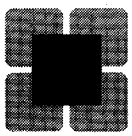

The role of multiple risk factors in cardiovascular morbidity and mortality

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■ **BACKGROUND** Cardiovascular disease remains the leading cause of death in the United States.

■ **OBJECTIVE** To identify important modifiable cardiovascular risk factors and appropriate interventions.

■ **DISCUSSION** The three most important modifiable risk factors are hypertension, cigarette smoking, and dyslipidemia. Systolic hypertension poses a greater risk than diastolic, but the prognostic significance of diastolic blood pressure may have been underestimated. When a smoker quits, the cardiovascular risk soon approaches that of the nonsmoker. Cardiovascular risk increases progressively with elevations of the serum total cholesterol level above 200 mg/dL. Recently identified risk factors include hyperinsulinemia and left ventricular hypertrophy.

■ **CONCLUSION** Each patient deserves an evaluation of cardiovascular risk followed by education about and therapy for those risk factors that can be changed. When more than one risk factor is present, as is often the case, the increase in risk may be synergistic rather than additive.

■ INDEX TERMS: CARDIOVASCULAR DISEASES; RISK FACTORS; SMOKING; HYPERTENSION; HYPERLIPIDEMIA ■ CLEVE CLIN J MED 1993; 60:211–218

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BETWEEN 1972 AND 1990, major declines were seen in the mortality rates of certain cardiovascular diseases. The age-adjusted mortality rate declined by 48% for coronary disease and by 57% for stroke, according to the National Center for Health Statistics.[1] By comparison, the death rate for noncardiovascular causes declined less than 10% during the same period.

Although the decrease in cardiovascular mortality is due in part to advances in treatment of these diseases, it also may be attributed to increased awareness of risk factors by the medical profession and the general public. Identification and treatment of hypertension and dyslipidemia have improved. From 1963 to 1980, Americans changed their dietary habits: they consumed less cream and animal fats and more fish and vegetable oils, and they smoked fewer cigarettes.[2] From 1980 to 1989, beef consumption decreased 11% in the United States, whereas the consumption of seafood increased by 23% and chicken by 36%.[3]

Nevertheless, we must not become complacent: cardiovascular

TABLE 1
RISK FACTORS FOR ATHEROSCLEROSIS

Nonmodifiable factors
Heredity
Male sex
Age
Black race
Fibrinogen
Modifiable factors
Major
Cigarette smoking
Dyslipidemia
Hypertension
Diabetes mellitus
Electrocardiographic or echocardiographic evidence of left ventricular hypertrophy
Minor
Central obesity with high waist-hip ratio
Menopause
Hyperuricemia with gout
Sedentary life-style
Excessive alcohol consumption
Oral contraceptives
Stress
Renin

and cerebrovascular disease still account for the majority of deaths in the United States. We should devote even more attention to identifying risk factors and providing guidance and therapy to reduce those that can be modified.

MODIFIABLE VS NONMODIFIABLE RISK FACTORS

Several prospective studies have identified risk factors for atherosclerosis and its clinical sequelae (atherosclerotic heart disease, stroke, and peripheral vascular disease).[4,5] Some of these risk factors can be modified, but others can not (*Table 1*).

Among the nonmodifiable risk factors, a family history of early death from cardiovascular disease is particularly ominous. Cardiovascular risk increases with age and is greater for men than for women, especially when the women are premenopausal. Race is a nonmodifiable factor because of its relation to hypertension, a modifiable risk factor that is more prevalent, more severe, and more likely to result in early complications in blacks than in whites.[6]

The major modifiable risk factors for cardiovascular disease are hypertension (systolic or diastolic), cigarette smoking, dyslipidemia, diabetes, and electrocardiographic or echocardiographic evidence of left ventricular hypertrophy (LVH). Of these factors, hypertension, cigarette smoking, and dyslipidemia are most closely associated with increased risk and offer the greatest opportunity for intervention.[7,8] Hypertension clearly ranks first in importance for stroke, but identifying the single most important risk factor for atherosclerotic heart disease is difficult. For all three factors, the risk is graduated: the more cigarettes smoked daily, the higher the serum total cholesterol level, and the higher the blood pressure, the greater the risk.[8] A systolic blood pressure of 180 mm Hg carries a greater risk than a serum total cholesterol level of 300 mg/dL or cigarette smoking.[9]

Martin et al[10] quantified the risks in men for total mortality and for mortality due to coronary heart disease so as to superimpose equivalent risks associated with diastolic blood pressure and serum total cholesterol; by their calculations, diastolic blood pressures of 80, 90, and 102 mm Hg confer risks equivalent to serum total cholesterol levels of 200, 238, and 281 mg/dL, respectively.

