pressure	≥140 mm Hg systolic
	≥90 mm Hg diastolic
LDL cholesterol	≥160 mg/dL
HDL cholesterol	<35 mg/dL
Plasma glucose	>126 mg/dL (fasting)

Coronary End Points

Risk estimates must be linked to specific end points. Previous prospective studies and clinical trials have used a variety of end points. For instance, Framingham investigators[19] recently related risk factors to total CHD. This outcome combined several coronary end points: angina pectoris, coronary insufficiency (unstable angina), nonfatal myocardial infarction, and coronary death. The summation thus included both soft and hard coronary end points. Diagnoses of angina pectoris and coronary insufficiency, however, depend on clinical judgment and not on objective data; this softer end point is open to some question because it overestimates risk for clinically solid CHD. As mentioned before, most clinical trials[8–11] have defined outcomes in terms of hard coronary end points: nonfatal myocardial infarction and coronary deaths. It might be noted that joint European societies[15] recently set cutpoints for initiation of aggressive primary prevention on earlier Framingham estimates of total CHD[20]; this inclusion of soft CHD in risk estimates seemingly sanctions aggressive medical therapies for many intermediate-risk patients.

Concept and Categories of Risk Factors

The identification of measurable correlates of CHD constitutes one of the foremost advances in cardiovascular medicine. These correlates are called risk factors.[19,21] Coronary risk factors are important both for assessment of risk and as targets for intervention. For these 2 purposes, a mechanistic classification of risk factors is helpful. Four categories according to mechanism emerge: (1) causal risk factors, (2) conditional risk factors, (3) predisposing risk factors, and (4) plaque burden as a risk factor. Each category requires some explanation.

Causal Risk Factors

The major causal risk factors are cigarette smoking, high blood pressure, elevated serum cholesterol (or LDL cholesterol), low HDL cholesterol, and high plasma glucose.[19] Categorical levels of these risk factors are shown in Table 1. Although the precise mechanisms whereby these 5 risk factors promote atherosclerosis and predispose to CHD are not fully understood, abundant evidence supports a directly causal role. Moreover, they act independently of one another. Even so, some elevation of serum LDL cholesterol seems to be required for atherogenesis; when LDL cholesterol levels are very low, atherogenesis proceeds slowly even when other risk factors are present.[22] Once the serum LDL cholesterol reaches a "permissive" level, the other causal risk factors come into play and independently accelerate atherogenesis. In

addition, the causal factors are called major risk factors because they occur commonly and act powerfully in societies that have high rates of CHD.

Conditional Risk Factors

Conditional risk factors consist of factors that are associated with an increased risk for CHD but whose causal link to CHD remains to be documented with certainty. Because of uncertainty about their role in atherogenesis, the conditional risk factors are not universally accepted as being major, causal risk factors. Two reasons could account for a failure to document causality: (1) the atherogenic potential of these factors may be relatively small compared with the major risk factors, and/or (2) their frequency in a population may not be high enough for a major, independent effect to be detected in prospective studies. The conditional risk factors include elevated concentrations of serum triglycerides, lipoprotein(a) [Lp(a)], small LDL particles, homocysteine, and coagulation factors (eg, fibrinogen and plasminogen activator inhibitor-1).[21]

Predisposing Risk Factors

Predisposing risk factors consist of obesity,[23,24] physical inactivity,[25,26] family history of premature CHD,[27] male sex,[19] and possibly behavioral, socioeconomic, and ethnic factors. Their association with CHD is complex. In one way or another, all of them contribute to the major, causal risk factors. One view holds that their influence on CHD risk is due almost entirely to intensification of the causal risk factors. Some of the predisposing factors also affect the conditional risk factors and potentially raise risk in this way. They also might act through unidentified causal risk factors. When the claim is made that predisposing risk factors are independent risk factors, what is meant is that their influence on CHD risk is mediated in part through unidentified but causal mechanisms.

Another predisposing risk factor appears to be insulin resistance, a condition in which cellular action is impaired by metabolic aberration. Many investigators[28–30] contend that insulin resistance predisposes to several of the causal (and/or conditional) risk factors. The major predisposing risk factors, obesity[31,32] and physical inactivity,[33,34] worsen insulin resistance, and their impact on causal and conditional risk factors may be mediated largely via this mechanism.

