Updating the Assessment of Cardiac Risk: Beyond Framingham

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Identification of the widely accepted cardiovascular risk factors of age, sex, hypertension, hyperlipidemia, smoking, obesity, diabetes, and physical inactivity from the Framingham Heart Study have led to dramatic reductions in cardiovascular morbidity and mortality. The Framingham estimation of coronary heart disease remains the mainstay of clinical risk assessment. However, novel risk predictors present opportunities to identify more patients at risk and to more accurately define that risk. Such predictors include lipoprotein analysis, measurement of lipoprotein-associated phospholipase A_2 and C-reactive protein, and assessment of hyperglycemia, liver function, and central obesity. Vascular imaging can also provide useful risk information. Using Framingham as a basis, several international groups have developed risk-scoring systems that more closely reflect their individual populations and the clinical practicalities of their countries. When used accordingly, the newer risk predictors build upon the Framingham framework to allow physicians and their patients to effectively minimize, or even avoid, the burden of cardiovascular disease.

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Key words: Framingham Heart Study • Coronary heart disease • Lipoprotein analysis • C-reactive protein • Hyperglycemia • Central obesity

Approximately 20 miles west of Boston lies the historic town of Framingham, MA. Incorporated in 1700, the town has played key roles in American history. Perhaps its most important role, however, began 60 years ago when researchers first enrolled 5209 Framingham men and women in the Framingham Heart Study.[1] Now compiling data on the third generation of Framingham participants, the study has made fundamental contributions to our understanding of the causes of coronary heart disease (CHD) and stroke.

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In early 2008, the American Heart Association released the most recent cardiovascular statistics showing that between 1994 and 2004, deaths from cardiovascular disease decreased by 24.7%. However, in 2004, CHD was still the cause of 1 in every 5 deaths (nearly half a million) in the United States. Risk factors such as uncontrolled hypertension have not improved as much as expected, and other risk factors, such as obesity and type II diabetes, are actually increasing.[2] Perhaps more concerning, in recent years, younger adults have not benefited from the same fall in cardiovascular mortality rates that has been observed in older adults.[3]

Thus, the need to evaluate and modify cardiovascular risk is as important as ever. Although the initial Framingham risk factors explain much of the CHD risk, emerging knowledge on risk is allowing physicians to better identify patients for whom early intervention can prevent the development of cardiovascular disease or control disease that already exists. Newer evaluations range from simple measurement of waist circumference to sophisticated laboratory assessments and complex risk prediction models. Although some of these risk indicators may not yet be ready for general clinical use, they contribute to the understanding of cardiovascular risk and may eventually become part of the physician's routine tool kit.

Starting With Framingham

The Framingham Heart Study provided the initial data-driven insights that the downstream effects of the 1940s American lifestyle of high-fat, high-salt diets, physical inactivity, and smoking led to coronary artery disease. The key elements of age, sex, diabetes, smoking, and degrees of hypertension and hyperlipidemia were found to be highly predictive of CHD. Based upon the large Framingham data set, risk prediction models were created that allowed physicians to predict the 10-year risk of CHD for women and men. Some risk factors were more predictive than others, and the more negative risk factors that a patient accumulated, the higher the 10-year risk. Moreover, physicians could recalculate the Framingham 10-year risk assuming risk reduction interventions, such as smoking cessation or blood pressure reduction, to demonstrate to patients how their risk would be lowered with these changes.

Although initially developed in a relatively homogenous, white population of people living in Massachusetts, the risk prediction model has been subsequently validated in a variety of geographic locations and ethnic populations. Some of these studies, however, such as the Multi-Ethnic Study of Atherosclerosis (MESA), have shown added benefit with newer risk predictors, as will be discussed below.[4-7] These risk prediction models have played instrumental roles in the development of national guidelines for the Joint National Committee (JNC 7) on blood pressure and the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP III) on cholesterol management and have been helpful in defining the extent of cardiovascular risk in the United States.[8-10] Clinically useful tools have been developed for use in the patient-care environment with either handheld personal digital assistants or web-based calculators.[11]

The Framingham estimation of CHD remains the mainstay of clinical risk assessment. However, novel risk predictors, some of which are currently being pursued within the Framingham Heart Study cohort, present opportunities to identify more patients at risk and to more accurately define that risk.

