GLOBAL RISK ASSESSMENT IN CARDIOVASCULAR DISEASE∗

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ABSTRACT

Cardiovascular disease is the leading cause of mortality in the United States. Importantly, atherosclerosis begins at an early age, and the first manifestation of coronary heart disease is often a myocardial infarction or sudden cardiac death. It is therefore critical to aggressively evaluate and manage patients in the primary care setting to prevent a potentially fatal event from occurring. Although many novel risk factors are associated with coronary disease, the causal risk factors, including hypertension, dyslipidemia, diabetes, and smoking, deserve the most attention. Eliminating or decreasing one of these risk factors decreases risk. Many patients have more than one of the causal risk factors, which interact to amplify risk. As demonstrated in large epidemiologic studies, each causal risk factor is associated with the risk of developing coronary heart disease (CHD) morbidity and mortality. Randomized placebo-controlled trials in hypertension and dyslipidemia, however, show that aggressive therapy decreases cardiovascular risk. A global approach to the management of risk factors, utilizing such tools as the Framingham Risk Score, allows physicians to determine the impact of one or more causal risk factors on future risk of developing CHD.


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Combination with the conventional or causal risk factors (eg, hypertension), CRP represents a moderately additive independent risk prediction when analyzed in combination with conventional risk factors or the Framingham risk factor score. Among 28,000 healthy, middle-aged women in the Women’s Health Study, CRP and LDL cholesterol independently are predictive of 8-year cardiovascular events, with relative risk increasing 8-fold in women with CRP levels greater than 3 mg/L and LDL cholesterol levels greater than 160 mg/dL. Compared with women with CRP levels <1 mg/L and LDL cholesterol <130 mg/dL; Figure 1. Although CRP independently adds to causal risk factors to predict risk of CHD, no data are presently available to demonstrate that lowering CRP reduces the risk of future events. Trials investigating CRP as a risk factor are ongoing.

In contrast to the novel risk factors, many studies demonstrate that the causal risk factors for CHD—namely, hypertension, dyslipidemia, diabetes, and smoking—are all independently associated with an increased risk of cardiovascular events. Reducing or controlling each risk factor has been demonstrated to lower the risk of developing CHD. Since this complete cycle of evidence for the causal, or conventional, risk factors contrasts with that of the novel risk factors, we should refocus our efforts on identifying and treating them. In addition, the majority of patients with CHD have one or more of the causal risk factors. In a cohort of over 120,000 patients presenting with acute coronary syndromes or need for percutaneous coronary intervention, at least 1 of the 4 causal risk factors was present. In patients 45 years of age and younger in this cohort, only 10% to 15% of patients lacked any of the 4 causal risk factors. Hypertension is the most frequent risk factor in women, and smoking is the most common risk factor in men. As the number of causal, or conventional, risk factors increases from 0 to 4, the age at presentation with acute coronary syndrome decreases linearly by about a decade.

SMOKING

Smoking is a powerful risk factor for the development of CHD, with a linear increase in risk as the number of cigarettes smoked increases. Smoking cessation, even following an MI, reduces future risk. In a cohort of about 2600 men and women who suffered an MI, about one third were active smokers, one third were former smokers, and one third were nonsmokers. One half of the active smokers quit at the time of their infarct. Compared with nonsmokers, the adjusted relative risk of a second cardiovascular event was 1 (eg, the same as nonsmokers) in 3 years following smoking cessation. Patients who continued to smoke had a relative risk of 1.5 of a second event compared with nonsmokers. These important data confirm that we need aggressive smoking cessation efforts to reduce recurrent cardiovascular events in patients who smoke following admission to the hospital for acute coronary syndromes.

DIABETES

Obesity is an epidemic in the United States, with alarming increases in its prevalence over the past 15 years (Figure 2). Many studies demonstrate that the prevalence of diabetes, a frequent consequence of obesity, is also increasing and remains a powerful risk factor for cardiovascular events. In a study of nearly 1400 nondiabetics and 1100 diabetics grouped by prior MI, 7-year risk of MI and death was evaluated. The incidence of MI was approximately 45% in patients with diabetes and prior MI. Patients without diabetes and with no known heart disease had the lowest risk.
Diabetic patients without prior heart disease and nondiabetic patients with prior MI had a similar 7-year risk of MI (approximately 20%) and survival. These data suggest that we need to treat diabetes aggressively, especially with aggressive blood pressure and lipid control. Furthermore, once a patient with diabetes manifests coronary disease, short- and long-term risk is very high, with a 7-year survival of only 50% (Figure 3).10

