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Prediction of Coronary Heart Disease Events Part 1: The role of traditional risk factors

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Coronary heart disease (CHD) is largely attributable to arteriosclerosis, a disease process that develops insidiously in late adolescence and early adulthood, although the clinical sequelae are often not manifest until after age 45 years. In the Third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988-1994, CHD was consistently more common in men than in women aged <75 years.[1]

The term "risk factor" was first used in publications associated with the Framingham Heart Study in the late 1950s and early 1960s. Analyses described higher levels of cholesterol, blood pressure, and cigarette smoking that together augmented the chances of developing CHD over 6 years of follow-up. However, as single factors, they were generally not responsible for the development of clinical vascular events (Figure 1). Since that time, a variety of advances have led to the development of key factors that are both easy to assess and consistently related to a greater risk of initial CHD events; these factors include age, gender, blood pressure, lipids, smoking, and diabetes mellitus.

Part 1 of this discussion, presented in this issue of *Cardiology Rounds*, will focus on traditional risk factors and how they can be used to estimate risk for an initial CHD event using separate equations for men and women. Part 2 of this topic, which will be presented in next month's *Cardiology Rounds*, will focus on the lifestyle aspects that underlie these risk factors, as well as newer factors for multivariable CHD risk assessment such as metabolic syndrome, genetic abnormalities, and subclinical cardiovascular and kidney disease.

Age and gender

The type of clinical CHD event that occurs first varies by age and sex. For example, angina pectoris is the most common first CHD event in women, followed by myocardial infarction (MI) and CHD death; unheralded sudden cardiac death without a preceding clinical event is relatively uncommon in women. On the other hand, among men, an MI is the most common first CHD event, followed by angina pectoris, and sudden coronary death is, unfortunately, not uncommon.[2]

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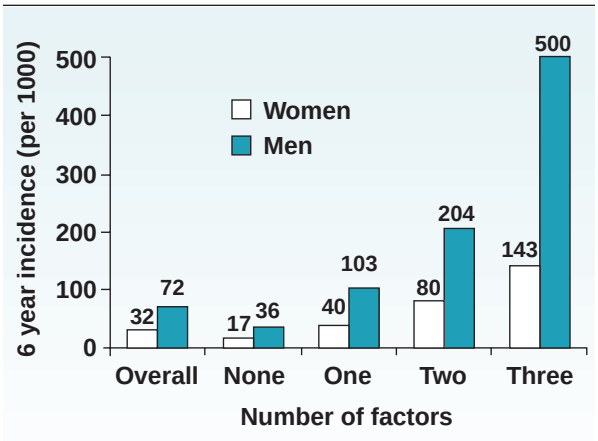
Figure 1: Risk of CHD according to elevated BP, elevated cholesterol and left ventricular hypertrophy. Framingham Cohort 6-year follow-up



Elevated BP (>160/95 or therapy), cholesterol (>260 mg/dL)

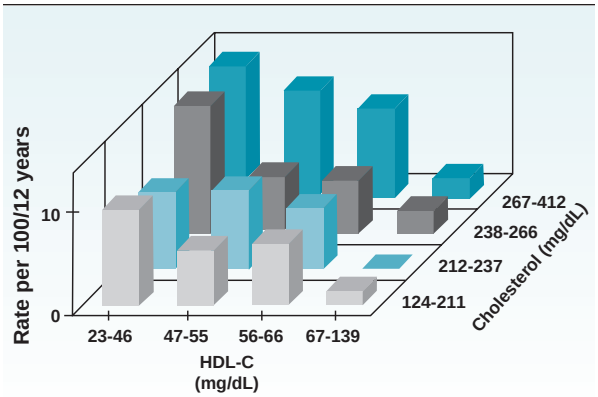
Kannel WB et al. Factors of risk in the development of coronary heart disease – 6-year follow-up experience. The Framingham Study. *Ann Intern Med* 1961;55:33-50.

In women, CHD tends to occur after menopause and rates are significantly higher than for other common diseases of aging (eg, fractures, cerebrovascular disease, breast cancer, and uterine cancer). Decreased estrogen production after menopause has been thought to be an important determinant of the increased risk of CHD in older women. The majority of observational studies undertaken in the 1970s and 1980s showed consistently lower CHD rates with use of postmenopausal estrogens.[3-5] Meta-analyses of observational studies have estimated a 50% reduction in the risk of a first heart attack with postmenopausal estrogens,[6] but randomized clinical trials from the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative prevention trial have not confirmed the observational study reports.[7-9]

Lipids

Higher levels of cholesterol have been consistently related to a greater risk for CHD. For example, in approximately 350,000 middle-aged men screened for the Multiple Risk Factor Intervention Trial (MRFIT), higher cholesterol levels led to an increased risk of cardiovascular disease (CVD) death.[10] Using a cholesterol level of 200 mg/dL as the comparison, a level of 250 mg/dL led to a 2-fold increased risk, while a level of 300 mg/dL led to a 3-fold increased risk of CVD death.[11]

Figure 2: 12-year incidence of myocardial infarction Framingham Cohort – Women



Abbott RD et al. High density lipoprotein cholesterol, total cholesterol screening and myocardial infarction. The Framingham Study. *Arteriosclerosis* 1988;8(3):207-11.

