AN UPDATE ON CORONARY RISK FACTORS

William B. Kannel, MD, MPH, and Peter W. F. Wilson, MD

Epidemiologic investigation of coronary heart disease (CHD) continues to yield additional important risk factors. CHD is best conceptualized as a multifactorial process, with no individual factor strictly essential or sufficient for causation. Invariably the hazard posed by any particular risk factor is markedly influenced by other risk factors that are often present. Multivariate risk assessment is required to ascertain the joint effect of risk factors, and use of a set of risk factors provides a substantially better risk estimate than any single factor. Multivariate analyses help attain a better understanding of the pathogenesis of the disease and guidelines for prevention.

Based on the absolute, relative, and attributable risks imposed by the various risk factors, concepts of normal have evolved from usual or average to more optimal values associated with long-term freedom from disease. Acceptable blood pressures, blood glucose levels, and lipid values have as a consequence been revised downward.

Decades of epidemiologic research at Framingham and elsewhere have quantified the effect of cardiovascular risk factors that strongly contribute to coronary disease. There are noteworthy differences in their impact on the various atherosclerotic cardiovascular sequelae. All of the major cardiovascular risk factors identified, however, contribute powerfully to coronary disease.

These various risk factors promote coronary disease in either sex at all ages but with different strengths. Diabetes and low high-density lipoprotein (HDL) cholesterol operate with greater power in women. Cigarette smoking is particularly influential in men, is noncumulative, and loses its adverse impact shortly after quitting. Fibrinogen levels, elevated leukocyte count, homocysti-

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neemia, and Lp(a) lipoprotein are more recent additions to the major risk factors for coronary disease. Some risk factors, such as blood lipids, impaired glucose tolerance, uric acid, and fibrinogen, have smaller risk ratios in advanced age, but this lower relative risk is offset by a high absolute risk. In fact, the major risk factors are relevant in the elderly. Obesity or weight gain promotes or aggravates all the atherogenic risk factors, and physical indolence worsens some of them and predisposes to coronary events at all ages. Systolic blood pressure and isolated systolic hypertension are major risk factors at all ages in either sex. The total-to-HDL cholesterol ratio is currently the most efficient and convenient lipid risk factor.

The Framingham Study and other observational studies have documented several categories of cardiovascular risk factors. These include atherogenic personal attributes, living habits that promote them, indicators of unstable lesions, signs of compromised circulation, and indicators of susceptibility to these influences.

**LIPIDS**

The atherogenic component of the serum total cholesterol is the low-density lipoprotein (LDL) cholesterol, which is also directly related to CHD incidence. The level of HDL cholesterol is inversely related to CHD incidence, consistent with its putative role in cholesterol removal. CHD incidence is independently associated with each of these lipoprotein cholesterol components (Fig. 1). Use of the total-to-HDL cholesterol ratio is recommended by the Framingham Study because this ratio is easy to calculate and was found to be more efficient for detecting coronary candidates than reliance on the LDL cholesterol as recommended by the U.S. Expert Panel Report (Fig. 2).

![Figure 1. Relative risk of CHD according to HDL and LDL with 4 years of follow-up in Framingham Study cohort men. (Adapted from Kannel WB: Lipids, diabetes, and coronary heart disease: Insights from The Framingham Study. Am Heart J 110:1100, 1985; with permission.)](image-url)
Figure 2. Four-year risk of CHD according to lipid ratios in Framingham men 50 to 79 years old at baseline. Average LDL-C/HDL-C and Total-C/HDL-C ratios are given for groups at four risk levels of CHD (morbidity ratio of 100 represents average overall risk). (Adapted from Kannel WB: Lipids, diabetes, and coronary heart disease: Insights from The Framingham Study. Am Heart J 110:1100, 1985; with permission.)