There is good evidence that eliminating tobacco use,[11,12] correcting dyslipidemia,[13,14] and treating hypertension[15–17] reduce cardiovascular morbidity and mortality. On the other hand, it has not been demonstrated that controlling blood glucose concentrations or regression of LVH lessens the risk.

When multiple risk factors are present, a synergistic rather than additive increase in risk often results.[8,9] Accordingly, even if a patient has nonmodifiable risk factors or has modifiable risk factors for which there is little or no evidence that treatment will reduce risk, a prodigious effort should be made to modify those risk factors for which there is evidence that reduction will be beneficial.

The minor modifiable risk factors should not be ignored in this endeavor, even though they do not have as great an effect on risk. Although hyperuricemia with gout is a minor risk factor, there is no evidence that asymptomatic hyperuricemia is a risk factor for cardiovascular disease, and its treatment is not recommended.

MAJOR MODIFIABLE RISK FACTORS

Hypertension

Systolic blood pressure is more important than diastolic as a risk factor,[8] and there is good evidence that elevated systolic blood pressure should be controlled even when diastolic pressure is normal.[17] For example, a follow-up of 317 871 white men who

were screened for the Multiple Risk Factor Intervention Trial (MRFIT) showed that men ages 50 to 57 with elevated systolic and normal diastolic blood pressure have a greater risk of "all-cause" mortality than those with elevated diastolic pressure.[18] For men ages 35 to 57, those with systolic blood pressure ≥ 160 mm Hg had similar mortality rates, whether the diastolic pressure was less than 80 mm Hg, between 80 and 100 mm Hg, or greater than 100 mm Hg (*Figure 1*).

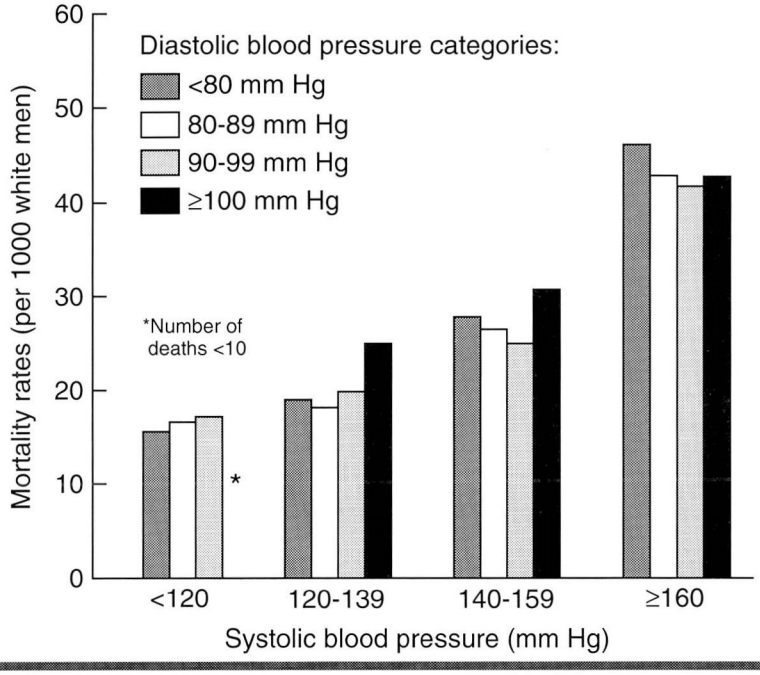

FIGURE 1. Age-adjusted, all-cause, 6-year mortality by level of systolic blood pressure and diastolic blood pressure for 317 871 white men ages 35 to 57 screened for the Multiple Risk Factor Intervention Trial. (From Rutan et al, reference 18, with permission from the American Heart Association.)

The Chicago Stroke Study[19] followed people ages 65 to 74 for 3 years. When diastolic pressure was less than 79 mm Hg and systolic pressure was less than 140 mm Hg, the incidence of all strokes was 42 per 1000, and the incidence of nonembolic brain infarction ("cerebral" infarction) was 22 per 1000. On the other hand, with the same diastolic pressure, if the systolic pressure was greater than 160 mm Hg, the incidence of all strokes increased to 110 per 1000, and the incidence of nonembolic brain infarction increased to 57 per 1000—2.5 times greater.

