Assessing Coronary Heart Disease Risk with Traditional and Novel Risk Factors

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Summary: Cardiovascular disease is the leading cause of death in the industrialized world, and a number of well-characterized factors, including advanced age, hypertension, dyslipidemia, diabetes, and smoking, contribute to cardiovascular risk. Integration of these factors using the Framingham calculation estimates the absolute 10-year risk for coronary heart disease (CHD), which can be used to guide therapy. Recent studies have demonstrated that additional markers, including elevated lipoprotein(a), homocysteine, sitosterol, and particularly C-reactive protein (CRP), are also associated with increased risk for CHD. In particular, high-sensitivity CRP has been shown to identify patients with high CHD risk who may not have elevated low-density lipoprotein cholesterol (LDL-C) and may add to the predictive value of the Framingham functions for CHD risk assessment. Assessment of global risk is particularly important in lipid management, as the LDL-C target goals are determined by risk category.

Introduction

Coronary heart disease (CHD) is the leading cause of death in the industrialized world. In the United States alone, 13.2 million Americans have CHD.¹ A number of factors, including hypertension, dyslipidemia, diabetes, obesity, and smoking contribute to CHD risk,^{2–5} and an increasing number of patients in the United States have two or more of these risk factors.⁶ A critical part of CHD prevention is comprehensive CHD risk assessment, in which the presence and/or severity of risk factors is used to estimate a patient's overall, or global, CHD risk. Information about global CHD risk can be used to

optimize therapy, an approach that is supported by guidelines from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) with respect to the setting of lipid target goals.⁷ This article describes CHD risk factors and their integration into a global risk score, as well as the use of this global risk score in guiding therapy. The potential effects of novel risk factors on current methods of risk assessment are also discussed.

Conventional Risk Factors for Coronary Heart Disease

Conventional risk factors for CHD include age, dyslipidemia, hypertension, smoking, and diabetes. It is well known that the risk for CHD increases with age,⁸ and this effect is independent of age-associated increases in other risk factors. Elevated cholesterol is a well-established risk factor, and an analysis from the Framingham Heart Study demonstrated a strong positive relationship between cholesterol and the lifetime risk for developing CHD (Fig. 1).⁹ Elevated low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) are highly related to the 10-year risk of CHD.⁸ Although not used in calculating CHD risk, results from both epidemiologic and interventional studies suggest that elevated triglycerides (TG) may also be an independent risk factor for CHD.¹⁰ Elevations in both diastolic blood pressure (DBP) and, to a greater extent, systolic blood pressure (SBP) are strongly correlated with CHD mortality.¹¹ A meta-analysis of 61 prospective studies that included 1 million adults demonstrated a doubling of risk for both stroke mortality and ischemic heart disease mortality with each 20/10 mmHg increase in SBP/DBP.¹² Smoking is also a strong risk factor for CHD, conferring a two-fold increase in the rates of myocardial infarction (MI), total CHD, and CHD death among smokers <55 years of age relative to nonsmokers of the same age range.¹³ Type 2 diabetes is associated with the presence of multiple CHD risk factors and a two- and three-fold increase in risk for vascular disease in men and women, respectively.¹⁴ Based on the comparable 10-year risk for a CHD event (>20%) between patients with diabetes who do not have CHD and patients with prior CHD but without diabetes, diabetes is considered a CHD risk equivalent by the NCEP ATP III guidelines (see next section).

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FIG. 1 Lifetime (to 80 years of age) risk for coronary heart disease for men and women from the Framingham Heart Study, stratified by different total cholesterol levels at baseline ages 40–49 years. Data are from Ref. No. 9.

Calculating Absolute Coronary Heart Disease Risk with Framingham Risk Score

Risk assessment is part of the management for persons who have or who are at risk for CHD.⁷ Patients with CHD or a CHD risk equivalent (diabetes, other atherosclerotic disease, abdominal aortic aneurism) have a 10-year risk for CHD of >20%⁷ and do not require Framingham calculation. For patients without these conditions, the Framingham equations can be used to calculate risk for CHD using information about gender, age, total cholesterol, HDL-C, SBP, and smoking status as shown for a 55-year-old man in Fig. 2. Points are assigned for values of all these factors, and the 10-year risk for CHD is calculated.⁷ Results from this analysis can be used to categorize patients as having low (<10%), intermediate (10–20%), or high (>20%) 10-year CHD risk.⁷ The NCEP ATP III guidelines use information derived from the number of risk factors and the Framingham risk score to set LDL-C targets for patients. For patients with CHD, a CHD risk equivalent, or a >20% 10-year CHD risk, the LDL-C target is <100 mg/dl; for patients with ≥2 risk factors and a calculated 10-