Subclasses of LDL particles have been described using electrophoretic methods. One system uses a pattern A and pattern B classification, and increased rates of CHD have been associated with pattern B. Another classification scheme identifies seven different sizes of LDL particles, ranging from those that are small and dense to those that are large and more buoyant. Coronary disease prevalence was increased in Framingham Offspring participants with small, dense LDL particles, but this association was no longer statistically significant after consideration of traditional lipid risk factors, such as HDL cholesterol and LDL cholesterol.

Lp(a), composed of an LDL particle that is bound to an apoprotein that bears homology to plasminogen, also exists in plasma. Higher concentrations of Lp(a), especially greater than 30 mg/dL (Fig. 3), have been associated with greater relative odds for CHD in most but not all studies. The concentrations of Lp(a) are typically only a few milligrams per deciliter in plasma in white population studies, and it may be that only high values are a risk factor for vascular disease.

The HDL particles also have subclasses. Classification techniques for these particles have evolved over the years, and double precipitation techniques are most commonly used at this time. The blood concentration of the predominant subclasses HDL₂ cholesterol and HDL₃ cholesterol are each highly correlated with the overall total HDL cholesterol, and published reports have failed to demonstrate any significant advantage in measuring the subclasses over and above the determination of the total HDL cholesterol alone.

Blood triglyceride concentration continues to be debated as a CHD risk factor. Both fasting and nonfasting triglyceride levels were associated with CHD risk in Framingham and other investigations. The debate centers around whether total triglycerides are significantly associated with CHD risk after adjustment by HDL cholesterol in prediction equations. Analyses of Lipid Research Clinics
Figure 3. Relative risk for CHD over 7 to 10 years of follow-up according to Lipoprotein (a) in men 35 to 59 years old at baseline who participated in the Lipid Research Clinics Program. (Adapted from Schaefer EJ: Lipoprotein (a) levels and risk of coronary heart disease in men: The Lipid Research Clinics Coronary Primary Prevention Trial. JAMA 274:1002, © 1994, American Medical Association; with permission.)

(LRC) and Framingham data\(^{16,112}\) show a significant impact of triglyceride levels after HDL cholesterol adjustment and that these relationships are more consistently demonstrated if logarithmic transformations of the lipid levels are used in the calculations. In addition, the residual effect of triglycerides after consideration of HDL cholesterol appears to be greater in women than in men.

**BLOOD PRESSURE**

Hypertension is a well-acknowledged CHD risk factor (Table 1), and the systolic pressure is at least as powerful a coronary risk factor as the diastolic pressure,\(^{55}\) and isolated systolic hypertension is now established as a major hazard for CHD and stroke (Fig. 4).\(^{106}\) Despite the established contribution of

<table>
<thead>
<tr>
<th>Cardiovascular Event</th>
<th>Age-Adjusted Biennial Rate Per 1000</th>
<th>Age-Adjusted Risk Ratio</th>
<th>Excess Risk per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>45</td>
<td>21</td>
<td>2.0*</td>
</tr>
<tr>
<td>Stroke</td>
<td>12</td>
<td>6</td>
<td>3.8*</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>10</td>
<td>7</td>
<td>2.0*</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>14</td>
<td>6</td>
<td>4.0*</td>
</tr>
<tr>
<td>Total cardiovascular disease</td>
<td>65</td>
<td>35</td>
<td>2.2*</td>
</tr>
</tbody>
</table>

\(^{*}P < 0.0001.\)

Unpublished Framingham data.
blood pressure to CHD incidence, controlled trials have been inconsistent in showing benefit of treatment. Antihypertensive agents commonly used in the trials have unwanted metabolic effects on lipids and carbohydrate tolerance, which could have attenuated the benefit of the blood pressure lowering. Because the excess risk of hypertension is concentrated in the subgroup with other risk factors, it is they who stand to benefit from antihypertensive therapy, and, unless the risk profile is improved by therapy, benefit is unlikely.