Plaque Burden as a Risk Factor

Once an atherosclerotic plaque reaches a certain stage of development, the plaque itself becomes a risk factor for major coronary events. This is because existing coronary plaques can undergo rupture or erosion, causing an occluding coronary thrombus.[2,3] Of critical importance, the more extensive the burden of coronary atherosclerosis is, the greater is the frequency of plaque rupture. Follow-up studies[35–37] on patients undergoing coronary angiograms reveal that the probability of future coronary events relates to the extent of coronary atherosclerosis. The usual way of estimating plaque burden in the clinical setting is to use age as a surrogate marker.[19] The severity of coronary atherosclerosis rises with age; hence, older persons on average have a greater plaque burden than do younger persons. This fact accounts for the well-known claim that age is a risk factor for CHD. Later in this article, the possibility of estimating coronary plaque burden by noninvasive techniques will be examined. Introducing the concept of plaque burden as a risk factor may be "pushing the envelope" of primary prevention into the territory of secondary prevention. Many investigators believe that there is a gray zone between primary prevention and secondary prevention. Use of age as an indicator of plaque burden generally has been acceptable for primary prevention[19]; however, once significant coronary atherosclerosis has been definitely identified, the patient is often designated as having coronary artery disease, even without anginal symptoms. In this article, the attempt will be made to integrate plaque burden into risk assessment in asymptomatic patients. An essential hypothesis of the article is that for the purpose of primary prevention, asymptomatic coronary artery disease (in the absence of myocardial dysfunction) can be viewed as a risk factor for CHD. Once clinically significant myocardial dysfunction supervenes in a patient with coronary atherosclerosis, the patient must be said to have CHD, even if asymptomatic.

Risk Assessment

Identification of Risk Factors

The first step in the assessment of risk is to identify the major, causal risk factors. This requires taking a smoking history; recording blood pressure; estimating cholesterol in total serum, LDL, and HDL; and measuring glucose in fasting plasma. The patient's age represents a first approximation of plaque burden as a risk factor. Predisposing risk factors—overweight and obesity, physical inactivity, family history of premature CHD, and probably insulin resistance—can be detected by history and physical examination. Body habitus is assessed by body weight, body mass index, and waist circumference. Body mass index approximates total body fat, but waist circumference gives a better estimate of the degree of insulin resistance.[24] A waist circumference of >102 cm (>40 in) in men and >88 cm (>36 in) in women usually denotes the presence of significant insulin resistance.[24,38] Finally, measurements of conditional risk factors—triglycerides, small LDL, Lp(a), homocysteine, and fibrinogen—may provide some information about a patient's risk beyond the causal risk factors; their presence also may modify therapeutic strategy.

Clinical Assessment of Risk

Exploring all classes of risk factors allows for a clinical synthesis of risk. A high-risk status will be obvious when a patient has multiple categorical risk factors. The National Cholesterol Education Program (NCEP)[14] and the National High Blood Pressure Education Program's Joint National Commission (JNC)[39] recommend the counting of categorical risk factors as the first step in clinical risk assessment. There is a growing consensus within the cardiovascular community, however, that more precision in absolute risk assessment is needed. Indeed, large epidemiological studies[40,41] have quantitatively defined the relation between the causal risk factors and incidence of CHD. The Framingham Heart Study[19,20] systematically created this quantitative link and

TABLE 2. Scoring for Global Risk Assessment (Adjusted Framingham Scoring)

Risk Factor	Risk Points			Adding Up the Points	
	Men	Women			
Age, y				Age__	Cholesterol__
<34	−1	−9		Diabetes__	HDL Cholesterol__
35–39	0	−4		Smoker__	Blood Pressure__
40–44	1	0			
45–49	2	3		Total__	
50–54	3	6			
55–59	4	7		Absolute Risk (Hard CHD), %	
60–64	5	8		Risk Points	Men	Women
65–69	6	9				
70–74	7	10		1	2	1
Total cholesterol, mg/dL				2	3	2
<160	−3	−2		3	4	2
169–199	0	0		4	5	2
200–239	1	1		5	6	2
240–279	2	2		6	7	2
≥280	3	3		7	9	3
HDL cholesterol, mg/dL				8	13	3
<35	2	5		9	16	3
35–44	1	2		10	20	4
45–49	0	1		11	25	7
50–59	−1	0		12	30	8
≥60	−2	−3		13	35	11
Blood pressure, mm Hg				14	45	13
<120	0	−3		15		15
120–129	0	0		16		18
130–139	1	1		17		20
140–159	2	2				
>160	3	3				
Plasma glucose, mg/dL						
<110	0	0				
110–126	1	2				
>126	2	4				
Smoker						
No	0	0				
Yes	2	2				

provided a scoring system derived largely from the white population of Framingham, Mass. Framingham scores probably are valid for most other populations in the United States[42]; population patterns of CHD incidence are similar although not identical among Americans of white, Hispanic, and black origin.[42] Framingham projections, however, may not be reliable in some ethnic groups; for example, they almost certainly underestimate risk in South Asians living in the United States.[43–45]