FIG. 2 Calculation of coronary heart disease risk using the Framingham equations and patient categorization. Adapted from Ref. No. 7. HDL-C = high-density lipoprotein, BP = blood pressure.

year CHD risk of ≤20%, the target is <130 mg/dl. The LDL-C goal for patients with <2 CHD risk factors is <160 mg/dl.⁷

The results of the Framingham Heart Study and the resulting equation for CHD risk calculation are based on follow-up of white middle-class men and women, raising the question of whether the predictive value of the Framingham calculation can be generalized to other populations. D'Agostino *et al.* evaluated the validity of the Framingham CHD prediction functions in six ethnically diverse cohorts that included whites, blacks, Native Americans, Japanese American men, and Hispanic men.² Analysis of 5-year CHD risk prediction showed that the Framingham functions performed well for white and black men and women. However, they systematically overestimated the 5-year CHD risk in Japanese American and Hispanic men and Native American women. Recalibration of the Framingham equations, taking into account different prevalences of risk factors and underlying rates of developing CHD in these groups, resulted in a significant improvement in risk prediction.²

Integrating Novel Risk Factors into Risk Assessment

Results from two recent epidemiologic studies^{3, 5} have shown that most patients with CHD have at least one of the four major modifiable risk factors for this condition (elevated total cholesterol, hypertension, diabetes, or smoking); however, these studies also report that most patients without CHD also have at least one risk factor, indicating that other factors may be important in predicting CHD.^{15, 16} Several novel factors have emerged that may add value to current methods of risk assessment. The utility of these factors in risk assessment depends on a standardized measurement, gradient of effects, clinical importance, response to intervention, and a degree of correlation with other risk factors. It is important to note that factors that correlate with CHD may not be involved in CHD pathology. These traits may serve as markers, and other factors may play causal roles in the disease and can be targets for intervention.

Lipoprotein(a)

Lipoprotein(a) (Lp[a]) consists of apolipoprotein (a) covalently linked to apolipoprotein B100, the main protein moiety of LDLs. There are strong structural homologies between Lp(a) and both plasminogen and LDLs, and it has been suggested that Lp(a) might link atherosclerotic and thrombotic mechanisms in the pathogenesis of CHD.¹⁷ Results from the Lipid Research Clinics Coronary Primary Prevention Trial clearly linked elevated Lp(a) to increased CHD risk. This study included 3,806 men, aged between 35 and 59 years, with total cholesterol ≥265 mg/dl, LDL-C ≥190 mg/dl, and TG <130 mg/dl, who were treated with cholestyramine or placebo. Lipoprotein(a) levels were measured in plasma samples obtained prior to randomization in 233 participants who developed CHD during the study and 390 patients who did not. Study results showed that Lp(a) levels were 21% higher in the patients who developed CHD than in those who remained disease free ($p < 0.02$). This difference remained sta-

tistically significant ($p < 0.01$) after correction for other CHD risk factors including age, body mass index, cigarette smoking, blood pressure, LDL-C, total cholesterol, and HDL-C.¹⁸ However, measurement of Lp(a) has not been standardized, and its role in routine risk assessment remains unclear.

Homocysteine

Homocysteine has multiple potentially toxic effects on the vascular endothelium, including stimulation of vascular smooth muscle proliferation, promotion of platelet aggregation, and creation of a prothrombotic environment.¹⁹ Advanced age, male gender, sedentary lifestyle, smoking, kidney disease, organ transplantation, hypothyroidism, psoriasis, vitamin and enzyme deficiencies, and specific medications (e.g., corticosteroids, cyclosporine, methotrexate, phenytoin, theophylline, and fibrates) may give rise to hyperhomocysteinemia,²⁰ and recent epidemiologic results have suggested that this condition may be at least weakly linked to increased CHD risk. In a meta-analysis, Christen *et al.*²¹ examined 43 studies published between 1966 and September 1998 that examined the relationship between homocysteine levels and risk for CHD or cerebrovascular disease. Although results from most cross-sectional and case-control studies indicated higher mean homocysteine levels and/or a greater frequency of elevated homocysteine in individuals with CHD, results from most prospective studies indicated a weak or no association between homocysteine and CHD. These investigators suggested that elevated homocysteine may be an acute-phase reactant that is predominantly a marker of atherogenesis, or a consequence of other factors more closely linked to CHD.²¹