**GLUCOSE METABOLISM**

Insulin resistance, hyperinsulinemia, and glucose intolerance have been reported to be atherogenic. Diabetes, impaired glucose tolerance, and high-normal levels of glycosylated hemoglobin in the Framingham Study were powerful contributors to atherosclerotic cardiovascular events, particularly in women (Table 2). Diabetics have a greater burden of atherogenic risk factors than nondiabetics. These include elevated blood pressure, raised triglycerides, increased total-to-HDL cholesterol ratio, hyperuricemia, elevated fibrinogen, and left ventricular hypertrophy (LVH). The risk of CHD in diabetics varies widely with the intensity of these cardiovascular risk factors.

Diabetics and hypertensive persons have been noted in the Framingham Study to be especially at risk for unrecognized myocardial infarctions, necessitating periodic surveillance with routine electrocardiogram (ECG) examinations (Table 3). Hypertension, obesity, insulin resistance, hyperinsulinemia, hypertriglyceridemia, and low HDL cholesterol tend to coexist as an insulin-resistance syndrome and jointly accelerate atherogenesis. A few prospective studies have demonstrated that insulin levels, either fasting or drawn 2 hours after a standard
oral glucose load, may help in the prediction of CHD over and above traditional risk factors.\textsuperscript{24, 76, 100}

**HEMATOLOGIC FACTORS**

The leukocyte count and the plasma fibrinogen each may indicate active, fissuring atherosclerotic lesions that undergo an inflammatory response to cholesterol and subintimal hemorrhage.\textsuperscript{21, 26} Prospective epidemiologic studies indicate that CHD incidence is related to the antecedent leukocyte count within the normal range.\textsuperscript{21, 26, 52} Also the leukocyte count has been found to be correlated with most of the established cardiovascular risk factors, particularly with cigarette smoking, fibrinogen, and hematocrit. In the Framingham Study, the 12-year-age-adjusted incidence of CHD increased progressively in each sex with each tertile increment in leukocyte count, over a threefold range in men and twofold range in women. There was an independent effect of the leukocyte count. One standard deviation increment in leukocyte count (1.15 $\times$ 10\(^9\)/L) in male nonsmokers from Framingham was associated with a 42% increase in CHD

Table 2. RISK OF CARDIOVASCULAR EVENTS IN DIABETICS: 36-YEAR FOLLOW-UP OF FRAMINGHAM SUBJECTS 35–64 YEARS OLD

<table>
<thead>
<tr>
<th>Cardiovascular Event</th>
<th>Age-Adjusted Biennial Rate Per 1000</th>
<th>Age-Adjusted Risk Ratio</th>
<th>Excess Risk per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>39</td>
<td>21</td>
<td>1.5*</td>
</tr>
<tr>
<td>Stroke</td>
<td>15</td>
<td>6</td>
<td>2.9†</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>18</td>
<td>18</td>
<td>3.4†</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>23</td>
<td>21</td>
<td>4.4*</td>
</tr>
<tr>
<td>Total cardiovascular disease</td>
<td>76</td>
<td>65</td>
<td>2.2†</td>
</tr>
</tbody>
</table>

*\(P <0.001\).
†\(P <0.0001\).

Unpublished Framingham data.

Table 3. PROPORTION OF MYOCARDIAL INFARCTION UNRECOGNIZED BY HYPERTENSIVE AND DIABETIC STATUS: 34-YEAR FOLLOW-UP OF FRAMINGHAM SUBJECTS 35–64 YEARS OLD

<table>
<thead>
<tr>
<th>Status</th>
<th>Diabetes</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Absent</td>
<td>27.3</td>
<td>34.1*</td>
</tr>
<tr>
<td>Present</td>
<td>40.7*</td>
<td>30.3</td>
</tr>
<tr>
<td>All</td>
<td>28.8</td>
<td>37.6</td>
</tr>
</tbody>
</table>

*\(P <0.05\).
†\(P <0.10\).