The Framingham technique[19] grades the major risk factors and sums these gradations to obtain aggregate risk. Risk points are assigned according to the severity of the risk factor. The total number of points defines absolute risk. One set of scores pertains to men, another to women. The points for each grade of risk factor, for men and women, are listed in Table

2. The gradation of scoring here has been slightly modified to accord with the categories of NCEP[14] and JNC[39]; in addition, points here are assigned to impaired fasting glucose (110 to 126 mg/dL) because of evidence that it is an independent risk factor.[46,47] Risk projections shown in Table 2 denote the 10-year likelihood of developing hard CHD. Projections for hard CHD are approximated from the published Framingham data.[19] They equate to total CHD minus stable angina pectoris. Framingham's hard CHD includes some end points not used in most clinical trials. The latter typically list documented myocardial infarction plus coronary death as the primary end point[8–11]; Framingham estimates for hard CHD go beyond these by including coronary insufficiency (unstable angina) and electrocardiographic evidence of silent myo-

cardial infarction. Compared with absolute risk estimates for the placebo group of major clinical trials, Framingham's more liberal definition of hard CHD will give a somewhat higher estimate for the absolute risk for fatal and nonfatal myocardial infarction.

Framingham investigators[19] assign no quantitative scores to either predisposing risk factors or conditional risk factors. If these additional factors are independently causative, Framingham scoring will underestimate the true absolute risk. The Framingham team[19] contends that most of the risk associated with predisposing risk factors is mediated through the major risk factors, whereas conditional risk factors seemingly carry little independent risk. Despite the great interest in a variety of other risk factors, the Framingham Heart Study[19] and other prospective studies[40] reveal that most of the excess risk for CHD occurring in high-risk societies can be explained by the known causal risk factors; according to these studies,[19,40] the incidence of CHD is extremely low in the subgroup of the population that is completely devoid of the major risk factors.

One weakness of Framingham-type scoring is that age becomes the overriding risk factor in older persons. Certainly coronary plaque burden increases with age; moreover, advancing coronary disease increases the danger of plaque rupture and acute myocardial infarction. Age alone, however, is not a particularly good indicator of the severity of coronary atherosclerosis for individuals; this is so even though age predicts average coronary atherosclerosis in populations. Quantitative risk assessment for individuals thus should be improved if coronary plaque burden could be assessed more directly.

Noninvasive Measures of Coronary Plaque Burden

In recent years, noninvasive techniques for estimating the severity of atherosclerosis have been investigated. Most promising are 2 techniques: sonography of the carotid arteries and electron-beam computerized tomography (EBCT) of the coronary arteries. Sonography measures intimal-medial thickness of the carotid arteries, an indicator of carotid atherosclerosis. EBCT measures coronary calcium, a correlate of coronary atherosclerosis. If either method could be made practical, their measurements of atherosclerotic disease burden might replace age as a surrogate for plaque burden.[48] This replacement should reduce uncertainty as to the extent of plaque burden in particular persons.

Several studies reveal that a moderately high correlation exists between severities of atherosclerosis in carotid and coronary arteries.[49–52] Measurement of carotid atherosclerosis by sonography thus might be used to estimate coronary plaque burden and to replace the surrogate of age. Recent reports[53,54] further claim that measurements of intimal-medial thickness by sonography predict major coronary events independently of other risk factors. These reports add support to the connection between carotid and coronary atherosclerosis. Carotid sonography, however, has not yet been standardized for routine clinical usage; recent studies nonetheless reveal the potential utility of this technique.

Even more promising is the direct measurement of coronary plaque burden by quantifying the calcium content of

coronary arteries. Coronary artery calcium measured by EBCT correlates positively with the extent of coronary atherosclerosis, whether the latter is determined by autopsy or coronary angiography.[55–60] Coronary scores therefore promise to yield a reliable measure of coronary plaque burden. Coronary calcium scores likewise could replace age as a risk factor.[48] Use of calcium scores for this purpose will require the wide availability of reproducible and standardized techniques for measuring coronary calcium; in addition, clinicians must have access to population-based cutpoints for calcium scores according to age and sex. Neither of these needs has been met, but they should be soon.

