AHA/ACC Scientific Statement

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

Scott M. Grundy, MD, PhD; Richard Pasternak, MD; Philip Greenland, MD; Sidney Smith, Jr, MD; Valentin Fuster, MD, PhD

The past decade has witnessed major strides in the prevention of coronary heart disease (CHD) through modification of its causes. The most dramatic advance has been the demonstration that aggressive medical therapy will substantially reduce the likelihood of recurrent major coronary syndromes in patients with established CHD (secondary prevention). The American Heart Association (AHA) and the American College of Cardiology (ACC) have published joint recommendations for medical intervention in patients with CHD and other forms of atherosclerotic disease.[1] A similar potential exists for risk reduction in patients without established CHD (primary prevention). However, the risk status of persons without CHD varies greatly, and this variability mandates a range in the intensity of interventions. Effective primary prevention thus requires an assessment of risk to categorize patients for selection of appropriate interventions. The present statement is being published jointly by the AHA and ACC to outline current issues and approaches to global risk assessment for primary prevention. The approaches described in this statement can be used for guidance at several levels of primary prevention; however, the statement does not attempt to specifically link risk assessment to treatment guidelines for particular risk factors. Nonetheless, it provides critical background information that can be used in the development of new treatment guidelines.

The major and independent risk factors for CHD are cigarette smoking of any amount, elevated blood pressure, elevated serum total cholesterol and low-density lipoprotein cholesterol (LDL-C), low serum high-density lipoprotein cholesterol (HDL-C), diabetes mellitus, and advancing age (Table 1). The quantitative relationship between these risk factors and CHD risk has been elucidated by the Framingham Heart Study[2] and other studies. These studies[2] show that the major risk factors are additive in predictive power. Accordingly, the total risk of a person can be estimated by a summing of the risk imparted by each of the major risk factors. Other factors are associated with increased risk for CHD (Table 2). These are of 2 types: conditional risk factors and predisposing risk factors. The conditional risk factors are associated with increased risk for CHD, although their causative, independent, and quantitative contributions to CHD have not been well documented. The predisposing risk factors are those that worsen the independent risk factors. Two of them—obesity and physical inactivity—are designated major risk factors by the AHA.[3,4] The adverse effects of obesity are worsened when it is expressed as abdominal obesity,[5] an indicator of insulin resistance.

Clinical Importance of Global Estimates for CHD Risk

Preventive efforts should target each major risk factor. Any major risk factor, if left untreated for many years, has the potential to produce cardiovascular disease (CVD). Nonetheless, an assessment of total (global) risk based on the summation of all major risk factors can be clinically useful for 3 purposes: (1) identification of high-risk patients who deserve immediate attention and intervention, (2) motivation of patients to adhere to risk-reduction therapies, and (3) modification of intensity of risk-reduction efforts based on the total risk estimate. For the latter purpose, patients at high risk because of multiple risk factors may require intensive modification of ≥1 risk factors to maximize risk reduction. Guidelines for the management of individual risk factors are provided by the second Adult Treatment Panel report (ATP II) of the National Cholesterol Education Program (NCEP),[6] the sixth report of the Joint National Committee (JNC VI) of the National High Blood Pressure Education Program,[7] and the American Diabetes Association (ADA).[8] All of these guidelines are currently endorsed or supported by the AHA and the ACC. These reports[6–8] advocate adjusting the intensity of risk factor management to the global risk of the patient. In ATP II and JNC VI,[6,7] overall risk is estimated by adding the categorical risk factors. They do not use a total risk estimate based on summation of risk factors that have been graded according to severity; this latter approach has been advocated recently by Framingham investigators.[2] The use of

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee in June 1999 and by the American College of Cardiology in July 1999. This document is available on the World Wide Web sites of the American Heart Association (www.americanheart.org) and the American College of Cardiology (www.acc.org). A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0177. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 214-706-1466, fax 214-691-6342, or e-mail pubauth@heart.org. To make photocopies for personal or educational use, call the Copyright Clearance Center, 978-750-8400.

(*Circulation*. 1999;100:1481-1492.)

***Circulation* is available at http://www.circulationaha.org**

TABLE 1. Major Independent Risk Factors

Cigarette smoking
Elevated blood pressure
Elevated serum total (and LDL) cholesterol
Low serum HDL cholesterol
Diabetes mellitus
Advancing age

categorical risk factors has the advantage of simplicity but may be lacking in some of the accuracy provided by graded risk factors.

Some researchers and clinicians believe that the summation of graded risk factors provides advantages over the addition of categorical risk factors. For instance, the use of graded risk factors has been recommended in risk-management guidelines developed by joint European societies in cardiovascular and related fields.[9] Advocates of this approach contend that the increased accuracy provided by the grading of risk factors outweighs the increased complexity of the scoring procedures. If the Framingham system is to be used, however, its limitations as well as its strengths must be understood. The AHA's Task Force on Risk Reduction recently issued a scientific statement[10] that reviewed and assessed the utility of Framingham scoring as a guide to primary prevention. The present report expands on this assessment and considers factors that must be taken into account when the Framingham algorithm is used.[2]

Primary Versus Secondary Prevention

The present report focuses mainly on risk assessment for coronary disease and not on risk for other cardiovascular outcomes. Framingham scores estimate risk for persons without clinical manifestations of CHD.[2] Therefore, the scores apply only to primary prevention, ie, to prevention in persons without established CHD. Once coronary atherosclerotic disease becomes clinically manifest, the risk for future coronary events is much higher than that for patients without CHD,[6] regardless of other risk factors, and in this case, Framingham scoring no longer applies. The AHA and ACC have issued joint guidelines for the management of risk factors for patients with established CHD and other forms of atherosclerotic disease.[1]

TABLE 2. Other Risk Factors

Predisposing risk factors
Obesity*†
Abdominal obesity†
Physical inactivity*
Family history of premature coronary heart disease
Ethnic characteristics
Psychosocial factors
Conditional risk factors
Elevated serum triglycerides
Small LDL particles
Elevated serum homocysteine
Elevated serum lipoprotein(a)
Prothrombotic factors (eg, fibrinogen)
Inflammatory markers (eg, C-reactive protein)

*These risk factors are defined as major risk factors by the AHA.[3,4]

†Body weights are currently defined according to BMI as follows: normal weight 18.5–24.9 kg/m^2; overweight 25–29 kg/m^2; obesity >30.0 kg/m^2 (obesity class I 30.0–34.9, class II 35.9–39.9, class III ≥50 kg/m^2). Abdominal obesity is defined according to waist circumference: men >102 cm (>40 in) and women >88 cm (35 in).[5]

Definition of CHD

Interpretation of risk estimates for CHD requires a precise definition of CHD. Framingham estimates traditionally predict total CHD, which includes angina pectoris, recognized and unrecognized myocardial infarction, coronary insufficiency (unstable angina), and CHD deaths. In contrast, many clinical trials[11–14] that have evaluated specific risk-reducing therapies have specified major coronary events (recognized acute myocardial infarction and CHD deaths) as the primary coronary end points. In accord, the recent Framingham report[2] also provided estimates for "hard" CHD, excluding angina pectoris. The inclusion of coronary insufficiency (unstable angina) and unrecognized myocardial infarction (defined by electrocardiography) probably gives estimates of hard CHD that are somewhat higher than combined end points reported in several clinical trials.[11–14] A recent clinical trial, the Air Force/Texas Coronary Artery Prevention Study (AFCAPS/TexCAPS),[15] specified acute coronary events, including unstable angina, acute myocardial infarction, and coronary death, as the primary end point. This combined end point probably corresponds closely to the Framingham study's definition of hard CHD. Definitions of coronary end points assume critical importance when risk cutpoints are defined to select patients for specific therapies.