Emerging Risk Factors

Multiple other risk factors that were not part of the traditional Framingham risk score have been demonstrated to predict cardiovascular disease. These indicators of risk vary in their supportive evidence, their ease of measurement, and their predictive ability. Nonetheless, they represent the next frontier in assessing cardiovascular risk.

Lipoprotein Analysis

The Framingham risk scoring system incorporates total cholesterol or low-density lipoprotein cholesterol (LDL-C) as well as high-density lipoprotein cholesterol (HDL-C). Such laboratory measurements assess the amount of cholesterol rather than the atherogenic circulating lipoproteins (lipid and protein molecules) and apolipoproteins (protein molecules) contained within the lipoproteins. Moreover, measurement of LDL-C alone fails to completely measure other atherogenic lipoproteins such as very low-density lipoproteins (VLDL). There are 2 potential methods to account for all the atherogenic lipoproteins. One method is to measure apolipoprotein B100 (apoB), which correlates with low-density lipoprotein (LDL) and VLDL particles and VLDL remnants, as these lipoproteins each contain 1 molecule of apoB. The second method is to measure non–HDL-C, particularly in individuals with high triglycerides, which correlates with apoB.[12]

Of the first method, postmortem analyses of the arterial walls of patients with symptomatic atherosclerosis show elevated levels of apoB as well as apolipoprotein E (apoE), which is also contained on circulating LDL.[13] Moreover, in comparison with the second method of measuring non–HDL-C, clinical evidence suggests that such assessments of the atherogenic lipoprotein particles, as measured by apoB, may be more predictive of CHD than measures of the cholesterol, such as LDL-C or non–HDL-C. A nested case-control study within the Health Professionals Follow-up Study revealed that among apoB, LDL-C, non–HDL-C, triglycerides, and lipoprotein(a), the apoB was the most predictive of CHD.[12] In that study, although both apoB and non–HDL-C predicted CHD, when mutually adjusted, only the apoB was predictive of CHD. A more recent post-hoc analysis of 2 lipid-lowering trials showed that a ratio of apoB to apolipoprotein A-I (a lipoprotein on high-density lipoprotein [HDL] particles) provided the strongest risk prediction compared with cholesterol values, cholesterol ratios, or apoB by itself.[14]

A variant on apoB named lipoprotein(a) confers significant added risk to the standard atherogenic particles. Lipoprotein(a) is a molecule with structural similarity to plasminogen that is linked to apoB and has been associated with inflammation and thrombosis.[15] Although the clinical utility of evaluating lipoprotein(a) has been hindered by technical variability in measurement and the limited therapeutic options available for treating an elevated lipoprotein(a), the marker does provide risk information. Measurements of lipoprotein(a) in the Women's Health Study (WHS) showed a 48% increase in cardiovascular events among women whose lipoprotein(a) level was at or above 32.8 mg/dL (75th percentile).[16] This association was most pronounced in women who had high levels of LDL-C. Perhaps with standardization of the measure, more prognostic data, and, eventually, more treatments, lipoprotein(a) may become a more widely used risk predictor.

Atherogenic Lipoprotein Phenotype

In addition to measuring the individual apolipoprotein components, newer laboratory technology, such as nuclear magnetic resonance spectroscopy and the vertical auto profile, allows evaluation of the particular atherogenic size characteristics of the lipoproteins. Although Framingham risk decreases as a patient's HDL-C increases, newer evidence suggests that not all HDL-C is the same and that higher levels of HDL-C and larger HDL particle size may actually confer increased risk.[17] The understanding of very high levels of HDL-C and large HDL particle size is preliminary and certainly requires further research.