The first requirement for use of either calcium scores or sonographic measures is a set of distributions of scoring in the general population as a function of age and sex. Such distributions have not been published. For EBCT, when these data become available, the 50th percentile for calcium scores for a given age can be assigned the number of Framingham points for that age. A higher percentile for calcium scores can be assigned incremental points, eg, 1 additional point for above the 75th percentile and 2 additional points for above the 90th percentile. Likewise, lower percentiles justify a subtraction of points from the age score. This approach will allow for immediate use of calcium scoring as a substitute for age as an indicator of plaque burden in global risk assessment.

Current studies are under way to determine more precisely the independent predictive power of coronary calcium measurements as an indicator of plaque burden. Previous investigations[35–37] have shown that extent of coronary plaque burden correlates with the likelihood for developing future coronary events; therefore, estimates of plaque burden by EBCT should have some independent predictive power. Clearly, coronary calcium measurements provide no information about the presence or absence of unstable plaques beyond the general correlation between plaque burden and clinical events.[35–37] Recent reports[61,62] are suggestive of incremental predictive power of EBCT scores, but prospective studies in different populations must be carried out before the true predictive power of calcium scores is known. In the meantime, use of calcium scores as a substitute for age as an indicator of plaque burden seems a reasonable compromise. This proposed usage is conservative, and future studies may reveal a greater predictive power. At the present time, when EBCT is used for quantitative assessment of risk as a guide to primary prevention, the findings of coronary plaques per se do not warrant the selection of patients for invasive procedures for diagnosis or treatment of coronary artery disease.

Detection of Subclinical Ischemia in Risk Assessment

The discovery of myocardial ischemia during exercise testing in asymptomatic patients is another indicator of plaque burden. Several large studies[63–67] found that a positive exercise tolerance test predicts an increased risk for acute coronary events. A review of previous studies by Froelicher et al[68] indicates that a positive versus negative exercise test imparts a risk ratio for total CHD (including angina pectoris)

of ≈12, whereas for hard CHD, the ratio is ≥4. According to Froelicher et al,[68] the major studies show that a positive exercise test remains a powerful predictor for myocardial infarction even after correction for the standard risk factors. Exercise testing in asymptomatic people is currently not recommended for diagnosis of subclinical coronary artery disease.[68] One concern is that false-positive tests will lead to many unnecessary invasive evaluations (eg, coronary angiography); the undeniable possibility exists that inappropriate invasive procedures would proliferate because of indiscriminate screening. Therefore, any use of exercise testing as a part of risk assessment as a guide to primary prevention carries an important caveat: most asymptomatic patients having a positive test should not be referred for further diagnostic procedures for subclinical coronary atherosclerotic disease, because no evidence indicates that invasive intervention in asymptomatic patients with a positive exercise test causes a reduction in major coronary events. Nonetheless, the potential usefulness of exercise testing for risk assessment and institution of preventive medical therapies for primary prevention should not be ruled out. If exercise testing is done in middle-aged to older people who have risk factors, a positive test probably justifies adding at least 2 points beyond age to the Framingham risk score. Again, this is a conservative estimate.

Therapeutic Approaches to Risk Factors

Causal Risk Factors

These risk factors are the primary targets of preventive therapy. A fundamental tenet of primary prevention is that all causal risk factors must be treated once they reach a categorical level (Table 1). Any single categorical risk factor, if left untreated for long periods, can produce major cardiovascular events. Treatment of the causal risk factors is best carried out by physicians. Examples of the dangers of unattended risk factors abound. Many years of cigarette smoking predispose to chronic lung disease and lung cancer, as well as to atherosclerotic cardiovascular disease.[69] Cigarette smokers therefore must be encouraged by their physicians to quit the habit.[70] Untreated hypertension can cause stroke, CHD, renal failure, and hypertension; categorical hypertension therefore must be treated, with drugs if necessary.[39] Persistent hypercholesterolemia raises the long-term risk for CHD.[71,72] An elevated LDL cholesterol needs to be lowered; to what extent and by what means depends on a patient's risk status.[14] Categorical hyperglycemia (diabetes mellitus) predisposes to both microvascular and macrovascular disease; thus, hyperglycemia in patients with diabetes should be treated adequately to achieve near normal concentrations of hemoglobin A1c.[73] Finally, low HDL levels are a powerful risk factor,[19] and if possible, HDL levels should be raised, preferably by changes in life habits.[14] Global risk assessment, with its emphasis on short-term dangers of multiple risk factors, must not be allowed to obscure the long-term dangers of single risk factors.