Absolute Risk Estimates

Absolute risk is defined as the probability of developing CHD over a given time period. The recent Framingham report[2] specifies absolute risk for CHD over the next 10 years. Although absolute risk scores can be used to evaluate preventive strategies, 4 caveats must be kept in mind. First, Framingham scores derive from measurements made some years ago; the possibility exists that absolute risk for any given level of risk factors in the general population may have changed since that time. Second, absolute risk in the Framingham population for any given set of risk factors may not be the same as that for all other populations, for example, those of differing ethnic characteristics. Third, Framingham risk scores represent average values; however, considerable individual variability in risk exists within the Framingham population. For example, several other factors not included in the Framingham scores potentially modify absolute risk for individuals (see Table 2). Finally, Framingham scores are not necessarily elastic; the magnitude of risk reduction achieved by modifying each risk factor may not equal (in reverse) the increment in risk accompanying the factors.

Definition of Low Risk

The Framingham report[2] defined low risk as the risk for CHD at any age that is conferred by a combination of all the

TABLE 3. Definition of a Low-Risk State*

Serum total cholesterol 160 to 199 mg/dL
LDL-C 100 to 129 mg/dL
HDL-C ≥45 mg/dL in men and ≥55 mg/dL in women
Blood pressure <120 mm Hg systolic and <80 mm Hg diastolic
Nonsmoker
No diabetes mellitus

*According to Framingham Heart Study.[2]

following parameters: blood pressure <120/<80 mm Hg, total cholesterol 160 to 199 mg/dL (or LDL-C 100 to 129 mg/dL), and HDL-C ≥45 mg/dL for men or ≥55 mg/dL for women in a nonsmoking person with no diabetes (Table 3). This definition of low risk seems appropriate and should be widely applicable; for example, in the follow-up of 350 000 screenees of the Multiple Risk Factor Intervention Trial,[16] most of the excess mortality from CHD could be explained by the presence of the major risk factors above these levels. The NCEP[6] designated a total cholesterol level of <200 mg/dL (or LDL-C of <130 mg/dL) as a desirable level. Framingham investigators[2] included total cholesterol levels in the range of 160 to 199 mg/dL (and LDL-C of 100 to 129 mg/dL) in their definition of the low-risk state. In addition, NCEP[6] recognized an LDL-C level of ≤100 mg/dL as optimal and as the goal of therapy for secondary prevention. This level corresponds to a total cholesterol level of ≈<160 mg/dL. An elevated LDL-C level appears to be the primary CHD risk factor, because some elevation of LDL seems to be necessary for the development of coronary atherosclerosis.[17] A very-low-risk state can be defined as an LDL-C level of <100 mg/dL in the presence of other low-risk parameters (Table 3). Therapeutic efforts to reestablish a very-low-risk state appear to be justified for secondary prevention[1,6]; in primary prevention, however, a very low LDL-C level is not currently deemed necessary.[6]

Relative Risk Versus Absolute Risk: Estimations From Framingham Scores

The relative risk is the ratio of the absolute risk of a given patient (or group) to that of a low-risk group. Literally, the term relative risk represents the ratio of the incidence in the exposed population divided by the incidence in unexposed persons. The denominator of the ratio can be either the average risk of the entire population or the risk of a group devoid of risk factors. The Framingham definition of the low-risk state provides a useful denominator to determine the effect of risk factors on a patient's risk. Both the absolute and relative risk can be derived from the recently published risk score sheets.[2]

The first step in estimating risk is to calculate the number of Framingham points for each risk factor (Table 4). For initial assessment, measurements of serum levels of total cholesterol (or LDL-C) and HDL-C are required.[2] The points for total cholesterol instead of LDL-C are listed in Table 4 because some of the Framingham database did not include LDL-C. Hence, total cholesterol gives more robust estimates. Evaluation for cholesterol disorders requires measurement of

TABLE 4. Global Risk Assessment Scoring

	Risk Points	
Risk Factor	Men	Women
Age, y		
<34	−1	−9
35–39	0	−4
40–44	1	0
45–49	2	3
50–54	3	6
55–59	4	7
60–64	5	8
65–69	6	8
70–74	7	8
Total cholesterol, mg/dL		
<160	−3	−2
169–199	0	0
200–239	1	1
240–279	2	2
≥280	3	3
HDL cholesterol, mg/dL		
<35	2	5
35–44	1	2
45–49	0	1
50–59	0	0
≥60	−2	−3
Systolic blood pressure, mm Hg		
<120	0	−3
120–129	0	0
130–139	1	1
140–159	2	2
>160	3	3
Diabetes		
No	0	0
Yes	2	4
Smoker		
No	0	0
Yes	2	2
Adding up the points		
Age _____		
Cholesterol _____		
HDL-C _____		
Blood pressure _____		
Diabetes _____		
Smoker _____		
Total points _____		

LDL-C, which is also the primary target of cholesterol-lowering therapy.[6] The blood pressure value used in scoring is that obtained at the time of assessment, regardless of whether the patient is taking antihypertensive drugs. The average of several blood pressure measurements is needed for an accurate determination of the baseline level. Finally, in the present report, Framingham risk scores for borderline eleva-

Age (Low-risk level)*	30-34 (2%)	35-39 (3%)	40-44 (3%)	45-49 (4%)	50-54 (5%)	55-59 (7%)	60-64 (8%)	65-69 (10%)	70-74 (13%)	Absolute Risk	Absolute Risk‡
Points †										Total CHD‡	Hard CHD¶
0	1.0									2%	2%
1	1.5	1.0	1.0							3%	2%
2	2.0	1.3	1.3	1.0						4%	3%
3	2.5	1.7	1.7	1.3	1.0					5%	4%
4	3.5	2.3	2.3	1.8	1.4	1.0				7%	5%
5	4.0	2.6	2.6	2.0	1.6	1.1	1.0			8%	6%
6	5.0	3.3	3.3	2.5	2.0	1.4	1.3	1.0		10%	7%
7	6.5	4.3	4.3	3.3	2.6	1.9	1.6	1.3	1.0	13%	9%
8	8.0	5.3	5.3	4.0	3.2	2.3	2.0	1.6	1.2	16%	13%
9	10.0	6.7	6.7	5.0	4.0	2.9	2.5	2.0	1.5	20%	16%
10	12.5	8.3	8.3	6.3	5.0	3.6	3.1	2.5	1.9	25%	20%
11	15.5	10.3	10.3	7.8	6.1	4.4	3.9	3.1	2.3	31%	25%
12	18.5	12.3	12.3	9.3	7.4	5.2	4.6	3.7	2.8	37%	30%
13	22.5	15.0	15.0	11.3	9.0	6.4	5.6	4.5	3.5	45%	35%
>14	26.5	>17.7	>17.7	>13.3	>10.6	>7.6	>6.6	>5.3	>4.1	>53%	>45%

* Low absolute risk level = 10-year risk for total CHD end points for a person the same age, blood pressure < 120/<80 mmHg, total cholesterol 160-199 mg/dL, HDL-C ≥45 mg/dL, nonsmoker, no diabetes. Percentages show 10-year absolute risk for total CHD end points.

† Points = number of points estimated from Table 4

‡ 10-year absolute risk for total CHD end points estimated from Framingham data corresponding to Framingham points (Table 4)

¶ 10-year absolute risk for hard CHD end points approximated from Framingham data corresponding to Framingham points (Table 4)

Color Key for Relative Risk

Green	Violet	Yellow	Red
Below Average risk	Average risk	Moderately above average risk	High risk

Figure 1. Relative and absolute risk estimates for CHD in men as determined for Framingham scoring.[2] The number of Framingham points is derived as shown in Table 4. Relative risk estimates for each age range are compared with baseline risk conferred by age alone (in the absence of other major risk factors). Relative risk is graded and color coded to include below average, average, moderately above average, and high-risk categories. Distinctions in relative risk are arbitrary. Average risk refers to that observed in the Framingham population. Absolute risk estimates are given in the 2 right-hand columns. Absolute risk is expressed as the percentage likelihood of developing CHD per decade. Total CHD risk equates to all forms of clinical CHD, whereas hard CHD includes clinical evidence of myocardial infarction and coronary death. Hard CHD estimates are approximated from the published Framingham data.[2]

tions have been modified to assign stepwise incremental risk in accord with current NCEP[6] and JNC VI[7] guidelines. Failure of Framingham scores to identify stepwise increments in risk in borderline zones probably reflects the relatively small size of the Framingham cohort. Diabetes is defined as a fasting plasma glucose level >126 mg/dL, to conform with recent ADA guidelines[18]; in the Framingham study, diabetes was defined as a fasting glucose level >140 mg/dL. The designation of "smoker" indicates any smoking in the past month. The total risk score sums the points for each risk factor.