A particularly high-risk patient group that is occurring with increasing frequency is the patient with the metabolic syndrome. The National Cholesterol Education Program guidelines define a patient with the metabolic syndrome with 3 or more of the following risk factors: abdominal obesity, elevated triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, elevated blood pressure, and glucose intolerance.11 These risk factors were assessed in nearly 6500 men who are moderately hypercholesterolemic and cardiovascular disease-free, in an effort to predict their 5-year risk for developing nonfatal MI or CHD death.12 As the number of metabolic syndrome risk factors increases, the risk of developing a cardiovascular endpoint increases stepwise. Risks of nonfatal MI and coronary death increase nearly 4-fold as risk factors for the metabolic syndrome increase from 0 to 4 or 5. Importantly, the totality of the metabolic syndrome is a risk factor for developing cardiovascular disease independent of the individual risks that contribute to the metabolic syndrome. Recent studies show that patients with the metabolic syndrome have elevated fibrinogen and plasminogen activator inhibitor-1.13 Additionally, most patients with the metabolic syndrome have elevated CRP,14 which is likely due to the increased cytokines released from adipocytes.

Aggressive risk factor evaluation and treatment are beneficial in high-risk patient populations, especially those with diabetes. Recent data from the Heart Protection Study of 6000 patients with diabetes and no preexisting cardiovascular disease demonstrate that statin therapy reduces the incidences of CHD, stroke, or need for coronary revascularization.15 The benefit of statin therapy is not affected by the baseline LDL cholesterol value (ie, ≤100 mg/dL, 100-130 mg/dL, or ≥130 mg/dL). The relative and absolute benefit of statin therapy in patients with diabetes is far greater than that achieved with aggressive glycemic control.

Epidemiologic trials show that patients with peripheral vascular disease, aortic disease, or carotid artery disease, similar to patients with diabetes, have a 10-year risk of developing CHD similar to patients with stable angina (about 20% over 10 years). It has been shown that aggressive lipid management lowers events in patients with carotid artery or peripheral vascular disease.16

Figure 2. Obesity Trends in the United States

Prevalence of growth by severity of obesity. Calculations are based on the Behavior Risk Factor Surveillance Survey. BMI calculated as weight in kilograms divided by the square of height in meters. BMI = body mass index.


Figure 3. Long-Term Survival

Kaplan-Meier estimates of the probability of death from coronary heart disease in 1059 subjects with type 2 diabetes and 1378 nondiabetic subjects with and without prior MI. Vertical bars indicate 95% confidence interval. MI = myocardial infarction.

Several recent clinical trials have demonstrated that statins can substantially reduce both morbidity and mortality from CHD.\textsuperscript{17}

**LDL Cholesterol**

Large observational trials, including the Framingham Study and the Multiple Risk Factor Intervention Trial (MRFIT) show convincingly that elevated cholesterol is an indicator for the development of CHD.\textsuperscript{17} Importantly, elevated LDL cholesterol and decreased HDL cholesterol independently predict risk.\textsuperscript{18} Therefore, cholesterol lowering is an important component of global risk assessment and therapy. Prospective, randomized, placebo-controlled studies also demonstrate that there is a relationship between statin therapy and a reduction in myocardial events. Early trials randomized subjects with very high entry cholesterol with known coronary artery disease. As each study showed a benefit for active therapy compared with placebo in reducing the primary endpoint, lower-risk patients were subsequently studied. Primary prevention studies also showed that many subjects without known coronary disease may benefit from statin therapy.\textsuperscript{19}

**Hypertension**

Evaluation and treatment of patients with hypertension include managing blood pressure measurements and treatments. In a recent study, 24-hour ambulatory blood pressure and office blood pressure were evaluated in 1963 patients with hypertension (Figure 4).\textsuperscript{20} During follow-up, cardiovascular event rates were doubled if mean ambulatory systolic blood pressure was greater than 135 mm Hg compared with less than 135 mm Hg, regardless of the office blood pressure. These data suggest that patients should monitor their blood pressure at home so that the treatment can be evaluated and the therapy adjusted as necessary.

Data from the Third National Health and Nutrition Examination Survey (NHANES III) show that systolic blood pressure rises linearly with increasing age in men and women of all races.\textsuperscript{21} Diastolic blood pressure in Americans increases until the age of about 50 to 59 years, after which diastolic blood pressure falls. This change in systolic and diastolic blood pressure with age results from changes in the aorta and great vessels, including a decrease in elastin, collagen, and endothelial function.\textsuperscript{22} Therefore, measures of arterial stiffness increase linearly with increasing age. A more rigid arterial system results in a rise in systolic blood pressure for any cardiac stroke volume. Furthermore, diastolic blood pressure falls with increasing age due to less elastic recoil of the aorta during diastole and return of reflected arterial pressure waves during late systole instead of diastole.\textsuperscript{23} These data may help explain the high percentage of older Americans with isolated systolic hypertension.