High-density lipoprotein (HDL) cholesterol is a major fraction of cholesterol in plasma and an important determinant of risk for CHD and MI, even when the total cholesterol level is known. The 12-year incidence of MI was positively related to cholesterol level and inversely related to HDL cholesterol level in Framingham women (Figure 2).[12] If the total cholesterol level was <211 mg/dL, HDL cholesterol levels were inversely related to risk of developing an MI in women. Similar results were obtained for men in other studies, helping to provide the rationale for total cholesterol, as well as HDL cholesterol screening to assess CVD risk.

Effective lipid therapies over the past 2 decades have demonstrated that improving total, low-density lipoprotein (LDL), and HDL cholesterol levels – with the emphasis on lowering the LDL fraction – leads to a reduced risk of initial and recurrent CHD events. In general, more cholesterol lowering has led to a greater reduction in the risk of initial and recurrent CHD in these studies. The effectiveness of therapy in these trials has largely been premised on the intention-to-treat, not on the ability to reach predefined target levels of cholesterol or LDL cholesterol.

Blood pressure

Although the age-adjusted prevalence of high blood pressure (BP) decreased in several ethnic groups in the U.S. during the late 1970s to 1990s, elevated BP remains a very important risk factor for the development of

CHD. U.S. national data from the 1990s reveal that although approximately 50% of persons with high BP are treated, only 15% to 24% are under control and a sizable fraction – ranging from 27% to 41% of persons with high BP – are unaware that they are affected.[13]

Typically, levels of systolic BP are more highly associated with the development of CHD than levels of diastolic BP. Systolic and diastolic hypertension generally confer a relative risk of 1.6 for CVD; for combined systolic and diastolic hypertension, the relative risk is 2.0.[14,15] Wider pulse pressure is also related to CVD outcomes, especially in older persons, as diastolic pressures are typically lower in the elderly than those observed in middle-aged people.[16]

Even BP levels that do not meet the current criteria for hypertension increase the risk for a first major vascular event. Long-term comparisons have shown that the risk of CVD is increased in persons with high normal BP (systolic BPs of 130-139 mm Hg and diastolic BPs of 85-89 mm Hg). Since high normal BP levels are common, this level of BP accounts for a sizable fraction of CVD events and, on a population basis, is nearly as important as hypertension itself.[17]

Summary analyses of BP treatment trials show convincing evidence that lower BP levels generally reduce the risk of CHD and cerebrovascular events. Newer efforts are also investigating the simultaneous lowering of BP and lipids; eg, the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) study of >40,000 U.S. participants and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which used BP medications and more statin therapies.[18,19]

Smoking

The prevalence of cigarette smoking has declined in the U.S. since the 1960s. This habit generally doubles the risk of vascular outcomes. Both regular and filter cigarettes have similar adverse effects on CHD risk[20] and low tar and low nicotine cigarettes have not been demonstrated to reduce CVD risk in comparison with standard products.[21] In men screened as part of the MRFIT study, cessation of cigarette smoking cut the risk for CVD death by half, 1 to 2 years after quitting.[22]

Passive smoking has been related to an increased risk of CHD that is approximately 30% greater than the risk for non-smokers.[23] It has also been reported that, compared to non-smokers, persons exposed to environmental smoke have increased intima-media thickness of their carotid arteries, an indication of subclinical arteriosclerosis.[24]

Diabetes mellitus

Risk of CHD is generally increased 2-fold among younger men and 3-fold among younger women with type 2 diabetes mellitus.[25] Data from Finland have suggested that the risk for a heart attack in a person with diabetes is very similar to the risk in a person who has had a heart attack and is at risk for a subsequent heart attack. This result led to the concept of type 2 diabetes mellitus as a CHD risk equivalent and emphasized the need for aggressive treatment of risk factors in persons with type 2 diabetes mellitus to prevent CVD events.[26]

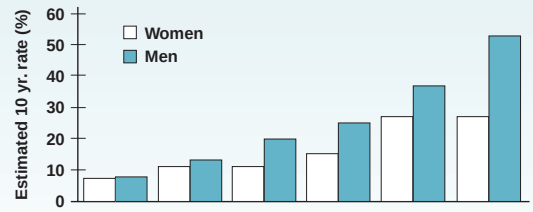
Cardiovascular risk reduction efforts have only recently targeted persons with type 2 diabetes mellitus and lower thresholds for LDL cholesterol and BP are now being recommended for people with this disease.[27-29] The basis for this aggressive approach comes from subgroup analyses of the treatment effects of lowering BP and lipids in type 2 diabetics in randomized clinical trials. The efficacy of this approach has been published in a Danish trial that studied aggressive combination therapies for hyperglycemia, hypertension, dyslipidemia, and microalbuminuria in persons with type 2 diabetes mellitus.[30]

Data supporting concerted glucose control as a prevention strategy for CVD have been reinforced by observational studies. In addition, more aggressive glucose control has led to impressive glucose and HbA_{1C} data in clinical trials studying the prevention of small vessel disease in the eye and kidney, with a smaller degree of added benefit observed for atherosclerotic events.[31-35] This issue is being addressed with ongoing, large-scale, multifactorial intervention trials in patients with type 2 diabetes mellitus.