In the Systolic Hypertension in the Elderly Program (SHEP), fatal and nonfatal stroke and myocardial infarction were significantly reduced in patients whose isolated systolic hypertension (≥160/<90 mm Hg) was treated with chlorthalidone plus a beta blocker or reserpine if needed, compared with a control group receiving placebo.[17] These results were seen in both men and women, and in both black and white patients.

Diastolic hypertension. All of the major prospective observational studies have required only one baseline blood pressure at the beginning of the study, a practice which can seriously underestimate the prognostic significance of diastolic blood pressure.[20] Accordingly, a recent meta-analysis of several prospective studies introduced a new concept, termed "usual diastolic blood pressure," which reflected the average of the first three biennial examinations at Framingham.[20] The authors found that the usual diastolic blood pressure has a closer relationship to the development of coronary disease and stroke than a single baseline blood pressure measurement does. The relative risk of stroke increases more than 10 times as usual diastolic pressure increases from 76 to 105 mm Hg (*Figure 2*). Similarly, the relative risk of coronary disease increases with diastolic blood pressure, but the incline is less steep: the risk at 105 mm Hg is roughly six times that at 76 mm Hg.

Risk increases with age. A common misconception is that high blood pressure in patients over age 60 or 65 is not a concern. Framingham data show that the total incidence of cardiovascular disease rose progressively with increasing systolic blood pressure, irrespective of age and sex. Risk in subjects of both sexes over age 64 was more than twice as great as that observed for younger persons at the same levels of systolic blood pressure. Elderly patients with definite hypertension (defined by Framingham

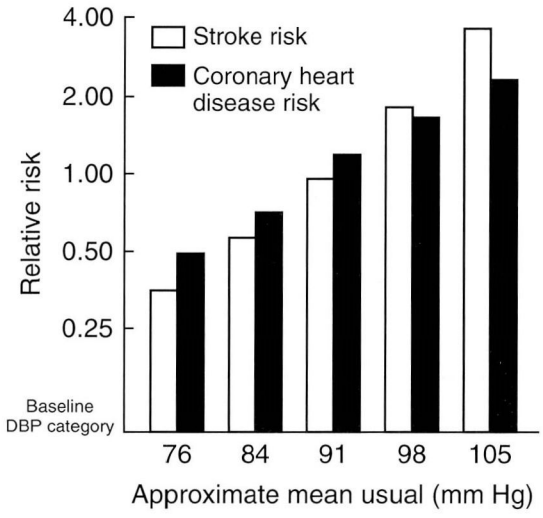

FIGURE 2. Relative risks of stroke and coronary heart disease, estimated from combined results of prospective observational studies. Baseline estimated usual diastolic blood pressures (DBP) are taken from mean DBP values 4 years post-baseline in the Framingham study. Bars indicate the risk of stroke or coronary heart disease in each DBP category. (Adapted from MacMahon et al, reference 20.)

criteria as ≥160/95 mm Hg) had two to three times the risk of cardiovascular events and death as normotensive subjects of the same age and gender. Indeed, because of its high prevalence and sustained effect with increasing age, hypertension has emerged as the dominant risk factor for cardiovascular disease in older persons.[21]

In white men ages 35 to 57 followed for 12 years, the relative risk of coronary heart disease with respect to serum cholesterol, systolic and diastolic blood pressure, and cigarette smoking tended to decrease with age; however, the excess risk attributable to these risk factors in terms of the total number of deaths due to coronary heart disease actually increased with age.[8] Consequently, risk factors cannot be ignored in the elderly.

Cigarette smoking

In a longitudinal study of 2674 persons ages 65 to 74, Jajich et al[11] reported that men and women who smoked 10 to 40 cigarettes a day had twice the risk of dying of coronary heart disease than nonsmokers had; those who smoked more than 40 cigarettes a day had five times the risk (*Table 2*). However, ex-cigarette smokers who stopped for 1 to 5 years had a risk similar to that of nonsmokers. Therefore, if a patient says, "I have smoked for 20 years, so it won't do any good to stop now," the physician can cite these data to demonstrate that it is worthwhile to stop smoking.