Lipoprotein analysis allows determination of HDL particle size, but more commonly it is used to define the LDL particle. Two subclass patterns of LDL particles emerge from these measurements: pattern A, with large, buoyant LDL particles, and pattern B, with small, dense LDL particles.[18] Prospective evidence has shown that pattern B is associated with more than a 3-fold increase in the risk for CHD, an increase only minimally attenuated when adjusted for cholesterol and apoB levels (Figure 1).[19] Additionally, the size and density of the LDL particles increase as the level of HDL-C increases, moving from pattern B to pattern A, suggesting a correlation between the LDL pattern and HDL-C.[20]

In fact, the LDL pattern B is associated with an "atherogenic lipoprotein phenotype" consisting of small, dense LDL particles, low HDL-C, and high triglycerides and is associated with insulin resistance, metabolic syndrome, and diabetes. Recent data support a role for both HDL-C and triglycerides in explaining cardiovascular risk, although this correlation may additionally reflect an unmeasured LDL particle pattern that, in

Figure 1. *Small, dense LDL particles predict the risk of IHD in men. LDL, low-density lipoprotein; IHD, ischemic heart disease; apoB, apolipoprotein B. Adapted with permission from Lamarche B et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men.* Circulation. *1997;95:69-75.*[19]
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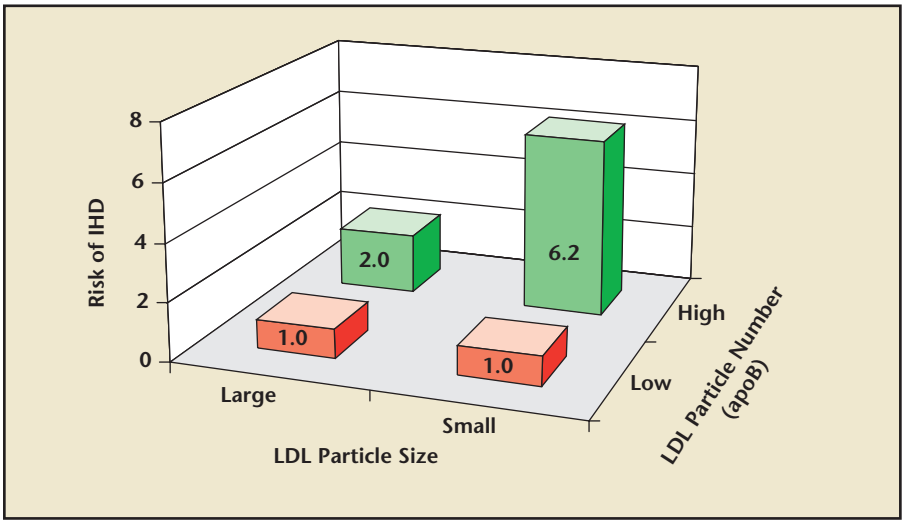


conjunction with the HDL-C and triglycerides, forms the "atherogenic lipoprotein phenotype." One of these studies, a post hoc analysis of the Treating to New Targets (TNT) study, showed that lower HDL-C predicted cardiovascular events across LDL-C levels among patients who were treated with atorvastatin, including those patients who had achieved an LDL-C of less than 70 mg/dL.[21]

Triglyceride levels can also predict rates of cardiovascular events. In the Heart Protection Study (HPS), the Cholesterol and Recurrent Events (CARE) trial, and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, patients on statin therapy who had elevated triglycerides had higher rates of cardiovascular events compared with those patients who had low triglycerides (Figure 2).[22,23] A subgroup analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT–TIMI 22) trial showed that in a post–acute coronary syndrome population, patients with triglycerides of less than 150 mg/dL had reduced 30-day CHD events; those patients who had both triglycerides of less than 150 mg/dL and LDL-C of less than 70 mg/dL had the lowest event rates of all.[24] Perhaps an even lower threshold for triglycerides should be considered. A retrospective study showed that, even when controlled for LDL-C, triglyceride levels of greater than or equal to 100 mg/dL were predictive of new coronary artery disease.[25]