Unpublished Framingham data.
Table 4. INCREMENT IN CARDIOVASCULAR DISEASE INCIDENCE PER 1000 INCREASE IN LEUKOCYTE COUNT: 12-YEAR FOLLOW-UP OF FRAMINGHAM STUDY

<table>
<thead>
<tr>
<th>Percent Increment in Cardiovascular Risk</th>
<th>Smokers</th>
<th>Non-Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>3</td>
<td>32†</td>
</tr>
<tr>
<td>Women</td>
<td>17*</td>
<td>8</td>
</tr>
</tbody>
</table>

*\( p < 0.05.\)
†\( p < 0.001.\)


Incidence.\(^2\) In men, but not women, the excess risk associated with a high normal white blood cell count was confined to nonsmokers (Table 4). The impact of white blood cell count elevation on risk rivals that of the other major established risk factors.

Fibrinogen (also within the usual range) was found be another major independent risk factor in several population studies, including Framingham (Fig. 5).\(^2\)\(^5\)\(^9\) A significant age-adjusted relationship of fibrinogen with CHD incidence was found in men (Table 5). Cardiovascular disease, CHD, and all-cause mortality were all increased in those with high normal fibrinogen in both sexes, and this excess mortality persisted on adjustment for the standard risk factors. Fibrinogen was found to enhance risk of the hypertensive, the cigarette smoker, and the diabetic candidate for CHD. Other hematologic factors have been linked to CHD as well. These included increased concentrations of tissue plasminogen activator (tPA) antigen, as described in a report from the Physicians Health Study.\(^7\)\(^9\)

![Figure 5. Summary estimates of the relative odds for cardiovascular disease associated with fibrinogen. (Adapted from Ernst E: Fibrinogen as a cardiovascular risk factor: A meta-analysis and review of the literature. Ann Intern Med 118:956, 1993; with permission. The American College of Physicians is not responsible for the accuracy of the translation.)](image-url)
Table 5. RISK OF CARDIOVASCULAR EVENT ASSOCIATED WITH ELEVATED FIBRINOGEN: 16-YEAR FOLLOW-UP OF FRAMINGHAM SUBJECTS 45–84 YEARS OLD

<table>
<thead>
<tr>
<th>Cardiovascular Events</th>
<th>Age-Adjusted 10-Year Rate Per 1000</th>
<th>Risk Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>304</td>
<td>134</td>
</tr>
<tr>
<td>Stroke</td>
<td>95</td>
<td>51</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Cardiovascular disease†</td>
<td>407</td>
<td>228</td>
</tr>
</tbody>
</table>

*Risk ratio third tertile/first fibrinogen.
†Cardiovascular disease events include cardiac failure.
‡P <0.001.
§P <0.05.
‖P = NS.
¶P <0.01.


Myocardial infarction rates appear to peak between 6 A.M. and noon, and the increased incidence during the period shortly after rising may relate to transiently increased coagulability and platelet aggregation.70, 103 Low-dose aspirin, an inhibitor of platelet aggregation, as used in the Physicians Health Study clinical trial and other similar investigations, appears to reduce the incidence of myocardial infarction effectively.27, 97

OTHER METABOLIC ISSUES

Both cross-sectional and prospective studies have now linked increased levels of homocystine to increased risk for CHD.31 In a study of elderly Framingham participants, it was noted that higher homocystine levels were frequently accompanied by decreased levels and intake of folate and vitamin B_{12}.86 This biologic link suggests that increased vitamin intake in the diet, or through supplementation, may be a potential way to decrease homocystine levels and improve CHD and other vascular disease risk.

The oxidation of LDL particles appears to be associated with increased risk of atherosclerosis in animal models,98 and there is growing interest to study the phenomenon in humans. Data on CHD and oxidation in populations have largely focused on the role of antioxidants, particularly vitamin E and beta-carotene. Increased intake of these nutrients, particularly vitamin E, has been associated with lower rates of CHD in both The Nurses Health Study and the Health Associates Study (Fig. 6).81, 94 Each report was based on observational data, and clinical trials to test the hypothesis that antioxidant vitamins protect against CHD are now being conducted.