Risk ratios, relative to the low-risk state (Table 3), are shown for men in Figure 1 and for women in Figure 2; for each age, the number shown gives the relative risk. In addition, 10-year absolute risk values are shown for both total and hard CHD. The definition of hard CHD is that used by Framingham investigators; values shown for hard CHD are approximately two thirds those for total CHD, which are in accord with the recent Framingham report.[2] Gradations of increasing relative risk are given in color. At the midpoint of this gradation is the average risk for the Framingham cohort for each age range. Ratios above average are divided into moderately high relative risk and high relative risk. A 3-fold increase in relative risk above the lowest risk level is designated moderately high risk; a 4-fold or greater increase is called high risk. Absolute risk levels rise progressively with age, even in the absence of risk factors.

Relative risk is useful for providing the physician with an immediate perspective of a patient's overall risk status relative to a low-risk state. This perspective can be helpful as a frame of reference for both physician and patient. Moreover, relative risk probably can be used to compare risk among individuals in populations in which baseline absolute risk has not been established. Absolute baseline risk (low-risk level) almost certainly varies among different populations, but the relative contributions of individual risk factors to total risk appear to be similar among all populations. Although the comparability of relative risk has not been proven rigorously, examination of available data from different epidemiological studies[19–28] suggests this to be the case.

It is apparent from Figures 1 and 2 that the relative risk associated with a given set of risk factor levels (expressed as a single Framingham number) declines with advancing age. At the same time, 10-year absolute risk rises with aging. Both changes have implications for prevention. Higher relative risk estimates in young adults are an indication of the high long-term risk accompanying the risk factors; they point to the need to institute a long-term risk-reduction strategy. On the other hand, the increasing absolute risk that accompanies advancing age reveals the opportunity for reducing absolute short-term risk by an immediate aggressive reduction of risk factors in older people. However, the best candidates for aggressive risk reduction among older patients may be those with moderately high or high relative risk. Recent guidelines have emphasized absolute risk estimates for use in treatment guidelines. Even so, the utility of relative risk estimates for areas of primary prevention that are most contentious, specifically, in young adults and elderly patients, should not be overlooked in the development of future guidelines.

Absolute Short-Term Risk

Estimates of short-term risk (absolute risk in the next 10 years) are potentially useful for the identification of patients who need aggressive risk reduction in the clinical setting.

Age	40-44	45-49	50-54	55-59	60-64	65-69	70-74		
(Low-risk level)*	(2%)	(3%)	(5%)	(7%)	(8%)	(8%)	(8%)	Absolute Risk	Absolute Risk
Points †								Total CHD‡	Hard CHD¶
0	1.0							2%	1%
1	1.0							2%	1%
2	1.5	1.0						3%	2%
3	1.5	1.0						3%	2%
4	2.0	1.3						4%	2%
5	2.0	1.3						4%	2%
6	2.5	1.7	1.0					5%	2%
7	3.0	2.0	1.2					6%	3%
8	3.5	2.3	1.4	1.0				7%	3%
9	4.0	2.7	1.6	1.1	1.0	1.0	1.0	8%	3%
10	5.0	3.3	2.0	1.4	1.3	1.3	1.3	10%	4%
11	5.5	3.7	2.2	1.6	1.4	1.4	1.4	11%	7%
12	6.5	4.3	2.6	1.9	1.6	1.6	1.6	13%	8%
13	7.5	5.0	3.0	2.1	1.9	1.9	1.9	15%	11%
14	9.0	6.0	3.6	2.6	2.3	2.3	2.3	18%	13%
15	10.0	6.7	4.0	2.9	2.5	2.5	2.5	20%	15%
16	12.0	8.0	4.8	3.4	3.0	3.0	3.0	24%	18%
≥ 17	>13.5	>9.0	>5.4	>3.9	5.4	5.4	5.4	>27%	>20%

* Low absolute risk level = 10-year risk for total CHD end points for a person the same age, blood pressure < 120/<80 mmHg, total cholesterol 160-199 mg/dL, HDL-C ≥55 mg/dL, nonsmoker, no diabetes. Percentages show 10-year absolute risk for total CHD end points.

† Points = number of points estimated from Table 4

‡ 10-year absolute risk for total CHD end points estimated from Framingham data corresponding to Framingham points (Table 4)

¶ 10-year absolute risk for hard CHD end points approximated from Framingham data corresponding to Framingham points (Table 4)

Key for Relative Risk

Green	Violet	Yellow	Red
Below average risk	Average risk	Moderately above average risk	High risk

Figure 2. Relative and absolute risk estimates for CHD in women as determined for Framingham scoring.[2] The number of Framingham points is derived as shown in Table 4. Relative risk estimates for each age range are compared with baseline risk conferred by age alone (in the absence of other major risk factors). Relative risk is graded and color coded to include below average, average, moderately above average, and high-risk categories. Distinctions in relative risk are arbitrary. Average risk refers to that observed in the Framingham population. Absolute risk estimates are given in the 2 right-hand columns. Absolute risk is expressed as the percentage likelihood of developing CHD per decade. Total CHD risk equates to all forms of clinical CHD, whereas hard CHD includes clinical evidence of myocardial infarction and coronary death. Hard CHD estimates are approximated from the published Framingham data.[2]

Patients at high short-term risk may need pharmacological agents to control risk factors. The precise level of absolute risk that defines a patient at high short-term risk has been an issue of some uncertainty and involves a value judgment. Theoretically, this level of risk justifies aggressive risk-reduction intervention and is set through an appropriate balancing of efficacy, costs, and safety of therapy. Over time and depending on economic considerations, the thinking about this critical cutpoint of risk may change. Furthermore, little dialogue has occurred in the United States regarding the process of choosing a single absolute risk cutpoint for high short-term risk. The NCEP has taken the lead in adjusting the aggressiveness of cholesterol-lowering therapy to the absolute risk of patients. The NCEP identified patients having established CHD and other atherosclerotic disease as being at very high risk and deserving of aggressive therapy. For primary prevention, LDL-C goals were established by counting risk factors, but they did not define absolute risk in precise, quantitative terms. Future guidelines for risk reduction in the United States likely will put greater emphasis on quantitative global risk assessment.

Recently, guidelines of the joint European Societies[9] have identified high short-term risk as an absolute risk that imparts a >20% probability of developing CHD in the next 10 years. Once a patient reaches this threshold of risk, guidelines similar to those for secondary prevention are triggered. This threshold may be reasonable, but several comments must be made about how the European guidelines were derived. The authors[9] made use of older Framingham risk equations,[29] but their own risk estimates were based only on age, cigarette smoking, blood pressure, and total cholesterol. HDL-C levels were not included. Framingham risk equations[2,29] consistently include HDL-C, which is a powerful independent risk factor. The absence of HDL-C as a risk factor in European guidelines must be considered a limitation. As previously mentioned, European guidelines[9] used Framingham's total CHD as the coronary end point, which is a liberal coronary outcome and lowers the barrier to initiation of secondary-prevention guidelines. Irrespective of these details, there appears to be considerable consensus in the European cardiovascular community that a 10-year risk for clinical coronary end points of >20% justifies the category of high short-term risk. One concern about European guidelines is that although they creatively bridge the gap between primary and secondary prevention, they seemingly deemphasize the need for long-term primary prevention in the clinical setting.