Among 316 000 white men ages 35 to 57 screened for MRFIT, the age-adjusted risk ratio for coronary mortality in men who smoked 26 to 35 cigarettes daily was greater than three times that for nonsmoking men after 12 years of follow-up.[8] In this study, coronary mortality was not appreciably greater for men who smoked more than 35 cigarettes a day than for men who smoked 26 to 35 cigarettes a day.

Dyslipidemia

Nothing is new under the sun. In the Bible (Leviticus 7:23–25), God admonishes Moses, "You shall eat no manner of fat, of ox, or of sheep, or of goat . . . For whosoever eateth fat of the beast . . . shall be cut off from his people." This must have been good advice, for "Moses was a hundred and twenty years old when he died; his eye was not dim, nor his natural force abated" (Deuteronomy 34:7).

In the 12-year follow-up of 316 000 white men who were screened for MRFIT, increasing concentrations of total serum cholesterol above 180 mg/dL were directly related to death rate from coronary heart disease.[8] For normotensive, nonsmoking men, the death rate from coronary disease per 10 000 person-years increased from 3.6 when serum cholesterol was less than 180 mg/dL to 11.2 when serum cholesterol was greater than 245 mg/dL.

In the Helsinki Heart Study, the ratio of low-density lipoprotein cholesterol (LDL-C) to high-density lipoprotein cholesterol (HDL-C) was better at predicting coronary disease events than either one alone, and it was also better than total serum cholesterol.[22] Particularly ominous was a ratio of LDL-C to HDL-C greater than 5, combined with a serum triglyceride concentration greater than 204 mg/dL.[22] On the other hand, serum triglycerides did not predict risk when the ratio of LDL-C to HDL-C was 5 or less.

Diabetes and hyperinsulinemia

Diabetes mellitus has long been recognized as a potent risk factor for cardiovascular disease and is frequently associated with other risk factors including obesity, dyslipidemia, and hypertension.[23] While

diabetes is a major risk factor, there is yet no convincing evidence that tight control of blood glucose levels reduces risk.

Increasing evidence suggests that insulin resistance, even in the absence of overt diabetes mellitus, is frequently associated with hypertension, particularly in obese patients, but also in nonobese patients.[24] Insulin resistance is manifested by higher-than-normal levels of circulating insulin, which some have considered to be hypertensinogenic and atherogenic.[24,25] The syndrome of insulin resistance, sometimes called "syndrome X"[25] or the "deadly quartet,"[26] is associated with upper-body obesity,[27] dyslipidemia, and hypertension. Therefore, it is difficult to ascribe independent risk to the high level of insulin per se, although in the Helsinki Policemen Study multivariate analysis suggested that hyperinsulinemia was an independent risk factor.[28] Furthermore, hyperinsulinemia may result from hypertension and an associated increase in sympathetic nervous system activity rather than cause it.[29]

Exercise and weight reduction decrease insulin resistance and ameliorate, if not reverse, the accompanying risk factors.[26]

Left ventricular hypertrophy

Another cardiovascular risk factor is LVH as determined by electrocardiography or echocardiography.[30–32] The all-cause mortality rate and the incidence of coronary artery disease increase significantly in both men and women when echocardiographic evidence of LVH is present. This risk is independent of diastolic blood pressure, cigarette smoking, cholesterol level, and diabetes.[32] Although all commonly used antihypertensive agents except direct vasodilators will cause regression of LVH,[33] no data indicate convincingly that regression will reduce risk.

MINOR MODIFIABLE RISK FACTORS

Obesity

One of the minor modifiable risk factors, obesity is difficult to isolate from major risk factors such as hypertension, dyslipidemia, and diabetes, with which it is frequently associated. The *distribution* of fat in obese patients has more significance than obesity itself.[27] Upper-body obesity, with fat concentrated around the abdomen and in the viscera, is more likely to be associated with coronary artery disease than when the fat is concentrated around the buttocks, hips, and thighs, and when the waist-hip ratio is less than 0.95 for men and 0.85 for women. Consequently, weight reduction is particularly beneficial in patients who have upper-body obesity.