Together, these data suggest that even when the traditional risk factor of LDL-C is treated with statin therapy, both HDL-C and triglycerides predict cardiovascular events. The 2 values can be combined into a triglyceride to HDL-C ratio which, with a value of 3.5 or greater, predicts insulin resistance. Perhaps the main connection between these elements of LDL particle size, HDL-C, and triglyceride is that they together form the "atherogenic lipoprotein phenotype" and are associated with insulin resistance and diabetes.[26]

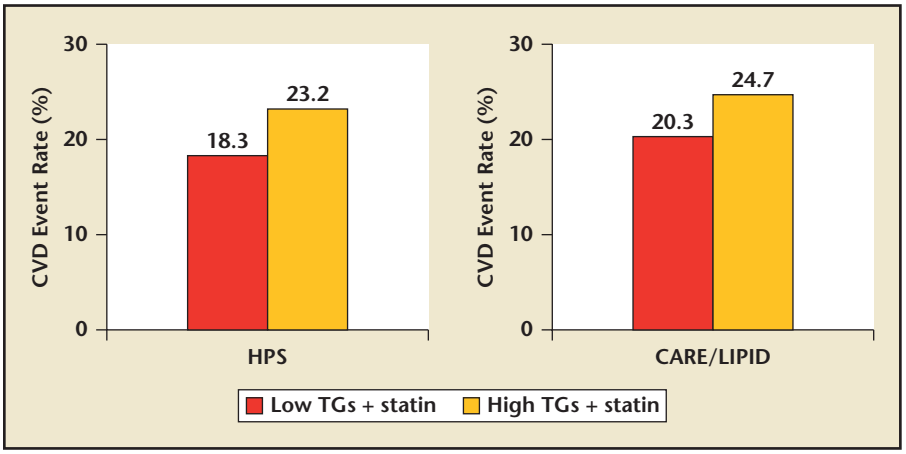
Hyperglycemia

Hyperglycemia has a multitude of deleterious effects, including impaired cell function, creation of oxidative damage through the generation of free radicals, and an increase in the atherogenicity of LDL-C through glycosylation. In patients with diabetes, high baseline fasting blood glucose correlates with cardiovascular mortality.[27] Even in nondiabetes patients and when controlling for other cardiovascular risk factors, hyperglycemia has been associated with the development of cardiovascular disease.[28] Thus, hyperglycemia, whether in the form of diabetes or in the form of impaired fasting glucose in patients without diabetes, should be considered a cardiovascular risk factor.

Lipoprotein-Associated Phospholipase A_2

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is a circulating enzyme in the blood that hydrolyzes a wide range of phospholipids and is associated with LDL-C. When LDL-C is retained in the vascular intima, it provides a substrate for Lp-PLA_2 that ultimately generates inflammatory elements that can lead to plaque propagation and instability. Clinically, elevated Lp-PLA_2 levels are found in the serum of patients with a heavy atherosclerotic burden and in those who subsequently develop cardiovascular events. Although there are some aspects of Lp-PLA_2 biology that suggest anti-inflammatory properties, the bulk of the evidence shows proinflammatory and proatherogenic effects of Lp-PLA_2.[29] Several studies have evaluated the impact of Lp-PLA_2 on cardiovascular risk, often in conjunction with high-sensitivity C-reactive protein (hs-CRP). Although analysis of the WHS did not demonstrate a strong predictive effect of Lp-PLA_2 in women, other studies have shown a correlation between elevated levels of Lp-PLA_2 and CHD, particularly in individuals with low levels of LDL-C.[30-32] Analysis of Lp-PLA_2 in the

Figure 2. *Statin monotherapy does not eliminate the CVD risk associated with high TGs. CVD, cardiovascular disease; TGs, triglycerides; HPS, Heart Protection Study; CARE, Cholesterol and Recurrent Events; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease. Data from Heart Protection Study Collaborative Group[22] and Sacks FM et al.[23]* www.medreviews.com