C-Reactive Protein

Several factors associated with inflammatory response have been linked to an increased risk for CHD and CHD-related

mortality.^{22,23} C-reactive protein (CRP), an acute-phase reactant that is elevated in response to tissue damage, inflammation, and infection, has emerged as a potentially useful marker of CHD risk.²⁴ A prospective, nested case-control study that included 28,263 healthy postmenopausal women who were followed for an average of 3 years indicated that the level of high-sensitivity CRP (hs-CRP) was a stronger univariate predictor of cardiovascular events (i.e., death from CHD, nonfatal MI, stroke, or the need for coronary revascularization procedures) than other inflammatory markers, including serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule type 1. This analysis showed that the incorporation of markers of inflammation with lipids was significantly better at predicting risk than models based on lipids alone ($p < 0.001$). Moreover, high levels of hs-CRP and serum amyloid A were significant CHD risk predictors even in women with LDL-C < 130 mg/dl.²⁵ A subsequent analysis carried out by this group indicated that elevated LDL-C and CRP identified largely distinct populations at increased CHD risk and that screening for both markers resulted in better risk prediction than assessment of either one alone. Results from this study also showed that CRP level is a stronger predictor of cardiovascular events than LDL-C (Fig. 3), and that it significantly adds to prognostic information provided by the Framingham risk score.²⁶

The strong evidence supporting CRP as a marker for CHD risk has prompted a recommendation from the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) that measurement of hs-CRP may be useful as an independent marker of risk and helpful in directing further evaluation and therapy in patients with intermediate (10–20%) 10-year CHD risk. The CDC/AHA recommendation also suggests that two assays, averaged—fasting or nonfasting, and optimally 2 weeks apart—provide a more stable estimate of the level of this marker than a single measurement. They noted that a CRP level > 10 mg/l proba-

FIG. 3 Event-free survival according to baseline quintiles of C-reactive protein and low-density lipoprotein (LDL) cholesterol. Reprinted from Ref. No. 26 with permission. Copyright © 2002 Massachusetts Medical Society. All rights reserved.

bly indicates infection or inflammation and should prompt re-measurement of hs-CRP in 2 weeks. Low, intermediate, and high relative risk of CHD correspond to CRP levels of < 1.0, 1.0–3.0, and > 3.0 mg/l, respectively, with the highest level indicating or corresponding to a two-fold increase in CHD risk relative to those with the lowest CRP levels.²⁷

Other Potential Markers of Coronary Heart Disease Risk

Phytosterols are plant-derived sterols that have structural similarity to cholesterol and are absorbed by the intestine with relatively low efficiency. Very high levels of sitosterols in patients with rare genetic disease result in premature atherosclerosis.²⁸ Highly elevated phytosterols are associated with premature CHD in individuals with an inherited metabolic disease, β -sitosterolemia.²⁸ Other studies have demonstrated that moderately elevated levels of phytosterols in normal individuals may also be associated with increased CHD risk.^{29,30} A recent evaluation of a subset of patients enrolled in the Prospective Cardiovascular Munster Study (PROCAM) indicated that participants in the highest quartile for sitosterol levels had a 1.8-fold increase in the risk for MI or sudden coronary death versus those in the lowest three quartiles.³⁰ Among patients with a 10-year global CHD risk > 20%, those who also had elevated sitosterol had an additional three-fold increase in risk. The potential role of phytosterols in CHD risk warrants further investigation.

Conclusions

The risk of a CHD event is multifactorial, and assessment of CHD risk entails an assessment of the presence of preexisting CHD, CHD risk equivalents, and CHD risk factors. In patients without CHD or CHD risk equivalents, the presence and number of conventional risk factors (age, hypertension, dyslipidemia, diabetes, and smoking) are integrated using the Framingham calculation to yield an absolute 10-year CHD risk, which can be used to guide therapy, particularly the aggressiveness of lipid-lowering therapy. Recent studies have demonstrated that additional markers, particularly CRP, are also associated with increased risk for CHD and may add predictive value to current methods of risk assessment.

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