Absolute Long-Term Risk

Framingham scoring does not directly project long-term risk (>10 years), although such risk can be approximated by the summing of risk scores over successive age categories and the subtraction of those persons removed by having CHD

events. Thus, 20-year risk should be at least twice the 10-year risk. An important aim of primary prevention is to reduce CHD over the long term and not just over the short term. For a patient in the age range of 50 to 54 years, a 20-year projection of absolute risk may be of more interest to both the physician and the patient than a 10-year projection. Such a patient whose 10-year risk for CHD is 15% may not qualify as being at high short-term risk, but this same patient has a >30% probability of developing CHD before age 75. This latter projection needs to considered when primary prevention strategies are planned.

Another critical point to make about long-term risk is that any single coronary risk factor, eg, cigarette smoking, hypertension, high serum cholesterol, or diabetes, can lead to premature CHD (or stroke) if left untreated over a period of many years. Therefore, each of the major risk factors deserves intervention in the clinical setting, regardless of the short-term absolute risk. The centerpiece of long-term risk reduction is modification of lifestyle habits, eg, smoking cessation, change in diet composition, weight control, and physical activity.[30] Nonetheless, in patients in whom long-term risk is high, the use of drugs for treatment of hypertension or serum cholesterol disorders may be warranted, as described in JNC VI[7] and ATP II,[6] respectively.

Severity of Major Risk Factors

Framingham scoring takes into account gradations in risk factors when estimating absolute risk. The scoring does not adequately account for severe abnormalities of risk factors, eg, severe hypertension, severe hypercholesterolemia, or heavy cigarette smoking. In such cases, Framingham scores can underestimate absolute risk. This underestimation is particularly evident when only 1 severe risk factor is present. Thus, heavy smoking[31] or severe hypercholesterolemia[32] can lead to premature CHD even when the summed score for absolute risk is not high. Likewise, the many dangers of prolonged, uncontrolled hypertension are well known. These dangers underscore the need to control severe risk factors regardless of absolute short-term risk estimates.

Diabetes Mellitus as a Special Case in Risk Assessment

That diabetes mellitus is a major risk factor for CVD is well established.[2] Both type 1 diabetes[33] and type 2 diabetes[34] confer a heightened risk for CVD. Type 2 diabetes is of particular concern because it is so common and usually occurs in persons of advancing age, when multiple other risk factors coexist. There is a growing consensus that most patients with diabetes mellitus, especially those with type 2 diabetes, belong in a category of high short-term risk. When the risk factors of diabetic patients are summed, their risk often approaches that of patients with established CHD.[35] The absolute risk of patients with type 2 diabetes usually exceeds the Framingham score for hyperglycemia because other risk factors almost always coexist. Another reason to elevate the patient with diabetes to a higher risk category than suggested by Framingham scoring is the poor prognosis of these patients once they develop CHD.[36] These factors point to the need to intensify the management of coexisting risk factors in patients with diabetes.[7,37] These considerations about the very high risk of patients with diabetes apply to ethnic groups that have a relatively high population risk for CHD. The inclusion of patients with type 2 diabetes in the very-high-risk category may not be appropriate when they belong to ethnic groups with a low population risk.

Absolute Risk Assessment in Elderly Patients

One of the more prominent features of the Framingham risk scoring is the progressive increase in absolute risk with advancing age (Figures 1 and 2). This increase undoubtedly reflects the cumulative nature of atherogenesis. With advancing age, people typically accumulate increasing amounts of coronary atherosclerosis. This increased plaque burden itself becomes a risk factor for future coronary events.[38–40] Framingham scoring for age reflects this impact of plaque burden on risk. Still, average scores mask the extent of variability in plaque burden in the general population. To apply average risk scores for age to individual patients may lead to miscalculation of true risk, particularly because Framingham applies so much weight to age as a risk factor. Miscalculation of risk could lead to inappropriate selection of patients for aggressive risk-reduction therapies. This fact points to the need for flexibility in adapting treatment guidelines to older persons. The tempering of treatment recommendations with clinical judgment becomes increasingly important with advancing age, particularly after the age of 65. In the future, measures of subclinical atherosclerosis may improve the accuracy of global risk assessment in older patients. When risk scoring is used to adjust the intensity of risk factor management in elderly patients, relative risk estimates may be more useful than absolute risk estimates. Relative risk estimates essentially eliminate the age factor and are based entirely on the major risk factors. These estimates allow the physician to stratify and compare patients of the same age, and patients at highest relative risk could be selected for the most aggressive risk management.

Certain Limitations of Framingham Database

Certain features of the Framingham scores reflect limitations of the data set. For example, LDL-C and HDL-C levels are known to be continuous in their correlation with CHD risk. Presumably because of an insufficient number of subjects in all categories, these continuous relationships are not consistently observed between each incremental category.[2] Moreover, the assigned scores for each category are not entirely consistent with the notations for graded risk proposed by the NCEP[6] and the JNC.[7] Framingham scores probably require adjustment to account for the continuous relationship between risk factors and CHD.[6,7] As stated previously, this adjustment was made in Table 4. Finally, there is no indication that Framingham scoring has been corrected for regression dilution bias[41]; this bias results from the random fluctuation of risk factors over time such that single measures of risk factors systematically underestimate the association between risk factors and CHD.

Prediction scores from Framingham illustrate the substantial difference in CHD risk between men and women before age 70. The difference between men and women particularly

stands out for hard CHD end points. The diagnosis of angina contributes a sizable fraction of all CHD end points in middle-aged women and accounts for the notable difference between total CHD and hard CHD in this age group. Nonatherosclerotic anginal syndromes may have been mislabeled among total CHD end points in some Framingham women. The relatively small rise in risk for total CHD events after age 55 should not obscure the progressive increase in risk for hard CHD in older women. Framingham findings on hard end points are more consistent with population studies that show a sharp rise in CHD morbidity and mortality in women after age 70. Even so, a discrepancy in CHD risk between men and women persists throughout all age groups.

Use of Conditional and Predisposing Risk Factors in Risk Assessment

In addition to the major risk factors (Table 1), a series of other risk correlates have been identified (Table 2). Their presence may denote greater risk than revealed from summation of the major risk factors. Their quantitative contribution and independence of contribution to risk, however, are not well defined. Usually, therefore, they are not included in global risk assessment. This does not mean that they do not make an independent contribution to risk when they are present. A sizable body of research supports an independent contribution of each. Their relation to CHD is more complex than is that of the major risk factors. In some cases, they are statistically correlated with the major risk factors; hence, their own independent contribution to CHD may be obscured by the major risk factors. In other cases, their frequency in the population may be too low for them to add significant independent risk for the entire population; in spite of this, they could be important causes of CHD in individual patients. Several of the other risk factors represent direct targets of therapy, either because they are causes of the major risk factors or because circumstantial evidence of a role in atherogenesis is relatively strong. Thus, even though these other risk factors are not recommended for inclusion in absolute risk assessment, their exclusion from this function should not be taken to imply that they are clinically unimportant. Their role in evaluation and management of patients at risk deserves some consideration.

Obesity

The AHA defines obesity as a major risk factor for CVD.[42] Risk is accentuated when obesity has a predominant abdominal component.[5] Obesity typically raises blood pressure and cholesterol levels[42–44] and lowers HDL-C levels.[43,44] It predisposes to type 2 diabetes.[5] It also adversely affects other risk factors: triglycerides[43,44]; small, dense LDL particles[45]; insulin resistance[46,47]; and prothrombotic factors.[48,49] Although not shown by the Framingham data,[2] other long-term longitudinal studies suggest that obesity predicts CHD independently of known risk factors. The association between excess body weight and CHD seems particularly strong in white Americans. For example, in one long-term prospective study,[50] men aged 40 to 65 years with body mass index (BMI) 25 to 29 kg/m^2 were 72% more likely to develop fatal or nonfatal CHD than were men who were not overweight. In another study,[51] women whose BMI was 23 to 25 kg/m^2 carried a 50% increase in risk for CHD compared with women with lower BMIs. The overall relation between body weight and CHD morbidity and mortality is less well defined for Hispanics,[52] Pima Indians,[53] and black American women[54]; even so, obesity is a risk factor for type 2 diabetes, which itself is a risk factor for CHD. Much remains to be learned about the biological mechanisms underlying the association between obesity and CHD, but without question, a strong association exists. Consequently, obesity is a strong risk factor for CHD[3] and is a direct target for intervention.[5] Prevention of obesity and weight reduction in overweight persons are integral parts of the strategy for long-term risk reduction. The recent report of the NHLBI Obesity Education Initiative[5] provides a comprehensive guideline for the management of overweight and obese patients in clinical practice.