CHD incidence increases in women after menopause and is believed to be secondary to a decrease in natural estrogen levels. Postmenopausal hormone replacement with low-dose exogenous estrogens in the 1980s and 1990s has consistently shown a cardioprotective influence.6, 11, 93 Because the risk of endometrial hyperplasia and uterine cancer may be increased among women of this age who take estrogens unopposed by progestins,29 it has become standard use to include progestins as part of the regimen. If low-dose progesterational preparations are included, favorable effects on the lipid profile have been demon-
The Postmenopausal Estrogen Progestin Intervention (PEPI) was designed to address the tolerability of such regimens, their effects on risk factors, and overall health benefit.

LIFESTYLE

The prevailing lifestyle that promotes CHD is characterized by unrestrained weight gain, cigarette smoking, and lack of exercise. Type A behavior typified by an overdeveloped sense of time urgency, drive, hostility, and competitiveness has been inconsistently found to predispose to CHD in large, prospective studies. Spouses of highly educated women in the Framingham Study were found to be at increased risk of coronary disease if their wives worked outside the home.

Diets rich in calories, saturated fat, and cholesterol contribute to risk factors that predispose to CHD. Weight gain promotes the major cardiovascular risk factors, and weight loss improves them. Obesity-induced risk factors include hypertension, glucose intolerance, insulin resistance, hypertriglyceridemia, reduced HDL cholesterol, hyperuricemia, and elevated fibrinogen. Abdominal obesity is a particularly atherogenic variety of adiposity. Largely as a result of these induced atherogenic risk factors, overweight and weight gain are associated with an increased incidence of coronary disease.

Exercise of even moderate degree has now been found to have a protective effect against CHD in young and old men, as exemplified by data from the Framingham Cohort. This protection has been noted at any level of other risk factors. A more physically active lifestyle is a useful component of a comprehensive risk reduction program because it raises HDL cholesterol, helps lower blood pressure, improves insulin resistance, and helps control overweight. It may also afford some independent protection against CHD.

Cigarette smoking is a dangerous risk factor for CHD because it lowers HDL cholesterol, raises fibrinogen, aggregates platelets, decreases the oxygen-
carrying capacity of the blood, and causes release of catecholamines making the myocardium more irritable. Because of these effects, smoking precipitates coronary attacks and sudden deaths, particularly in coronary candidates with other risk factors or a compromised arterial circulation. Even among persons who have smoked heavily in the past, risk of coronary events can be halved by smoking cessation, compared with those who choose to continue smoking. This benefit of cessation accrues regardless of how long or how much persons have previously smoked.

Epidemiologic data indicate a protective effect of alcohol intake in moderation for CHD. This benefit applies only at moderate intakes; is not seen with alcohol abuse; and does not apply for hemorrhagic stroke, traumatic death, or cancer, which may be increased at higher levels of reported alcohol intake.

SLEEP DISTURBANCE

There are at least six studies, three of them prospective, that have shown an association between sleep disturbance and occurrence of CHD. Excess risk has been noted in persons complaining of difficulty in falling asleep, difficulty in staying asleep, awaking too early, and waking up feeling tired and worn out.

Snoring, a common symptom of sleep-disordered breathing, has been implicated in hypertension, coronary disease, and stroke. These sequelae have been attributed to a high prevalence of obstructive sleep apnea among habitual snorers. Reported relative risks of CHD and strokes range from 1.5 to 4.0 in snorers versus nonsnorers. Hypertension is common in sleep apnea, and some 22% to 60% of hypertensive persons may have sleep apnea. Persons with sleep apnea or heavy snoring have been reported to have as much as a 50% reduction in blood flow to the brain during REM sleep, which may explain its association with the occurrence of strokes. Sleep apnea is also common and may affect 30% or more of the elderly.

ELECTROCARDIOGRAM AND LEFT VENTRICULAR HYPERTROPHY PREDICTORS

ECG abnormalities in asymptomatic persons at rest and during exercise often indicate an ischemic myocardium because of a compromised coronary circulation. ECG LVH, blocked intraventricular conduction, and even nonspecific repolarization abnormality are all hazards for CHD. Major population determinants of LVH include blood pressure, body weight, alcohol intake, and glucose intolerance. ECG and anatomic LVH (enlarged cardiac silhouette on a chest roentgenogram) each independently influence risk of cardiovascular disease in the Framingham Study. The ECG version is more ominous than the roentgenographic version, but those who have both are at greater risk than those with either alone.