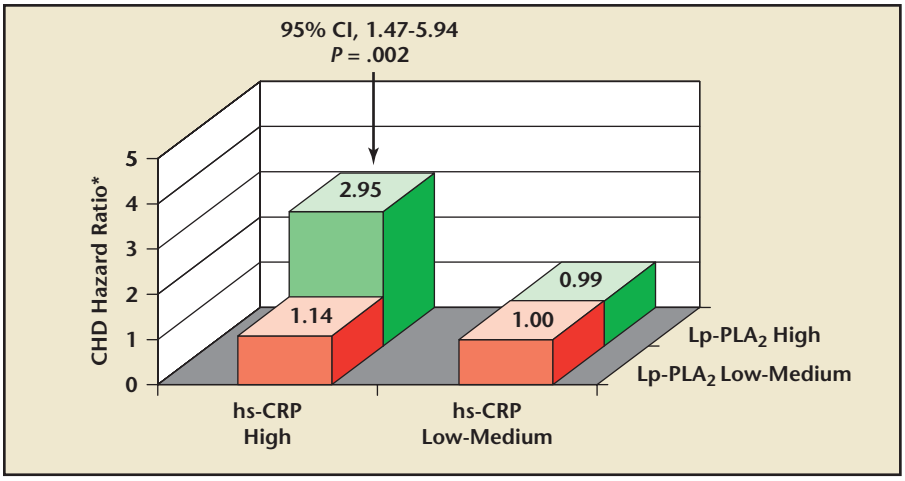


Figure 3. *Additive risk for incident CHD for LDL below 130 by Lp-PLA$_2$ and hs-CRP tertiles in the ARIC study. *Adjusted for demographics, current smoking status, blood pressure, diabetes, and high-density lipoprotein. CHD, coronary heart disease; LDL, low-density lipoprotein; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; hs-CRP, high-sensitivity C-reactive protein; ARIC, Atherosclerosis Risk in Communities; CI, confidence interval. Adapted with permission from Ballantyne CM et al. Lipoprotein-associated phospholipase A$_2$, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study.* Circulation. *2004;109(7):837-842.*[32] www.medreviews.com

Atherosclerosis Risk In Communities (ARIC) study showed that the predictive benefit of Lp-PLA$_2$ was more pronounced when LDL-C levels were less than 130 mg/dL, although when added to a basic risk factor model, the Lp-PLA$_2$ added only marginal incremental predictive benefit (Figure 3).[33,34] Nonetheless, as more evidence accumulates regarding measurement of Lp-PLA$_2$, an elevated Lp-PLA$_2$ may aid clinicians in deciding to more aggressively treat risk factors in high-risk patients with normal LDL-C values.

C-Reactive Protein

Similar to Lp-PLA$_2$, hs-CRP may also help identify patients at higher cardiovascular risk who have normal or low LDL-C. This acute phase reactant reflects inflammation. Because inflammation contributes to both atherosclerosis and thrombosis, a marker may indicate cardiovascular risk. Several prospective studies have demonstrated the predictive effect of hs-CRP, including the WHS, which showed that elevated hs-CRP correlated with cardiovascular events even in those patients whose LDL-C was less than 130 mg/dL.[35] The ARIC study, with both men and women, also showed the correlation of hs-CRP with CHD, but the predictive effect was not significant when added to a basic model of traditional risk factors.[32,34] The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), which randomized patients with an elevated hs-CRP (≥ 2 mg/dL) but normal LDL-C to either rosuvastatin or placebo, was stopped prematurely due to a 44% reduction in cardiovascular morbidity and mortality.[36-38] This study supports the concept that hs-CRP can be used to identify patients with intermediate risk who can benefit from statin therapy.

Liver Function

In addition to measurements of direct lipoprotein and inflammatory markers, assessments of other organ systems can inform cardiovascular risk. In particular, hepatic pathology correlates with atherosclerosis. Nonalcoholic fatty liver disease is associated with diabetes, hyperlipidemia, and obesity.[39] It has been found that γ-glutamyl transferase (GGT) can be elevated in nonalcoholic fatty liver disease as well as in hepatobiliary disease and alcohol abuse, may be proinflammatory, and has been correlated with atherosclerotic lesions. Clinically, elevated GGT is associated with the development of diabetes, hypertension, and hyperlipidemia as well as CHD and death from CHD.[40]