In addition, a noninvasive measure of arterial stiffness, pulse pressure (the difference between systolic and diastolic blood pressure), increased linearly with increasing age in the Framingham cohort.\textsuperscript{29} Furthermore, studies show that pulse pressure is a powerful predictor of future cardiovascular events in a wide range of populations, including those with and without established cardiovascular disease. In the Framingham Study of healthy subjects, pulse pressure was an independent predictor (independent of systolic, diastolic, and mean blood pressure) of future CHD.\textsuperscript{29}

**Global Risk Assessment**

The Framingham risk score predicts a 10-year risk of developing CHD based on age, sex, lipid profile, smoking status, and systolic blood pressure. The causal risk factors discussed previously often occur together.

![Prognostic Value of Ambulatory Blood Pressure Measurements in Treated Hypertension](image-url)
in patients and amplify risk. As a result of this finding, healthcare providers have developed appreciation for how different risk factors, when combined with each other, produce global risk. The Framingham risk score helps healthcare providers stratify risk in patients to determine the goals of risk factor modification therapies. Importantly, age has the greatest point range in this model and remains a powerful predictor of future cardiovascular events.

**Aerobic Exercise and Global Risk**

There is a progressive decline in physical activity with increase in age beginning in high school. The adult US population is becoming increasingly sedentary. Physical fitness is a powerful predictor of morbidity and mortality in asymptomatic subjects, as well as subjects with known cardiovascular disease. In a study of 6,200 men referred for an exercise stress test, the variables predicting long-term survival were determined. In both normal and cardiovascular disease subjects, the degree of physical fitness expressed as metabolic equivalents performed on an exercise test was the most powerful predictor of long-term survival. Exercise capacity far outweighed symptoms (i.e., chest pain) of CHD or electrocardiographic changes in predicting mortality. Similarly, in a large cohort of healthy women from the Nurses Health Study, the amount of time spent walking per week was inversely related to the long-term risk of developing future cardiovascular disease. The lowest risk was in women who not only walked at least 10 metabolic equivalent of task-hours/week but also participated in at least 100 minutes of vigorous exercise per week. The relative risk of death or nonfatal MI in the most physically active women was 63% lower compared with the most sedentary women. The risk of cardiovascular events decreased among walkers as the walking pace increased. These data in healthy men and women suggest that physical fitness is an important predictor of cardiovascular health.

**Global Risk in Low- and High-Risk Subjects**

Two recent studies highlight the relevance of global risk impact on future events. In an analysis of 121,000 women from the Nurses Health Study, health habits were related to risk of developing nonfatal MI or death. In this cohort, 12% of women had 3 low-risk behaviors: eating a diet low in glycemic load and fat, exercising 30 minutes daily, and not smoking. The relative risk of death or nonfatal MI over 8 years in this group was reduced by 57% compared with women not practicing these 3 low-risk behaviors. Normal body mass index reduced the low-risk group to 7% of the entire cohort with a relative risk of a cardiovascular event reduced by 66%. Finally, 3% of the entire cohort practiced 5 low-risk behaviors: not smoking, eating a healthy diet, participating in aerobic exercise, maintaining a normal body mass index, and drinking 5 g of alcohol daily. The relative risk of MI in these women was 83% lower compared with women ignoring these 5 low-risk behaviors. These data suggest that risk reduction via a healthy lifestyle reduces future risk of cardiovascular events.

In a high-risk population, the recently published Steno-2 trial suggests that an aggressive interventional risk factor approach reduces vascular events. In this study of an aggressive global risk factor intervention group versus usual care, 160 patients with type 2 diabetes and microalbuminuria were randomized and followed for nearly 8 years for the primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, need for revascularization, or amputation. The aggressive global risk factor intervention group was treated...
with angiotensin-converting enzyme inhibitors, aspirin, and statins, with glycosylated hemoglobin and blood pressure targets lower than the conventionally treated high-risk group. Long-term outcomes were significantly lower in the aggressive group compared with usual care (Figure 5). These data suggest that global risk assessment and intervention can reduce events in the high-risk patient.

**CONCLUSION**

Although recent studies focus on novel risk factors for CHD, we cannot lose our perspective on the importance of the causal risk factors for disease. We know that the Framingham risk score is a good predictor of cardiovascular events. We also know that therapy for these risk factors reduces risk of future cardiovascular events. To determine risk and optimize therapeutic recommendations, we need to think about the patient’s overall condition and not just the individual risk factors. An aggressive global approach to risk factors may be the optimal approach to reduce risk of cardiovascular events.

**REFERENCES**