ECG, radiographic and echocardiographic indications of LVH are common in the course of hypertension, diabetes, or progressing obesity. LVH is not an incidental compensatory phenomenon because manifestations of atherosclerosis occur at two to three times the general population rate in persons who develop ECG LVH. Investigations in Framingham indicate that both ECG and echocardiographic evidence of LVH impose an increased risk. Cardiovascular events occur in proportion to the degree of increase in left ventricular mass with no
FAMILIAL AND GENETIC PREDISPOSITION

Innate susceptibility to CHD is often denoted by a family history of premature cardiovascular disease. Framingham Study subjects who had a brother who developed coronary disease were at more than a doubled risk of CHD, and increased risk was not entirely attributable to shared risk factors. A family history of a coronary death in parents of Framingham cohort subjects was associated with a 30% independent increased risk of coronary disease. A positive family history predisposed to an early CHD event. This adverse effect of a positive parental history of CHD death was also not entirely mediated by shared risk factors.

Data suggest that the presence of the apolipoprotein E ε4 allele is associated with dyslipidemia and an increased risk of CHD among middle-aged men and women. This marker is present in approximately 25% of the population and is associated with a relative odds of approximately 1.6 for CHD. Data for an angiotensin-converting enzyme polymorphism and for an angiotensinogen gene also suggest potentially increased CHD risk, and several confirmatory investigations are underway.

PREVENTION IN THE ELDERLY

Disability and death from cardiovascular disease are major problems in the elderly, who constitute the fastest growing segment of most affluent populations. In the United States, approximately this 11% of the population accounts for 29% of health costs, and cardiovascular disease is responsible for 70% of all deaths beyond age 75. Atherosclerosis, hypertension, and diabetes are responsible for most of the cardiovascular disease afflicting the elderly.

The major cardiovascular risk factors also impact in the elderly. Hypertension, dyslipidemia, impaired glucose tolerance, physical indolence, and cigarette smoking are all highly prevalent in the elderly. With aging, there is also a longer exposure to these risk factors and a diminished capacity to cope with them.

There is a somewhat attenuated impact of some risk factors in the elderly, which is offset by a greater absolute risk of coronary disease. The multivariate coronary risk profile predicts coronary events as efficiently in the elderly as in the young, making it possible to target high-risk candidates efficiently for treatment. Because of its high prevalence and sustained impact, hypertension is a dominant risk factor for coronary disease in the elderly, whether the hypertension is systolic or diastolic. Isolated systolic hypertension, which is especially common in the elderly, is a major hazard.

Blood lipids are also relevant, particularly the LDL-to-HDL cholesterol ratio and the serum triglyceride. Exercise appears to sustain its protective effect in advanced age. Diabetes independently promotes coronary disease in the elderly, especially in women. Rapid heart rates in men and reduced vital capacity in women are also important risk factors for coronary disease and cardiac failure. Elevated fibrinogen remains associated with coronary disease in advanced age. ECG evidence of LVH and nonspecific repolarization abnormality often indicate
an ischemic myocardium in the elderly and are associated with increased risk of coronary events.

Proof of the efficacy of modifying risk factors in older persons is limited, but declines in coronary mortality in the United States have included the elderly, which justifies optimism. More evidence of the efficacy of modifying risk factors in the elderly is needed because extrapolation from demonstrated benefits of preventive measures in the middle-aged may be too speculative.