Central Obesity

Obesity, defined as a body mass index greater than or equal to 30 kg/m^2, has been known to be a cardiovascular risk factor. However, abdominal obesity, with increased superficial subcutaneous fat and deeper intraperitoneal visceral fat on the intestines and omentum, appears to have an even stronger correlation with CHD.[41] In particular, the visceral fat associated with abdominal obesity seems to be more proinflammatory and proatherogenic. Waist-to-hip ratio (WHR), which measures the degree of abdominal obesity and, accordingly, visceral obesity, is associated not only with CHD, but also with heart failure and total mortality.[42] A study examining the impact of liposuction on metabolic risk factors showed that removal of subcutaneous adipose tissue did not improve obesity-associated metabolic abnormalities.[43] Although it is not clearly understood whether abdominal obesity is causative or simply correlates with cardiovascular disease, it does appear that WHR or other measurements of central obesity do perform well as cardiovascular risk predictors.

Vascular Imaging

Although most of the risk assessment described above relates to the measurement of laboratory values,

imaging can also provide useful risk information. Atherosclerosis in any vessel—whether the coronary, carotid, renal, or peripheral arteries—suggests that atherosclerosis exists in other vessels because the causative factors are the same. Measurement of increased carotid artery intima and medial thickness (CIMT) with high-resolution ultrasonography independently predicts the development of myocardial infarction and stroke.[44] Within the coronary arteries themselves, calcium deposition, as a measure of vascular injury, often accompanies the formation of atherosclerosis. Computed tomography (CT), whether through electron-beam computed tomography (EBCT) or through multislice computed tomography (MSCT), allows for coronary artery calcium scoring, which is an independent predictor of CHD events.[4,45] Although both imaging modalities have predictive abilities, with CT, the clinician must consider the radiation exposure associated with a test being used for primary prevention risk evaluation. The radiation dose for coronary calcium scoring with an MSCT is currently about 2 to 4 mSv, although that amount is decreasing with improving technology and is less with EBCT.[46] While that amount of radiation is unlikely to itself result in concern, repeated radiation exposure with multiple imaging examinations could produce a cumulative hazard.[47]

When evaluating the overall effectiveness of imaging in risk prediction, it is useful to consider what incremental value the screening adds beyond the Framingham risk score. In particular, several recent studies have shown that imaging can be most effective in recategorizing intermediate-risk patients into either higher or lower risk groups, thereby changing treatment goals. A study of nondiabetic hyperlipidemic patients demonstrated that CIMT recategorized 22% of intermediate risk patients (Framingham 10-year risk of 6% to 20%) into different risk groups: 15% to the low-risk group and 7% to the high-risk group.[48] Similarly, the previously mentioned study in the MESA cohort demonstrated that adding coronary calcium scoring to traditional risk factor analysis improved the operating characteristics of the overall risk analysis.[4]

Lastly, the Screening for Heart Attack Prevention and Education (SHAPE) Task Force proposed a novel algorithm for assessing cardiovascular risk. The SHAPE document recommended screening of all asymptomatic at-risk individuals, defined as men between the ages of 45 and 75 years and women between the ages of 55 and 75 years (except those at very low risk), with either CIMT or with coronary calcium scoring.[49] Although not prospectively evaluated, the SHAPE screening algorithm represents a novel and thought-provoking approach to incorporating imaging into the detection of early cardiovascular disease.

Profiling Risk

Although each of the above risk factors independently predicts cardiovascular events, the power of the Framingham risk scoring system is its ability to combine multiple risk factors. This assessment of global risk rather than individual factor risk, and absolute risk as opposed to relative risk, has made the Framingham risk scoring system useful in a variety of different populations worldwide and in a multitude of treatment guidelines. Using Framingham as a basis, several groups have developed similar risk-scoring systems internationally that more closely reflect their individual populations and, in some cases, the clinical practicalities of their countries.