Physical Inactivity

The AHA also classifies physical inactivity as a major risk factor.[4] Many investigations,[55] including the Framingham Heart Study,[56–59] demonstrate that physical inactivity confers an increased risk for CHD. The extent to which physical inactivity raises coronary risk independently of the major risk factors is uncertain.[60] Certainly, physical inactivity has an adverse effect on several known risk factors.[60] Even though physical inactivity is an independent risk factor, physical activity levels are difficult to reliably measure in individual patients. For these reasons, physical inactivity is not included in quantitative risk assessment. In spite of these limitations in assessment, previous studies[61,62] document that regular physical activity reduces risk for CHD. Physical inactivity constitutes an independent target for intervention. Physicians should encourage all of their patients to engage in an appropriate exercise regimen, and high-risk patients should be referred for professional guidance in exercise training. The AHA recently published practical recommendations for exercise regimens designed to reduce risk for CVD.[63]

Family History of Premature CHD

There is little doubt that a positive family history of premature CHD imparts incremental risk at any level of risk factors. This association has been shown by the Framingham Heart Study.[64] Nonetheless, the degree of independence from other risk factors and the absolute magnitude of incremental risk remain uncertain. For this reason, Framingham investigators did not include family history among the major independent risk factors. The NCEP[6] counts a positive family history of CHD as an independent risk factor that modifies the intensity of LDL-lowering therapy. Regardless of whether family history is used to modify risk management in individual patients, the taking of a family history is undoubtedly important. A positive family history for premature CHD calls forth the need to test a patient's relatives for both premature CVD and the presence of risk factors.

Psychosocial Factors

There has long been an interest in the contribution of personality and socioeconomic factors to CHD risk. Recently, specific factors including hostility, depression, and social

isolation have been shown to have predictive value.[65–67] These factors, however, are not included in the Framingham data and cannot be incorporated into the model currently. Nonetheless, they might be taken into account in individual patients when an overall strategy for risk reduction is being developed.

Ethnic Characteristics

The Framingham population represents the world's most intensively studied population for cardiovascular risk factors. This study is of great value in developing population-based risk estimates in this population. Because Framingham residents are largely whites of European origin, it is uncertain whether baseline absolute risk is similar to that in other populations. Available evidence suggests that absolute risk varies among different populations independently of the major risk factors. For example, absolute risk among South Asians (Indians and Pakistanis) living in Western society appears to be about twice that of whites, even when the 2 populations are matched for major risk factors.[68–70] This higher baseline risk should be considered when South Asians living in the United States are evaluated. Available comparisons of non-Hispanic white, non-Hispanic black, and Hispanic Americans[71,72] point to a comparable absolute risk status, but large systematic comparisons are in the early stages. It is also possible that some populations have a lower baseline risk than the whites studied in Framingham. For example, results of the Honolulu Heart Study[27] suggest that Hawaiians of East Asian ancestry have only about two thirds the absolute risk of Framingham subjects. In the Seven Countries Study,[73] the population of Japan exhibited a much lower risk for CHD for a given set of risk factors than other populations. Differences in absolute risk among different demographic groups suggest the need for adjustments in estimates of absolute risk from Framingham scores depending on racial and ethnic origins. Although absolute risk scores may not be transportable to all populations, relative risk estimates probably are reliable across groups. To date, comparison studies are insufficient to provide quantitative estimates of the adjustments needed for Framingham scores when they are applied to individuals from different demographic backgrounds. In spite of the limitations of the Framingham data, absolute risk estimates as applied to some populations seem applicable to the large populations of non-Hispanic white, Hispanic, and black Americans in the United States. For other groups, relative risk estimates still seem applicable.

Hypertriglyceridemia

Framingham scoring does not ascribe independence to triglyceride levels in risk assessment. Framingham investigators[74] nonetheless have reported that elevated serum triglycerides are an independent risk factor, as have other reports.[75–77] Hypertriglyceridemia is correlated with other risk factors[78]; however, its degree of independent predictive power is difficult to assess. Several clinical trials[79–81] found that drugs that primarily affect triglyceride-rich lipoproteins reduce CHD risk when used with patients with hypertriglyceridemia. Elevated triglycerides consequently may become a target of therapy independent of LDL lowering. The reduction of serum triglyceride levels will also decrease the concentrations of small LDL particles, another putative risk factor.[82,83] Of course, weight reduction in overweight patients and adoption of regular exercise by sedentary persons will lower triglyceride levels, which is one way in which these changes in lifestyle reduce CHD risk.

Insulin resistance is another risk correlate for CHD.[84,85] The mechanisms of association between insulin resistance are complex and likely multifactorial. Regardless, a large portion of all patients who are candidates for global risk assessment have insulin resistance and its accompanying metabolic risk factors (the metabolic syndrome). The components of this syndrome include the atherogenic lipoprotein phenotype (elevated triglycerides, small LDL particles, and low HDL-C levels),[78,86] elevated blood pressure, a prothrombotic state, and often, impaired fasting glucose.[87] The metabolic syndrome is a clinical diagnosis, but the risk accompanying it can be assessed in large part by Framingham scoring. This scoring does not count impaired fasting glucose as an independent risk factor, although Framingham publications[88–90] would support doing so. Insulin resistance can be assumed to be present in a patient with obesity (BMI >30 kg/m^2)[46,47] or overweight (BMI 25 to 29.9 kg/m^2) plus abdominal obesity,[46,47] especially when accompanied by elevated plasma triglycerides,[78,91] low HDL-C,[92] or impaired fasting glucose.[93] Insulin resistance is acquired largely through obesity and physical inactivity, although a genetic component undoubtedly exists. The only therapies presently available for insulin resistance for patients without diabetes are weight reduction[94] and increased physical activity.[95]

Homocysteine

A high serum concentration of homocysteine is associated with increased risk for CHD.[96–98] The AHA recently published an advisory on homocysteine that provides an in-depth review of the relation between homocysteine and CVD.[99] Several mechanisms whereby elevated homocysteine predisposes to CVD have been postulated. However, it remains to be proved in controlled clinical trials that a reduction in serum homocysteine levels will reduce risk for CHD. In some patients, nonetheless, high levels of homocysteine can be lowered by recommended daily intake of folic acid.[99–101] If homocysteine levels are elevated, patients should be encouraged to consume the recommended daily intake of folic acid, as well as vitamins B_6 and B_{12}. Routine measurement of homocysteine levels was not recommended for purposes of risk assessment, but measurement is optimal in high-risk patients.[99]

Other Risk Correlates

Other potential risk factors include elevated concentrations of lipoprotein(a), fibrinogen, and C-reactive protein. Routine measures of these risk factors currently are not recommended. An elevated serum lipoprotein(a) correlates with a higher incidence of CHD in some studies[102,103] but not in others.[104,105] Furthermore, specific therapeutics to reduce lipoprotein(a) levels are not available; some investigators have suggested that an elevated lipoprotein(a) level justifies a more

aggressive lowering of LDL-C. An elevated fibrinogen level also is correlated with a higher CHD incidence.[106,107] Again, no specific therapies are available, except that in smokers, smoking cessation may reduce fibrinogen concentrations.[108] Finally, C-reactive protein is promising as a risk predictor.[109,110] The preferred method for measurement appears to be a high-sensitivity test.[111] C-reactive protein appears to be related to systemic inflammation; however, its causative role in atherogenesis is uncertain.