Predisposing Risk Factors

The foremost modifiable risk factors of this type are overweight (and obesity) and physical inactivity. These conditions occur commonly in our society and predispose to multiple risk factors, both causal and conditional. Because the latter risk factors accompanying obesity and physical inactivity result from metabolic aberration and often cluster in individuals, their clustering has been called the metabolic syndrome. Many investigators[28–30] believe that the risk factors that constitute the metabolic syndrome derive largely from insulin resistance. Certainly, obesity[31,32] and physical inactivity[33,34] are the dominant causes of insulin resistance, although genetic factors undoubtedly affect its severity. The most effective therapies for insulin resistance are weight loss and increased physical activity.[74,75] Efforts to achieve a desirable body weight and to enhance physical activity are essential components of primary prevention, in both the public health and the clinical arenas. Pharmacological treatment of insulin resistance also may become a reality before long. Metformin[76] and thiazolidenediones[77] are first-generation agents for reducing insulin resistance; however, they are not ideal agents, and their use in insulin-resistant patients without diabetes is problematic. Undoubtedly, improved agents will be developed in the future.

Conditional Risk Factors

Because the atherogenicity of the conditional risk factors remains uncertain, the benefit of their modification is open to question. Limited evidence nonetheless suggests some benefit from intervention. For instance, treatment of hypertriglyceridemia with fibrates and/or nicotinic acid appears to reduce the risk for major coronary events.[78,79] Dietary folic acid lowers an elevated homocysteine and in this way may reduce CHD risk.[80,81] Low-dose aspirin should mitigate a prothrombotic state; in accord with this, clinical trials demonstrate efficacy in primary prevention of CHD.[6,7] Use of low-dose aspirin in high-risk patients having a prothrombotic state thus seems reasonable. High Lp(a) concentrations resist currently available lipid-lowering drugs; a high level of Lp(a) nonetheless may justify more aggressive modification of other lipid risk factors.

High-Risk Primary Prevention

Short-Term, High-Risk Prevention

Patients are at high risk in the short term when their likelihood of experiencing a major coronary event is similar to that of patients with established CHD. As previously noted, risk in patients with established CHD is ≥20% per decade.[9,10,16,17] The concept of CHD risk equivalents has previously been set forth by NCEP.[14] Patients with CHD risk equivalents are those without symptomatic coronary disease in whom absolute risk for new major coronary syndromes is equivalent to that for recurrent major coronary events of patients with established CHD. The NCEP[14] identified 3 CHD equivalents: (1) documented abdominal aortic aneurysm; (2) clinical signs and symptoms of ischemia to the extremities, accompanied by substantial atherosclerosis on angiograms or abnormalities of segment-to-arm pressure ratios or velocities; and (3) substantial carotid atherosclerosis documented by cerebral symptoms (transient ischemic attacks or stroke) accompanied by the demonstration of significant atherosclerosis on sonogram or angiogram. The concept

TABLE 3.   Primary Prevention in Coronary Asymptomatic Patients at High Short-Term Risk (CHD Risk Equivalents)

Patient selection (CHD risk equivalents)

   Symptomatic peripheral arterial disease

   Abdominal aortic aneurysm

   Symptomatic carotid artery disease

   Type 2 diabetes*

   Multiple risk factors (Framingham risk for hard CHD >20%/10 years)†

Smoking goal: complete cessation

Blood pressure goal: ≤149/90 mm Hg (≤130/85 mm Hg in type 2 diabetes)

Primary lipid goal: LDL cholesterol ≤100 mg/dL‡

Glucose goal: near normal glucose and near normal hemoglobin A1c (<7%)

Antiplatelet therapy: aspirin 80 mg/d if not contraindicated

Life habits: NCEP/AHA Step II diet, weight loss in overweight patients (goal body mass index 21–25 kg/m²), moderate-intensity exercise (30–60 minutes) 3 or 4 times weekly

*Includes Americans of white, Hispanic, black, and South Asian origin. May not include Americans of East Asian origin.

†Accuracy of absolute risk enhanced by substitution of noninvasive estimates of coronary plaque burden for age as a risk factor.