TABLE 2
CORONARY HEART DISEASE MORTALITY AND SMOKING IN MEN AND WOMEN AGES 65 TO 74*

Smoking status	Death rate (per 1000 person-years)
Nonsmoker	25.6
Current cigarette smoker	49.7
10 cigarettes/day	44.0
40 cigarettes/day	50.0
>40 cigarettes/day	122.0
Former cigarette smoker	
1 to 5 years	27.3

*Data from Jajich et al, reference 11

Sedentary life-style

A sedentary life-style is generally considered to be a cardiovascular risk factor, but few data indicate that it is an independent factor. Nevertheless, participating in an aerobic training program helps to control weight, blood pressure, and dyslipidemia, and reduces insulin resistance. Exercise does not have to be vigorous but should be carried out on a regular basis. Even walking briskly five times a week for 30 minutes will be beneficial.[34]

Ethanol

Ethanol has complex effects on risk factors for, and the incidence of, atherosclerotic vascular disease. Consuming more than 1 or 2 ounces of ethanol daily tends to increase blood pressure and the incidence of hypertension.[35] On the other hand, ethanol consumption is directly related to serum HDL-C concentrations.[36] Epidemiologic studies have shown that moderate alcohol consumption is inversely related to incidence of coronary disease in men and women, with abstainers having the highest incidence.[36–38] Moderate alcohol consumption also seems to protect against nonhemorrhagic stroke, increases the risk for hemorrhagic stroke,[38,39] and has no effect on all-cause mortality.[39]

Abstainers should not be advised to start drinking, but those who enjoy drinking should be counseled to limit their intake to no more than 1 ounce

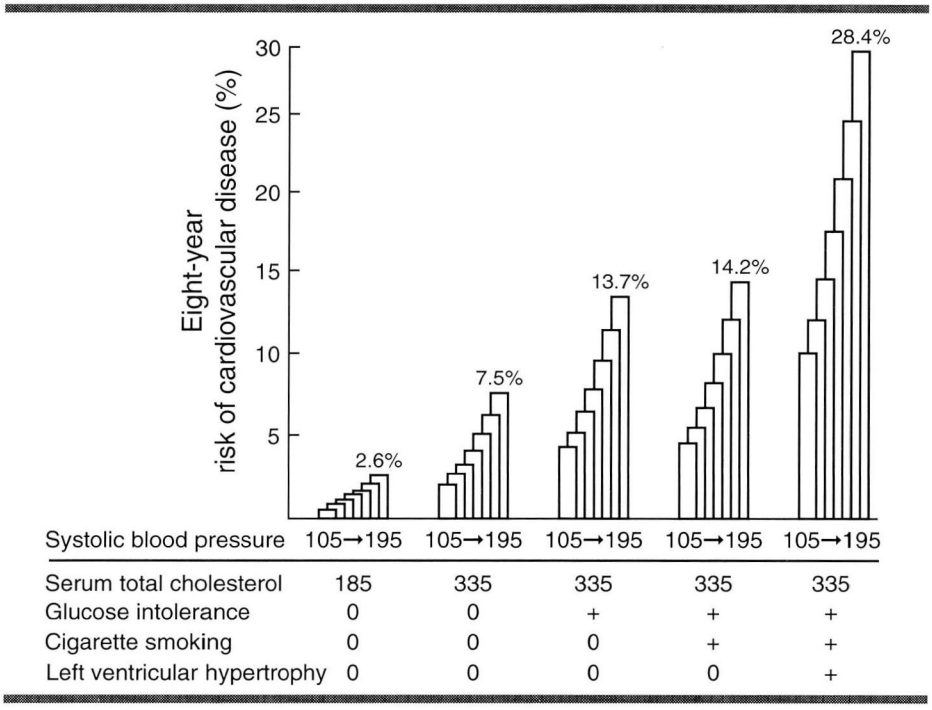

FIGURE 3. Eight-year risk of cardiovascular disease in 40-year-old women is shown to increase according to the number of risk factors present at seven different levels of systolic blood pressure from 105 to 195 mm Hg. (Adapted from Kannel, reference 5.)

of ethanol (ie, 2 ounces of 100-proof whiskey, 8 ounces of wine, or 24 ounces of beer) daily.[1]

Menopause

The prevalence of cardiovascular disease, especially myocardial infarction, is much lower in premenopausal women than it is for men of the same age. This protection for women disappears after menopause, possibly due to loss of estrogen. Estrogen replacement therapy for postmenopausal women reduces cardiovascular risk, perhaps because of its beneficial effect on LDL-C and HDL-C concentrations.[40] Estrogen replacement should therefore be considered, especially for women with other risk factors for atherosclerotic vascular disease.