Multivariable CHD risk estimation

Risk for CVD events can be estimated with multivariable prediction equations that use a score sheet, pocket calculator, or computer. These variables – age, systolic BP, smoking, cholesterol, HDL cholesterol,

Figure 3: Estimated coronary heart disease risk according to combinations of risk factors in persons aged 55 years followed for 10 years[36]



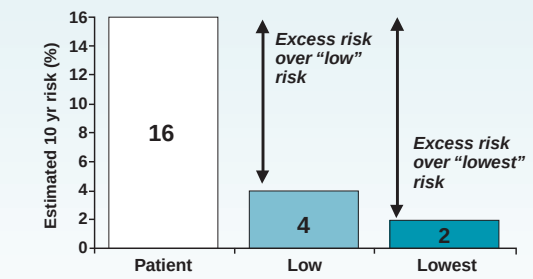
BP systolic	120	160	160	160	160	160
Cholesterol	220	220	260	260	260	260
HDL-C	50	50	50	35	35	35
Diabetes	–	–	–	–	+	+
Cigarettes	–	–	–	–	–	+

and diabetes mellitus – are commonly used to estimate risk for initial CHD events, employing separate equations for men and women; the risk varies according to the combination of risk factors (Figure 3).[36] This approach has been validated in the U.S. across several observational studies. A variety of population research techniques have been used in this setting, including testing the ability of the variables to discriminate new cases from non-cases and calibrating equations for use in other locales.[37]

Estimating CHD risk using Framingham data is generally valid for middle-class white populations in North America and Europe, where risk factors and heart disease rates approximate the experience of studies such as Framingham that provided the estimates. A useful approach for clinicians is to estimate a patient's risk from the available data and then compare those 10-year CHD estimates to other estimates (Figure 4). In this way, persons can be compared to others at "low" or "lowest" risk who are of the same age and sex. The distributions of 10-year hard CHD risks for Framingham men and women were recently published and it can be seen that age is an extremely important determinant of risk (Figures 5 and 6).[38] Overestimates of CHD risk may be obtained in other locales, especially where CHD risk is low, such as in Spain or Hawaii,[37,39] and caution should be taken when using CHD risk-estimating equations in those regions or similar areas.

Using a slightly different set of variables, equations that estimate CHD risk have been developed in Germany to predict initial CHD events in men.[39] European investigators from several countries have also developed algorithms to estimate risk of CHD disease mortality.[40] For persons with type 2 diabetes mellitus, British investigators have developed a CHD risk estimating equation, an approach that includes factoring in levels of glycosylated hemoglobin and duration of diabetes mellitus.[41]

Figure 4: Estimated 10-year hard CHD risk in 55-year-old men according to levels of various factors[36]



Cholesterol	250	160-199	<160
HDL-C	39	50-59	>60
BP systolic	146	<130	<120
Cigarettes	No	No	No
BP Rx	No	No	No

Figure 5: Estimated 10 hard CHD risk Framingham offspring and cohort – men[38]

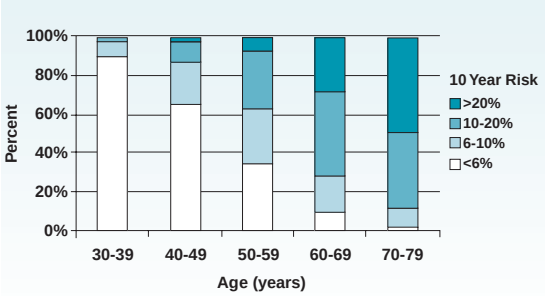
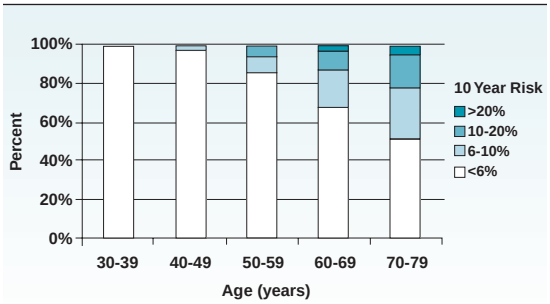


Figure 6: Estimated 10 hard CHD risk Framingham offspring and cohort – women[38]



Summary

Estimating CHD risk can help clinicians to match the estimated risk of CHD with aggressiveness of risk factor management. Using a multivariable equation approach is a dynamic process and new information is constantly being evaluated as it may change the approach. It is important to assess whether new information improves the overall prediction of CHD within a population. Accuracy and precision of the new measurement, standardization of the technique, low correlation with existing predictive variables, validation in other observational studies, and biological relevance are examples of features that need to be considered prior to the inclusion of newer variables into risk estimating approaches.[42,43] The most important aspect of risk assessment is identifying an individual's profile to assist in appropriate risk reduction measures.

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