POST–MYOCARDIAL INFARCTION RISK FACTORS

Analysis of myocardial infarction survivors in the Framingham Cohort indicated that the risk of reinfarction is increased in persons with elevated blood pressure and serum cholesterol. It has been estimated that a 10% reduction in blood cholesterol in persons who have sustained a myocardial infarction would be associated with a 19% reduction in nonfatal reinfarctions. Coronary mortality was strongly associated with blood glucose, systolic blood pressure, serum cholesterol, heart rate, and diabetes. In multivariate analysis, systolic blood pressure, serum cholesterol, and diabetes were independent risk factors. Curiously, relative weight was inversely associated with reinfarction.

Left ventricular mass by echocardiogram in men and left ventricular end-diastolic diameter in women were independent predictors of new cardiovascular disease events in the Framingham Cohort (Table 6). Cardiovascular risk was also associated with left ventricular end-systolic diameter in both sexes. Reduced fractional shortening in men, LVH and high end-systolic diameter in women, and the combination of low fractional shortening and left ventricular dilatation in both sexes were associated with the incidence of clinical outcome.

Following a myocardial infarction, women are at higher risk of reinfarction and death than are men. When adjustment is made for the effects of the higher burden of risk factors at time of infarction, however, women with myocardial infarction have only half the risk of death of men with infarctions. Congestive heart failure is an increasingly important diagnosis in the elderly and is often preceded by a myocardial infarction, although a history of hypertension, valvu-

<table>
<thead>
<tr>
<th>Cardiovascular Event</th>
<th>Men</th>
<th>Women</th>
<th>Age-Adjusted Biennial Rate Per 1000</th>
<th>Age-Adjusted Risk Ratio</th>
<th>Excess Risk per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>79</td>
<td>55</td>
<td>3.0*</td>
<td>4.6*</td>
<td>52</td>
</tr>
<tr>
<td>Stroke</td>
<td>29</td>
<td>20</td>
<td>5.8*</td>
<td>6.2*</td>
<td>24</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>16</td>
<td>17</td>
<td>2.7*</td>
<td>5.3*</td>
<td>10</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>71</td>
<td>36</td>
<td>15.0*</td>
<td>12.8*</td>
<td>67</td>
</tr>
<tr>
<td>Total cardiovascular disease</td>
<td>164</td>
<td>135</td>
<td>4.7*</td>
<td>7.4*</td>
<td>129</td>
</tr>
</tbody>
</table>

*P < 0.0001.
†P = NS.
Unpublished Framingham data.
lar disease, and other diagnoses may be precursors. If congestive heart failure intervenes following a myocardial infarction, the overall prognosis is poor, and recurrent myocardial infarction and cardiovascular death are particularly increased in affected persons.44

MULTIVARIATE RISK PROFILES

CHD risk can now be conveniently estimated from ordinary office procedures and simple laboratory tests (Table 7). Trials have been undertaken to examine the prospects for primary prevention by correcting risk factors, and some, such as the antihypertension trials, have been disappointing, probably because of failure to improve the multivariate risk profile.15

Categorical risk assessments according to the number of arbitrarily defined risk factors identify high-risk persons, but they tend to reassure persons at high risk falsely because of multiple marginal abnormalities. The segment of the population with borderline abnormalities of blood pressure and lipids yields most of the coronary events, so it is important not to overlook them. Multivariate risk factor formulations have been produced that facilitate estimation of the conditional probability of a coronary event, which can be compared with the average risk for persons the same age (Table 7, Fig. 7).1

SECULAR TRENDS

Declining cardiovascular coronary mortality over the past three decades in the United States is well documented, but the reasons for the decline are uncertain. Framingham Study cohort data were explored to examine the relation of change in risk factors to cardiovascular mortality over three decades.101 The 10-year cumulative cardiovascular mortality in the 1970 cohort was found to be 43% lower than that in the 1950 and 37% less than that in the 1960 cohort. Among the men who were free of cardiovascular disease at baseline, the 10-year cumulative incidence of cardiovascular disease declined approximately 19% whereas the 10-year cardiovascular death rate declined 60%.