Implications for Clinical Risk Reduction

Identification of risk factors lies at the heart of clinical efforts to reduce risk for CVD and/or CHD. Every major risk factor predisposes to CHD and other cardiovascular events, particularly if left unattended for long periods. In addition, when multiple risk factors occur in a single individual, risk is compounded, which justifies efforts to estimate global risk. The summation of contributions of individual risk factors can be a valuable first step in planning a risk-reduction strategy for individual patients. This first step should be divided into 2 phases. First, absolute risk should be estimated from the major risk factors (listed in Table 1). Framingham risk scoring provides an acceptable tool for most non-Hispanic white, Hispanic, and black Americans. People of South Asian origin appear to have about twice the absolute risk for any set of risk factors as whites. In contrast, East Asian Americans may have a lower absolute risk than other ethnic groups in the United States. Second, when absolute risk has been estimated from the major risk factors, consideration can be given to modifying the estimate in the presence of other risk factors (Table 2). Clinical judgment is required to estimate incremental risk incurred by these latter factors. Risk estimates are useful both for short-term, high-risk primary prevention and for long-term (or lifetime) primary prevention. Implications for global risk assessment can be considered for each.

Short-Term Prevention

Recent clinical trials demonstrate that significant risk reduction can be achieved by aggressive reduction of risk factors in high-risk patients. Clinical trials have shown that excess risk can be reduced by ≈33% to ≈50% in ≈5 years. This is particularly the case when risk-reduction strategies use smoking cessation, blood pressure–lowering agents, cholesterol-lowering drugs, and aspirin. Clinical trials strongly suggest that glucose control reduces the incidence of various cardiovascular end points in patients with either type 1 diabetes[112] or type 2 diabetes.[113] Other clinical trials[114,115] strongly suggest that aggressive LDL-lowering therapy reduces risk for CHD in patients with type 2 diabetes. For this reason, detection of patients at high risk, with the aid of global risk assessment, should be an important aim of routine medical evaluation of all patients. Specific therapies for risk reduction in high-risk patients are described in the NCEP ATP II report for cholesterol management,[6] the JNC VI report for treatment of hypertension,[7] and by the ADA's guidelines for treatment of diabetes mellitus.[8] Once appropriate therapies are selected, global risk scores can also be used to help instruct patients and to improve compliance with preventive interventions.

Long-Term Prevention

Global risk assessment is particularly useful in young and middle-aged adults for assessing relative risk and absolute long-term risk (Figures 1 and 2). Even though short-term risk may not be high in younger patients who have multiple risk factors of only moderate severity, long-term risk can be unacceptably high. Risk assessment in these patients will highlight the need for early and prolonged intervention on risk factors. In young adults, relative risk ratios help to reveal long-term risk for CHD. Although long-term prevention may not call for the use of risk-reducing drugs, it definitely will require the introduction of lifestyle modification (ie, smoking cessation in smokers, weight control, increased physical activity, and a diet low in cholesterol and cholesterol-raising fats). The AHA provides guidelines to assist healthcare professionals in the implementation of life-habit modifications.[30] There is a common misconception that most of the excess risk accumulated over many years can be erased by aggressive short-term prevention introduced later in life. Although the use of risk-reducing drugs can significantly lower risk when begun in later years, there is no evidence that it can return a patient to the low-risk status of a younger person. This reduction can only be accomplished by decreasing the magnitude of coronary plaque burden through long-term control of risk factors. Therefore, appropriate intervention, guided by risk assessment that is performed periodically in early adulthood and early middle age, has the potential to bring about a significant reduction in long-term risk.

References

1. Smith SC Jr, Blair SN, Criqui MH, Fletcher GF, Fuster V, Gersh BJ, Gotto AM, Gould L, Greenland P, Grundy SM, Hill MN, Hlatky MA, Houston-Miller N, Krauss RM, LaRosa J, Ockene IS, Oparil S, Pearson TA, Rapaport E, Starke R, and Secondary Prevention Panel. Preventing heart attack and death in patients with coronary disease. *Circulation*. 1995;92:2–4.
2. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.
3. Eckel RH. Obesity and heart disease: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation*. 1997;96:3248–3250.
4. Fletcher GF, Balady G, Blair SN, Blumenthal J, Caspersen C, Chaitman B, Epstein S, Froelicher ESS, Froelicher VF, Pina IL, Pollock ML. Statement on exercise: benefits and recommendations for physical activity programs for all Americans: a statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 1996; 94:857–862.
5. NHLBI Obesity Education Initiative Expert Panel. *Clinical Guidelines on Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report*. Bethesda, Md: National Institutes of Health, National Heart, Lung, and Blood Institute; 1998.
6. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program: second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol (Adult Treatment Panel II). *Circulation*. 1994; 89:1329–1445.
7. *The Sixth Report of the Joint National Committee on 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.
8. American Diabetes Association. Clinical practice recommendations. *Diabetes Care*. 1999;22(suppl 1):S1–S114.
9. Wood D, De Backer G, Faergemann O, Graham I, Mancia G, Pyorala K. Prevention of coronary heart disease in clinical practice: recommen-