Renin

Alderman and colleagues[41] have reported that elevated plasma renin activity is a risk factor for myocardial infarction but not for stroke. It is difficult to conceive of a situation in which the level of plasma renin activity would prompt a decision about whether to treat hypertension; therefore, routine determination of plasma renin activity is not recommended for this purpose.

NONMODIFIABLE RISK FACTORS

Fibrinogen

Fibrinogen concentration is an important independent risk factor for stroke and myocardial infarction, especially in patients who already have evidence of atherosclerotic vascular disease.[42] It is a logical assumption that high fibrinogen levels enhance thrombosis, but no mechanism for this has been identified. Until there is a drug that safely and consistently lowers fibrinogen levels, there is no reason to measure fibrinogen routinely in evaluating cardiovascular risk. Although treatment with low-dose aspirin or other antiplatelet drugs has been shown to be effective in preventing stroke and myocardial infarction,[43] this is probably not related to the activity or concentration of fibrinogen.

EFFECT OF MULTIPLE RISK FACTORS

When more than one risk factor is present, the effect is often synergistic rather than additive.[5] For example, in the MRFIT 12-year follow-up, the age-adjusted death rate from coronary heart disease for nonsmoking men was 3.1 per 10 000 person-years when systolic blood pressure was less than 120 mm Hg and serum cholesterol concentration was less than 182 mg/dL. For those with systolic blood pressure over 142 mm Hg, it was 13.7; and for those with serum cholesterol level over 245 mg/dL it was 12.2.[8] On the other hand, for nonsmoking men with both systolic blood pressure over 142 mm Hg and serum cholesterol level over 245 mg/dL, coronary mortality was 33.7 per 10 000 person-years. When three risk factors were combined, as in smokers with systolic pressure over 142 mm Hg and serum cholesterol concentration over 245 mg/dL, the

coronary mortality rate was 62.6 per 10 000 person-years. The addition of LVH and glucose intolerance greatly increases this risk.[9] *Figure 3* shows similar data for 40-year-old women.[5] The risk of coronary heart disease is nearly 10 times as great for diabetic women who smoke 15 to 24 cigarettes per day, compared with diabetic women who do not smoke.[44]

IMPLICATIONS FOR PRACTICE

Clearly, physicians should evaluate the cardiovascular risk profile for every new patient. The components of such an evaluation are listed in *Table 3*. A patient with a history of transient ischemic attacks, angina pectoris, or intermittent claudication already has atherosclerotic disease. Since such patients are even more susceptible to major complications such as a stroke or myocardial infarction, the importance of identifying and addressing other risk factors increases.

In the physical examination, the distribution of body fat should be considered. The presence of xanthomas may indicate an elevated serum cholesterol level. An absence of peripheral arterial pulsations is evidence of occlusive disease in the extremities.

If the serum total cholesterol or triglycerides are elevated, then both the LDL-C and HDL-C levels should be determined. The electrocardiogram should be evaluated for evidence of LVH.

Once risk factors have been identified, therapy and patient education should be instituted for any modifiable factors. Unfortunately, physicians tend to approach a single risk factor of great magnitude more aggressively than multiple risk factors of lesser magnitude.

An example of four 50-year-old men emphasizes the synergistic effect of multiple risk factors. One man has a serum total cholesterol concentration of 300 mg/dL but no other risk factors for atherosclerosis. The second man's only risk factor is smoking three packs of cigarettes a day. The third man's only risk factor is a systolic blood pressure of 195 mm Hg. And the fourth man has a serum total cholesterol level of 235 mm Hg, smokes one pack of cigarettes a day, and has a systolic pressure of 150 mm Hg. Which of these men has the greatest cardiovascular risk?

Their risks are equivalent, and the fourth situation is by far the most common. Such persons account for most cases of heart disease in this country. Attempts to lower their cholesterol levels and blood pressure and to persuade them to stop smoking should be as vigorous as any attempts directed toward single risk factors of greater magnitude.

TABLE 3
EVALUATION OF CARDIOVASCULAR RISK

History
Family history of cardiovascular disease, diabetes, hypertension
Smoking
Exercise habits
Diabetes
Alcohol consumption
Stress
Oral contraceptive use
Gout
Transient ischemic attacks
Angina pectoris
Intermittent claudication
Physical examination
Blood pressure (sitting or supine, and standing)
Pulse rate
Body weight and height
Xanthomas
Carotid bruits
Arterial pulsations
Laboratory
Serum total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol
Serum triglycerides
Serum glucose
Electrocardiography

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