There were significant improvements in risk factors for cardiovascular disease between 1950 and 1970 in men free of cardiovascular disease, which included lower serum cholesterol, lower systolic blood pressure, and reduced cigarette smoking. These improvements in cardiovascular risk factors over the decades appear to have made an important contribution to the 60% decline in mortality noted. There was not a comparable decline in incidence of cardiovascular disease, however.7, 42, 102 Improved medical care and lifestyle changes may have contributed importantly to the observed decline in mortality.34

PREVENTIVE IMPLICATIONS

Epidemiologic data demonstrating the hazards of elevated blood pressure and blood lipids prompted trials to determine the benefits of treating mild hypertension and hypercholesterolemia. These trials and the availability of a variety of pharmaceuticals that can effectively lower blood pressure, raise HDL cholesterol, and reduce LDL cholesterol, without inducing dangerous side effects, produced national guidelines for early detection and control of blood lipids and blood pressure. Clinical trials to lower blood cholesterol by drugs
Table 7. CORONARY HEART DISEASE RISK FACTOR PREDICTION CHART

1. Find Points for Each Risk Factor

<table>
<thead>
<tr>
<th>Age (If Female)</th>
<th>Points</th>
<th>Age (If Male)</th>
<th>Points</th>
<th>HDL-Cholesterol</th>
<th>Total-Cholesterol</th>
<th>Systolic Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age</td>
<td>Points</td>
<td>Age</td>
<td>Points</td>
<td>HDL-C Points</td>
<td>Total-C Points</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>-2</td>
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</table>
2. Sum Points for All Risk Factors

\[
\text{Age} + \text{HDL-C} + \text{Total-C} + \text{SBP} + \text{Smoker} + \text{Diabetes} + \text{ECG-LVH} = \text{Point Total}
\]

NOTE: Minus Points Subtract from Total.

3. Look Up Risk Corresponding to Point Total

<table>
<thead>
<tr>
<th>Points</th>
<th>5 Year Probability</th>
<th>10 Year Probability</th>
<th>Probability</th>
<th>Probability</th>
<th>Probability</th>
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<td>7%</td>
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<tr>
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<td>2%</td>
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<td>3%</td>
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<td>3%</td>
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<td>4%</td>
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<tr>
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<td>3%</td>
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</tr>
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<td>5%</td>
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4. Compare To Average

<table>
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<th>Age</th>
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<td>60-64</td>
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<td>65-69</td>
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<td>70-74</td>
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</tbody>
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These charts were prepared with the help of William B. Kannel, MD, Professor of Medicine and Public Health, and Ralph D'Agostino, PhD, Head, Department of Mathematics, both at Boston University; Keeven Anderson, PhD, Statistician, NHLBI, Framingham Study; Daniel McGee, PhD, Associate Professor, University of Arizona. Framingham Heart Study. *Risk Factor Prediction Kit*, © 1990, American Heart Association; reproduced with permission.
Figure 7. Estimated 10 years’ risk of CHD according to various combinations of risk factor levels. (Estimates derived from equations provided by Anderson KM: An updated coronary risk profile: A statement for health professionals. Circulation 83:357, 1991.)

and diet have shown convincing benefits for CHD and angiographically evaluated lesions. The trials of antihypertensive treatment have been consistently successful in preventing strokes but have been relatively disappointing against CHD except in the SHEP Trial for isolated systolic hypertension. For coronary disease, it is likely that longer duration of treatment with agents that do not adversely affect other features of the coronary risk profile, such as lipids or glucose tolerance, is required.

Although rational for coronary risk reduction, controlled trial evidence to show the benefits of exercise, weight control, smoking abatement, and correction of hyperglycemia is lacking. These measures are likely to be effective, however, and are worthwhile for other reasons as well. Optimal preventive management of coronary candidates should be multifactorial. Preventive strategies should include public health measures that improve the distribution of risk factors to more favorable average levels, health education to enable people to protect their own health, and preventive medicine for high-risk candidates requiring drugs. Implementation of preventive measures, such as diet modification, exercise, smoking abatement, and weight reduction, requires behavior modification and community efforts to promote healthy lifestyles.

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