‡Most patients with baseline LDL cholesterol levels >130 mg/dL will require cholesterol-lowering drugs to achieve the target of therapy.[87] When on-treatment serum LDL cholesterol is in the range of 100 to 129 mg/dL, several therapeutic options are available: to increase the drug dose (or to combine with another cholesterol-lowering drug) to achieve an LDL cholesterol <100 mg/dL,[14] to add another lipid-lowering drug to improve triglyceride and HDL cholesterol levels, or to aggressively modify other risk factors. Clinical judgment is required whether to start (or to increase the dose of) cholesterol-lowering drugs in patients >65 years old.[86]

of CHD equivalents can be extended to other coronary asymptomatic patients at high short-term risk who also have a likelihood of experiencing a major coronary event equal to that of patients with established CHD.

One group of patients at very high risk appears to be those with type 2 diabetes. There is a growing consensus that type 2 diabetes represents a CHD risk equivalent. Not only are patients with diabetes at high risk for CHD,[82] but once they develop CHD, their prognosis is poor.[83,84] Conferring CHD risk equivalency to patients with type 2 diabetes probably holds for Americans of non-Hispanic white, black, Hispanic, and South Asian origin.[42–45]

Other asymptomatic patients can be designated as having a CHD equivalent if their absolute risk for developing hard CHD is >20% in 10 years. One conceptual advance of recent European joint-society guidelines[15] was the logic of applying similar risk reduction therapies to patients with similar risk, whether or not they manifest CHD. Application of Framingham scoring provides a method for estimating absolute risk and for defining patients who have CHD risk equivalents. The present document suggests that risk assessment can be enhanced by substituting noninvasive estimates of coronary plaque burden for age as a risk factor.

For asymptomatic patients with a CHD risk equivalent, general therapeutic recommendations for secondary prevention can be used[1] (Table 3). Smoking cessation has a high priority. Blood pressure should be normalized, by medication if necessary.[39] Low-dose aspirin is warranted for high short-term risk, and its use is supported by primary prevention

trials.[6,7] Glucose levels and hemoglobin A1c levels should be reduced to near normal in patients with type 2 diabetes.[73] Life habits should be modified to minimize risk.[1] Finally, the LDL cholesterol goal is a level ≥100 mg/dL[1,14]; this is the goal designated by NCEP[14] for patients with established CHD. This goal was equated to NCEP's assessment of the optimal LDL cholesterol level as it relates to CHD risk. This assessment was based on evidence derived from epidemiological studies, coronary angiographic studies, and randomized clinical trials.[14] Most patients with baseline LDL cholesterol levels >130 mg/dL will require cholesterol-lowering drugs to achieve the optimal LDL cholesterol.[85] The favored drugs are the statins; the usefulness of statins has been demonstrated both for patients with established CHD[8–10] and for those at high short-term risk without CHD.[11] When LDL cholesterol levels have been reduced to the range of 100 to 129 mg/dL on standard doses of statins, several clinical options are open: to increase the statin dose (or to add a different cholesterol-lowering drug) to achieve an LDL cholesterol level of ≤100 mg/dL, to add another lipid-lowering drug (eg, nicotinic acid or fibrate), to reduce triglycerides, and to raise HDL cholesterol levels or aggressively modify the nonlipid risk factors. NCEP[14] favors the first option; some investigators opt for the latter 2.

A recurring theme of uncertainty pertains to risk assessment and risk management in elderly patients (ie, patients >65 years old).[86] Most investigators agree that patients in the age range of 65 to 75 years deserve management of categorical risk factors as would be done in middle age. Above age 75 years, however, decisions about choices in management depend increasingly on clinical judgment, although control of systolic hypertension in the elderly is considered essential. Framingham scoring[19] confers a high short-term risk on a large portion of the male population between ages 65 and 75 years. These risk estimates nonetheless contain considerable uncertainty because of use of soft CHD end points and because age is a poor indicator of plaque burden for individuals. Particularly for decisions about institution of cholesterol-lowering drugs and low-dose aspirin, noninvasive estimates of plaque burden may be valuable as a replacement for age as a risk factor in global risk assessment in the elderly population.