dations of the second joint task force of European and other societies on coronary prevention. *Eur Heart J*. 1998;19:1434–1503.
10. Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, Houston-Miller N, Kris-Etherton P, Krumholz HM, LaRosa J, Ockene IS, Pearson TA, Reed J, Washington R, Smith SC Jr. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the American Heart Association's Task Force on Risk Reduction. *Circulation*. 1998;97: 1876–1887.
11. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
12. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia: West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301–1307.
13. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels: Cholesterol And Recurrent Events Trial Investigators. *N Engl J Med*. 1996;335:1001–1009.
14. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
15. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA*. 1998;279: 1615–1622.
16. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256: 2823–2828.
17. Grundy SM, Wilhelmsen L, Rose R, Campbell RWF, Assman G. Coronary heart disease in high-risk populations: lessons from Finland. *Eur Heart J*. 1990;11:462–471.
18. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 1997;20:1183–1202.
19. Epstein FH, Ostrander LD Jr, Johnson BC, Payne MW, Hayner NS, Keller JB, Francis T Jr. Epidemiological studies of cardiovascular disease in a total community: Tecumseh, Michigan. *Ann Intern Med*. 1965;62:1170–1187.
20. Paul O, Lepper MH, Phelan WH, Dupertuis GW, MacMillan A, McKean H, Park H. A longitudinal study of coronary heart disease. *Circulation*. 1963;28:20–31.
21. Stamler J, Lindberg HA, Berkson DM, Shaffer A, Miller W, Poindexter A. Prevalence and incidence of coronary heart disease in strata of the labor force of a Chicago industrial corporation. *J Chronic Dis*. 1960; 11:405–420.
22. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project: the Pooling Project Research Group. *J Chronic Dis*. 1978;31:201–306.
23. Keys A, ed. Coronary heart disease in seven countries. *Circulation*. 1970;41(suppl 4):1–211.
24. Marmot MG, Syme SL, Kagan A, Kato H, Cohen JB, Belsky J. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: prevalence of coronary and hypertensive heart disease and associated risk factors. *Am J Epidemiol*. 1975;102:514–525.
25. Worth RM, Kato H, Rhoads GG, Kagan K, Syme SL. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: mortality. *Am J Epidemiol*. 1975;102: 481–490.
26. Fraser GE. Determinants of ischemic heart disease in Seventh-Day Adventists: a review. *Am J Clin Nutr*. 1988;48:833–836.
27. Wilson PWF, Abbott RD, D'Agostino RB Jr, Rodriguez BL, Curb JD, Burns JA. Prediction of coronary heart disease in Japanese-American men. *Circulation*. 1998;98(suppl I):I-323. Abstract.
28. Karter AJ, Gazzaniga JM, Cohen RD, Casper ML, Davis BD, Kaplan GA. Ischemic heart disease and stroke mortality in African-American, Hispanic, and non-Hispanic white men and women, 1985 to 1991. *West J Med*. 1998;169:139–145.
29. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile: a statement for health professionals. *Circulation*. 1991; 83:356–362.
30. Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, Houston-Miller N, Kris-Etherton P, Krumholz HM, LaRosa J, Ockene IS, Pearson TA, Reed J, Washington R, Smith SC Jr. Guide to primary prevention of cardiovascular diseases: a statement for healthcare professionals from the Task Force on Risk Reduction, American Heart Association Science Advisory and Coordinating Committee. *Circulation*. 1997;95:2329–2331.
31. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. *Circulation*. 1998;96:3243–3247.
32. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 7th ed. New York, NY: McGraw Hill; 1995:1981–2030.
33. Lloyd CE, Kuller LH, Ellis D, Becker DJ, Wing RR, Orchard TJ. Coronary artery disease in IDDM: gender differences in risk factors but not risk. *Arterioscler Thromb Vasc Biol*. 1996;16:720–726.
34. Wilson PW. Diabetes mellitus and coronary heart disease. *Am J Kidney Dis*. 1998;32:S89–S100.
35. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229–234.
36. Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB, Turi ZG, Strauss HW, Willerson JT, Robertson T, Braunwald E, Jaffe AS, and the MILIS Study Group. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis: the MILIS Study Group. *J Am Coll Cardiol*. 1989;14:49–57.
37. Management of dyslipidemia in adults with diabetes: American Diabetes Association. *Diabetes Care*. 1998;21:179–182.
38. Ringqvist I, Fisher LD, Mock M, Davis KB, Wedel H, Chaitman BR, Passamani E, Russell RO Jr, Alderman EL, Kouchoukas NT, Kaiser GC, Ryan TJ, Killip T, Fray D. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). *J Clin Invest*. 1983;71:1854–1866.
39. Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR Jr, Chaitman BR, Kaiser GC, Alderman E, Killip T III. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1994;90:2645–2657.
40. Storstein O, Enge I, Erikssen EJ, Thaulow E. Natural history of coronary artery disease studied by coronary arteriography: a seven-year study of 795 patients. *Acta Med Scand*. 1981;210:53–58.
41. Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. *BMJ*. 1994;308:363–366.
42. Krieger DR, Landsberg L. Mechanisms in obesity-related hypertension: role of insulin and catecholamines. *Am J Hypertens*. 1988;1:84–90.
43. Denke MA, Sempos CT, Grundy SM. Excess body weight: an underrecognized contributor to dyslipidemia in white American women. *Arch Intern Med*. 1994;154:401–410.
44. Denke MA, Sempos CT, Grundy SM. Excess body weight: an underrecognized contributor to high blood cholesterol levels in white American men. *Arch Intern Med*. 1993;153:1093–1103.
45. Tchernof A, Lamarche B, Prud'Homme D, Nadeau A, Moorjani S, Labrie F, Lupien PJ, Despres JP. The dense LDL phenotype: association with plasma lipoprotein levels, visceral obesity, and hyperinsulinemia in men. *Diabetes Care*. 1996;19:629–637.
46. Bogardus C, Lillioja S, Mott D, Reaven GR, Kashiwagi A, Foley JE. Relationship between obesity and maximal insulin-stimulated glucose uptake in vivo and in vitro in Pima Indians. *J Clin Invest*. 1984;73: 800–805.
47. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest*. 1995;96:88–98.
48. Mykkanen L, Ronnemaa T, Marniemi J, Haffner SM, Bergman R, Laakso M. Insulin sensitivity is not an independent determinant of plasma plasminogen activator inhibitor-1 activity. *Arterioscler Thromb*. 1994;14:1264–1271.