The Sheffield table was created out of the Scottish health survey and validated against the Framingham risk function. This simple, clinically useful scoring system aimed to be more relevant for physicians in Great Britain who used slightly different treatment guidelines than physicians in the United States.[50] The European Systematic Coronary Risk Evaluation (SCORE) project sought to develop a novel scoring system, unique from Framingham, that more closely matched European populations.[51] One of the reasons for developing these international risk scoring systems has been the concern that the Framingham risk scoring system, derived from a largely homogenous, white United States population, overestimates risk elsewhere in the world.

Although the scoring systems themselves may differ based on the population, the key risk factors are widely applicable. The INTERHEART case-control study, conducted in 52 countries worldwide, demonstrated that the risk factors of dyslipidemia, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, diet, and exercise were associated with more than 90% of the risk of an acute myocardial infarction.[52] These risk factors stem from and expand upon those described in Framingham.

Beyond increasing the geographic reach of cardiovascular risk scoring, other studies have expanded on the Framingham risk scoring with newer risk factors. The Prospective Cardiovascular Münster (PROCAM) study replaced total cholesterol with LDL-C and added the risk factors of triglycerides and family history to create another accurate scoring system.[53] Utilizing the WHS, investigators created the Reynolds Risk Score, a simple scoring system that added to the traditional Framingham risk

factors the predictors of hemoglobin A_{1c} (in diabetes patients), hs-CRP, and parental history of myocardial infarction before the age of 60.[54,55] In that cohort of women, the Reynolds Risk Score was highly effective at recategorizing intermediate-risk women more accurately into higher or lower risk categories.

In bringing the risk scoring full circle, the Framingham investigators have pushed the short-term and intermediate-term risk into long-term risk by developing a lifetime risk for cardiovascular disease. Using the Framingham data set, individuals free of cardiovascular disease at age 50 were assessed for risk factors and followed for the development of such disease. Study subjects with no risk factors at age 50 years had very low lifetime rates of cardiovascular disease. Among subjects who did have risk factors at age 50 years, there was a direct correlation with the number of those risk factors and the later development of cardiovascular disease.[56] These data suggest that early identification and prevention of cardiovascular risk factors portends significant long-term benefits.

Conclusions

The Framingham Heart Study was truly groundbreaking in establishing the concept of cardiovascular risk factors. The intervening years since 1948, when the Framingham study began, have led to a much deeper understanding of cardiovascular risk and novel indicators to predict that risk. Often these newer risk predictors help to further classify intermediate-risk patients into higher or lower classes of risk, which then impacts the therapies that they receive. Even with the development of novel risk markers, the traditional risk factors described by Framingham still make the most significant contribution to the determination of future cardiovascular events.

Whether using the Framingham risk scoring system, or the newer tools to assess cardiovascular risk, the clinician still proceeds through a similar algorithm. First, the clinician must evaluate the patient's cardiovascular risk to the highest degree possible. Second, the clinician works with the patient and utilizes a combination of therapeutic lifestyle and pharmacologic approaches to modify that risk. Third, the clinician and the patient must remain vigilant to monitor the cardiovascular risk and maintain the use of risk-modifying therapies. When used accordingly, the newer risk predictors build upon the Framingham framework to allow physicians and their patients to effectively minimize, or even avoid, the burden of cardiovascular disease. ■

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Main Points

- Data from the Framingham Heart Study showed that age, sex, diabetes, smoking, and degrees of hypertension and hyperlipidemia were found to be highly predictive of coronary heart disease (CHD).
- Multiple other risk factors that were not part of the traditional Framingham risk score have been demonstrated to predict cardiovascular disease.
- Lipoprotein(a) has been associated with inflammation and thrombosis. Although the clinical utility of evaluating lipoprotein(a) has been hindered by technical variability in measurement and limited therapeutic options available for treatment of elevated levels, the marker does provide risk information.
- Hyperglycemia has been associated with the development of cardiovascular disease, even in nondiabetes patients and when controlling for other cardiovascular risk factors.
- C-reactive protein is an acute phase reactant that may help identify patients at higher cardiovascular risk who have normal or low low-density lipoprotein cholesterol.
- Abdominal obesity, with increased superficial subcutaneous fat and deeper intraperitoneal visceral fat on the intestines and omentum, appears to have a strong correlation with CHD.

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