Long-Term Primary Prevention in the Clinical Setting

A high long-term risk can be conferred either by multiple marginal risk factors or by a single categorical risk factor. As previously indicated, all categorical risk factors should be treated regardless of absolute risk status. Patients with a high risk in the long term deserve attention and intervention by physicians. One possible limitation of the current guidelines of European joint societies[15] is failure to pay sufficient clinical attention to patients at long-term risk. These guidelines nonetheless reflect a widely held view in the cardiovascular field, a view based on 2 postulates. First is the belief that most risk can be reversed by modifying risk factors later in life; second is the belief that intervention in patients who are not at high short-term risk is not cost effective. The first idea is erroneous because intervention later in life never restores

TABLE 4. Long-Term Primary Prevention in the Clinical Setting

All categorical risk factors should be treated professionally

Smoking goal: smoking cessation

Blood pressure goal: <140/90 mm Hg

Serum cholesterol and lipid goals

  Desirable LDL cholesterol: <130 mg/dL

  Very high LDL cholesterol (≥190 mg/dL)

    Most patients will require cholesterol-lowering drugs[14]

  Two or more risk factors* (absolute risk <20%/10 years for hard CHD)

    LDL cholesterol goal: <130 mg/dL

  Zero to 1 risk factor*:

    Acceptable LDL cholesterol: 130 to 159 mg/dL

  Elevated triglycerides (>200 mg/dL) or low HDL cholesterol (<35 mg/dL)

    Emphasize weight reduction and increased physical activity

    Consider nicotinic acid or fibric acid only after LDL cholesterol goal of <130 mg/dL is achieved (limited clinical trial evidence of efficacy)

Life habits: NCEP/AHA Step I diet,[14] weight loss in overweight patients (goal: body mass index 21–25 kg/m^2), moderate-intensity exercise (30–60 minutes) 3 or 4 times weekly

*Includes risk factors other than LDL cholesterol >160 mg/dL, ie, cigarette smoking, hypertension, low HDL cholesterol (<35 mg/dL), family history of premature CHD, age (men ≥45 years; women >55 years or postmenopausal).[14]

absolute risk to the level of low-risk, younger persons; once a person has acquired a substantial burden of coronary plaque, absolute risk will remain relatively high even if risk factors are reduced. Moreover, including only patients at high risk in the short term under any circumstances has only a limited potential for reducing the burden of CHD in our society; if only the small fraction of the whole population at recognizable short-term risk is treated, the benefit to the overall population will be relatively small. Conversely, physicians have an opportunity to broaden their impact by lending their authority and expertise to long-term prevention. The second belief fails to recognize the relatively low cost of early clinical intervention for patients at risk in the long term. Long-term intervention will require some modification of the healthcare system to encourage clinicians to give more priority to primary prevention. Philosophical and institutional opposition couched in economic terms is inappropriate. The issue relates more to allocation of resources than to their availability. The health of the nation requires a broader commitment to preventive strategies.

AHA recommendations[87] for primary prevention generally apply to patients at long-term risk (Table 4). Most important, all categorical risk factors should be managed under the care of a professional, regardless of a patient's absolute risk estimate. Efforts to achieve smoking cessation deserve highest priority. Categorical hypertension must be treated in all patients, according to current JNC reports.[39] Healthy eating and exercise habits should be encouraged. Low-dose aspirin therapy is more difficult to justify in patients who are at high risk in the long term than in those who are in danger of developing CHD in the next few years; its side effects may outweigh its benefits.

The issue of cholesterol management for long-term clinical prevention has become critical. The NCEP defines a desirable LDL cholesterol for primary prevention as a level <130 mg/dL.[14] Thus, all persons without established CHD ideally should have an LDL cholesterol level <130 mg/dL. The recent AFCAPS/TexCAPS[12] study demonstrated the benefit in risk reduction that would accrue from such low levels. However, because for many persons diet alone cannot achieve this target, widespread use of cholesterol-lowering drugs would be required to obtain this goal universally. NCEP therefore mandated this target for LDL cholesterol only for patients considered to be at high risk from multiple risk factors. Essentially, 2 major risk factors (excluding elevated LDL cholesterol but including advancing age) were selected as the level of risk that warrants medical intervention to achieve an LDL cholesterol of <130 mg/dL. For patients with <2 risk factors, an LDL cholesterol level reduced to the range of 130 to 159 mg/dL was considered acceptable although not desirable. Most patients with an LDL cholesterol level >190 mg/dL will require a cholesterol-lowering drug to achieve NCEP's goal. If a patient has an elevated serum triglyceride (>200 mg/dL) or a low HDL cholesterol (<35 mg/dL), weight reduction (in overweight patients) and increased physical activity should be encouraged.[14] Triglyceride-lowering drugs should be used for long-term primary prevention only after an LDL cholesterol of <130 mg/dL has been achieved. Clinical trial support for triglyceride-lowering therapy in primary prevention is limited.[79]