49. Giltay EJ, Elbers JM, Gooren LJ, Emeis JJ, Kooistra T, Asscheman H, Stehouwer CD. Visceral fat accumulation is an important determinant of PAI-1 levels in young, nonobese men and women: modulation by cross-sex hormone administration. *Arterioscler Thromb Vasc Biol*. 1998;18:1716–1722.
50. Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, Willett WC. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *Am J Epidemiol*. 1995;141:1117–1127.
51. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. Body weight and mortality among women. *N Engl J Med*. 1995;333:677–685.
52. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. Overweight and mortality in Mexican Americans. *Int J Obes*. 1990;14:623–629.
53. Pettitt DJ, Lisse JR, Knowler WC, Bennett PH. Mortality as a function of obesity and diabetes mellitus. *Am J Epidemiol*. 1982;115:359–366.
54. Stevens J, Keil JE, Rust PF, Tyroler HA, Davis CE, Gazes PC. Body mass index and body girths as predictors of mortality in black and white women. *Arch Intern Med*. 1992;152:1257–1262.
55. US Department of Health and Human Services. *Physical Activity and Health: A Report of the Surgeon General*. Atlanta, Ga: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996.
56. Kannel WB, Sorlie P. Some health benefits of physical activity: the Framingham Study. *Arch Intern Med*. 1979;139:857–861.
57. Kannel WB, Wilson PWF, Blair SN. Epidemiological assessment of the role of physical activity and fitness in development of cardiovascular disease. *Am Heart J*. 1985;109:876–885.
58. Kannel WB, Belanger A, D'Agostino R, Israel I. Physical activity and physical demand on the job and risk of cardiovascular disease and death: the Framingham Study. *Am Heart J*. 1986;112:820–825.
59. Dannenberg AL, Keller JB, Wilson PW, Castelli WP. Leisure time physical activity in the Framingham Offspring Study: description, seasonal variation, and risk factor correlates. *Am J Epidemiol*. 1989;129:76–88.
60. Rodriguez BL, Curb JD, Burchfiel CM, Abbott RD, Petrovitch H, Masaki K, Chiu D. Physical activity and 23-year incidence of coronary heart disease morbidity and mortality among middle-aged men: the Honolulu Heart Program. *Circulation*. 1994;89:2540–2544.
61. Blair SN. Physical activity, fitness, and coronary heart disease. In: Bouchard C, Shephard RJ, Stephens T, eds. *Physical Activity, Fitness and Health: International Proceedings and Consensus Statement*. Champaign, Ill: Human Kinetics; 1994:579–590.
62. Blair SN, Kohl HW III, Barlow CE, Paffenbarger RS Jr, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality: a prospective study of healthy and unhealthy men. *JAMA*. 1995;273:1093–1098.
63. Fletcher GF. How to implement physical activity in primary and secondary prevention: a statement for healthcare professionals from the Task Force on Risk Reduction, American Heart Association. *Circulation*. 1997;96:355–357.
64. Myers RH, Kiely DK, Cupples LA, Kannel WB. Parental history is an independent risk factor for coronary artery disease: the Framingham Study. *Am Heart J*. 1990;120:963–969.
65. Christensen AJ, Smith TW. Cynical hostility and cardiovascular reactivity during self-disclosure. *Psychosom Med*. 1993;55:193–202.
66. King KB. Psychologic and social aspects of cardiovascular disease. *Ann Behav Med*. 1997;19:264–270.
67. Eaker ED. Psychosocial risk factors for coronary heart disease in women. *Cardiol Clin*. 1998;16:103–111.
68. Williams R, Bhopal R, Hunt K. Coronary risk in a British Punjabi population: a comparative profile of non-biochemical factors. *Int J Epidemiol*. 1994;23:28–37.
69. Pugh RN, Hossain MM, Malik M, El Mugamer IT, White MA. Arabian Peninsula men tend to insulin resistance and cardiovascular risk seen in South Asians. *Trop Med Int Health*. 1998;3:89–94.
70. Seedat YK, Mayet FG. Risk factors leading to coronary heart disease among the black, Indian and white peoples of Durban. *J Hum Hypertens*. 1996;10(suppl 3):S93–S94.
71. Goff DC Jr, Ramsey DJ, Labarthe DR, Nichaman MZ. Greater case-fatality after myocardial infarction among Mexican Americans and women than among non-Hispanic whites and men: the Corpus Christi Heart Project. *Am J Epidemiol*. 1994;139:474–483.
72. Goff DC, Nichaman MZ, Chan W, Ramsey DJ, Labarthe DR, Ortiz C. Greater incidence of hospitalized myocardial infarction among Mexican Americans than non-Hispanic whites: the Corpus Christi Heart Project, 1988–1992. *Circulation*. 1997;95:1433–1440.
73. Keys A, Menotti A, Aravanis C, Blackburn H, Djordevic BS, Buzina R, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, Mohaček I, Nedeljkovič S, Puddu V, Punsar S, Taylor HL, Conti S, Kromhout D, Toshima H. The Seven Countries Study: 2,289 deaths in 15 years. *Prev Med*. 1984;13:141–154.
74. Castelli WP. The triglyceride issue: a view from Framingham. *Am Heart J*. 1986;112:432–437.
75. Austin MA. Plasma triglyceride and coronary heart disease. *Arterioscler Thromb*. 1991;11:2–14.
76. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol*. 1998;81:7B–12B.
77. Assman G, Schulte H, Funke H, von Eckardstein A. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. *Eur Heart J*. 1998;19(suppl M):M8–M14.
78. Grundy SM. Hypertriglyceridemia, atherogenic dyslipidemia, and the metabolic syndrome. *Am J Cardiol*. 1998;81:18B–25B.
79. Manninen V, Huttunen JK, Heinonen OP, Tenkanen L, Frick MH. Relation between baseline lipid and lipoprotein values and the incidence of coronary heart disease in the Helsinki Heart Study. *Am J Cardiol*. 1989;63:42H–47H.
80. Carlson LA, Rosenhamer G. Reduction of mortality in the Stockholm ischaemic heart disease secondary prevention study to combined treatment with clofibrate and nicotinic acid. *Acta Med Scand*. 1988;223:405–418.
81. Kaplinsky E. The Bezabifrate Infarction Prevention Study. Paper presented at: Annual Meeting of the European Society of Cardiology; August 1998; Vienna, Austria.
82. Krauss RM. Dense low density lipoproteins and coronary artery disease. *Am J Cardiol*. 1995;75:53B–57B.
83. Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA*. 1996;276:875–881.
84. DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14:173–194.
85. Reaven GM. Insulin resistance and compensatory hyperinsulinemia: role in hypertension, dyslipidemia, and coronary heart disease. *Am Heart J*. 1991;121:1283–1288.
86. Austin MA, King M-C, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype: a proposed genetic marker for coronary heart disease risk. *Circulation*. 1990;82:495–506.
87. Stern MP. Impaired glucose tolerance: risk factor or diagnostic category. In: LeRoith D, Taylor SI, Olefsky JM, eds. *Diabetes Mellitus: A Fundamental and Clinical Text*. Philadelphia, Pa: Lippincott-Raven Publishers; 1996:467–474.
88. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham Study. *Circulation*. 1979;59:8–13.
89. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care*. 1979;2:120–126.
90. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham Study. *JAMA*. 1979;241:2035–2038.
91. Mostaza JM, Vega GL, Snell P, Grundy SM. Abnormal metabolism of free fatty acids in hypertriglyceridaemic men: apparent insulin resistance of adipose tissue. *J Intern Med*. 1998;243:265–274.
92. Karhapaa P, Malkki M, Laakso M. Isolated low HDL cholesterol: an insulin-resistance state. *Diabetes*. 1994;43:411–417.
93. Gerich JE. Metabolic abnormalities in impaired glucose tolerance. *Metabolism*. 1997;46:40–43.
94. Pi-Sunyer FX. Short-term medical benefits and adverse effects of weight loss. *Ann Intern Med*. 1993;119:722–726.
95. Perseghin G, Price TB, Petersen KF, Roden M, Cline GW, Gerow K, Rothman DL, Shulman GI. Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects. *N Engl J Med*. 1996;335:1357–1362.
96. Beresford SA, Boushey CJ. Homocysteine, folic acid, and cardiovascular disease risk. In: Bendich A, Deckelbaum RJ, eds. *Preventive Nutrition: The Comprehensive Guide for Health Professionals*. Totowa, NJ: Humana Press; 1997.
97. Graham IM, Daly LE, Refsum HM, Robinson K, Brattstrom LE, Ueland PM, Palma-Reis RJ, Boers GH, Sheahan RG, Israelsson B, Uiterwaal

CS, Meleady R, McMaster D, Verhoef P, Witteman J, Rubba P, Bellet H, Wautrecht JD, de Valk HW, Sales Luis AC, Parrot-Rouland FM, Tan KS, Higgins I, Garcon D, Andria G. Plasma homocysteine as a risk factor for vascular disease: the European Concerted Action Project. *JAMA*. 1997;277:1775–1781.

98. Mayer EL, Jacobsen DW, Robinson K. Homocysteine and coronary atherosclerosis. *J Am Coll Cardiol*. 1996;27:517–527.
99. Malinow MR, Bostom AG, Krauss RM. Homocyst(e)ine, diet, and cardiovascular diseases: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation*. 1999;99:178–182.
100. Landgren F, Israelsson B, Lindgren A, Hultberg B, Andersson A, Brattstrom L. Plasma homocysteine in acute myocardial infarction: homocysteine-lowering effect of folic acid. *J Intern Med*. 1995;237: 381–388.
101. Ubbink JB, Becker PJ, Vermaak WJ, Delport R. Results of B-vitamin supplementation study used in a prediction model to define a reference range for plasma homocysteine. *Clin Chem*. 1995;41:1033–1037.
102. Dahlen GH. Lp(a) lipoprotein in cardiovascular disease. *Atherosclerosis*. 1994;108:111–126.
103. Bostom AG, Cupples A, Jenner JL, Ordovas JM, Seman LJ, Wilson PWF, Schaefer EJ, Castelli WP. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger: a prospective study. *JAMA*. 1996;276:544–548.
104. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA*. 1993;270: 2195–2199.
105. 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.
106. Montalescot G, Collet JP, Choussat R, Thomas D. Fibrinogen as a risk factor for coronary heart disease. *Eur Heart J*. 1998;19(suppl H):H-11–H-17.
107. Meade TW. Fibrinogen in ischaemic heart disease. *Eur Heart J*. 1995; 16(suppl A):A-31–A-34.
108. Rigotti NA, Pasternak RC. Cigarette smoking and coronary heart disease: risks and management. *Cardiol Clin*. 1996;14:51–68.
109. Anderson JL, Carlquist JF, Muhlestein JB, Horne BD, Elmer SP. Evaluation of C-reactive protein, an inflammatory marker, and infectious serology as risk factors for coronary artery disease and myocardial infarction. *J Am Coll Cardiol*. 1998;32:35–41.
110. Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, Hutchinson WL, Pepys MB. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (monitoring trends and determinants in cardiovascular disease) Augsburg cohort study, 1984 to 1992. *Circulation*. 1999;99:237–242.
111. Eda S, Kaufmann J, Roos W, Pohl S. Development of a new microparticle-enhanced turbidimetric assay for C-reactive protein with superior features in analytical sensitivity and dynamic range. *J Clin Lab Anal*. 1998;12:137–144.
112. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993;329:977–986.
113. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837–853.
114. Pyorala K, Pederson TR, Kjeksyhus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care*. 1997;20:614–620.
115. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial: the CARE Investigators. *Circulation*. 1998;98: 2513–2519.

KEY WORDS: AHA/ACC Scientific Statement ■ coronary disease ■ risk factors ■ risk assessment

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

Scott M. Grundy, Richard Pasternak, Philip Greenland, Sidney Smith, Jr and Valentin Fuster

Circulation. 1999;100:1481-1492
doi: 10.1161/01.CIR.100.13.1481
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539