Some authorities[15] essentially equate clinical management with pharmacological therapy. This oversimplification should be resisted for primary prevention. The physician can play an important role in the application of nondrug therapy in prevention. Physicians and ancillary personnel (nurses, physician assistants, and dietitians) can and should facilitate and support patients in their efforts to favorably modify life habits. Importantly, the borderline between drug therapy and nondrug therapy is becoming increasingly blurred. Use of antihypertensive agents and cholesterol-lowering drugs at low doses, along with novel approaches to risk-factor reduction, promise to bridge the gap between drug and nondrug therapies. Physician involvement in the application of these measures offers the greatest assurance that this combination of approaches will be used appropriately.

Lifetime Primary Prevention

The success of recent secondary prevention trials of statin therapy mandates more emphasis on high-risk primary prevention. The selection of patients for intensive risk-reducing therapy has become a prime issue and is the major focus of the present article. The fact remains, however, that reduction of the clinical burden of CHD in the United States and other high-risk populations requires broad application of risk-reduction strategies. These include 4 categories of life habits: cigarette smoking, diet composition, body weight, and physical activity. Each deserves a major public health commitment and can be examined briefly.

Cigarette Smoking

Smoking remains a major cause of CHD.[69] It promotes the buildup of coronary plaques and predisposes to premature

plaque rupture and coronary thrombosis. It accelerates the development of peripheral arterial disease. Efforts to achieve smoking cessation by physicians are worthwhile. Aggressive urging by physicians will convince some patients to give up the smoking habit. Although clinical efforts for smoking cessation are important,[70] the public health approach nevertheless holds greater promise overall. Involvement by government at every level and by health-related organizations is necessary and has reduced the proportion of the American population that smokes. However, not all the news is good. The apparent increase in smoking among American teenagers and women is alarming and a reminder of the necessity to sustain and expand public health efforts. Finally, the export of American tobacco to other nations and the tobacco industry's promotion of smoking worldwide are a national scandal.

Diet Composition

The American diet is far from ideal for CHD prevention. Advances nonetheless have been made in reducing intakes of dietary cholesterol and cholesterol-raising fatty acids.[88] The latter include saturated fatty acids and *trans*-fatty acids. A decline in population intake of cholesterol-raising nutrients has decreased average serum cholesterol levels in the United States[89] and probably has contributed to the age-adjusted fall in CHD. Current intakes of saturated plus *trans*-fatty acids account for ≈14% of total energy in the US diet.[88] If this intake could be cut in half, serum cholesterol levels would fall by another 10%, reducing lifetime risk of CHD by another 25%.[41] Recent research suggests that dietary adjuncts may facilitate serum cholesterol lowering beyond what can be achieved by modifying diet composition; most promising are the stanol esters, which reduce absorption of cholesterol entering the intestine.[90] Other changes in diet composition may help to prevent CHD. Many investigators believe that lower intakes of salt and increased consumption of fruits, vegetables, fiber, ω-3 fatty acids, and antioxidants will protect against CHD. This belief is supported by prospective epidemiological studies, but so far, it lacks verification from large controlled clinical trials.

Obesity

The prevalence of obesity in the United States is high and increasing.[23,24] Obesity is the major factor underlying insulin resistance and the metabolic syndrome. It must be considered the foremost predisposing risk factor for CHD in the American population. The public health challenge to control body weight rivals that for prevention and cessation of smoking. The leading cause of obesity is an excessive intake of energy, but sedentary life habits contribute as well. Multiple factors underlie obesity, and multiple changes in American culture will be required to bring it under control.

Physical Inactivity

Most Americans practice sedentary life habits and suffer the consequences: obesity, increased insulin resistance, metabolic risk factors, earlier onset of type 2 diabetes, poor cardiovascular fitness, and impaired body function. Several prospective studies reveal physical inactivity to be a predisposing risk factor for CHD, and physical fitness and regular activity appear to protect against CHD.[26] Changing American society to promote physical activity is a priority for the public health prevention of CHD.

In summary, the time is ripe to integrate high-risk primary prevention into standard clinical practice. The tools for risk assessment and for management of the high-risk patient are available. However, the issue of high-risk primary prevention should not divert attention from lifetime prevention; population-wide, lifetime prevention is the larger challenge and promises more in return.

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