Framingham and European Risk Algorithms: Implications for African Americans

Peter W.F. Wilson, MD

General Clinical Research Center, Medical University of South Carolina, Charleston, SC

Based on data from the African American population, it appears that the Framingham estimates for the risk of coronary heart disease are reasonably predictive of cardiovascular outcomes in this group. However, a variety of factors exist in this population that may lead to a greater degree of misclassification than might be expected. Therefore, caution should be exercised when implementing risk algorithms, especially when effects in observational studies are incongruent with the experience of controlled clinical trials. Estimation of risk for cardiovascular events is a dynamic field, and current approaches will likely be modified as newer information is obtained.
[Rev Cardiovasc Med. *2004;5(suppl 3):S34-S41*]

Key words: African Americans • Blood pressure • Cholesterol • Coronary heart disease

A variety of methods have been suggested to estimate the risk for initial coronary heart disease (CHD) events. The origins of this approach date back to the late 1940s, when observational investigators began long-term CHD studies over intervals that typically spanned 5 to 15 years. The earliest reports noted that a combination of high cholesterol, high blood pressure, and cigarette smoking led to a greater risk of CHD events. Risks were generally higher in men than in women, and age was a critical factor for both sexes.

Age, sex, blood pressure, cholesterol, cigarette smoking, and diabetes mellitus history were universally related to CHD risk in observational studies, but prior to the availability of modern computer methods, there was no easy way to adapt risk estimates to clinical practice. The advent of testing for different lipoprotein particles and the general use of high-density lipoprotein (HDL) cholesterol screening on a population basis provided yet another variable to be considered by the early 1980s.

In the office setting, physicians have tended to emphasize relative risk for CHD. This approach compares risks for individuals of the same age and sex with others who have different combinations of factors. Longitudinal studies, however, led to the development of risk equations that provided absolute risk estimates. In the early 1990s, this approach was adapted to score sheets, as described by Anderson and colleagues.[1] Experts in preventive cardiology across Europe adopted this approach, recognizing that no single algorithm was optimal. The Framingham experience served as a reasonable source for estimates, and various modifications were used to guide prevention programs.

In 1998, the Framingham CHD risk approach was simplified, a step that increased interest in using risk prediction algorithms in clinical care. The 1998 formulation used categories for blood pressure, total cholesterol, HDL cholesterol, smoking, and diabetes mellitus to assess CHD risk. The blood pressure category followed levels set forward and still followed by the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, and the cholesterol and HDL cholesterol categories used lipoprotein levels set by the National Cholesterol Education Program.[2,3]

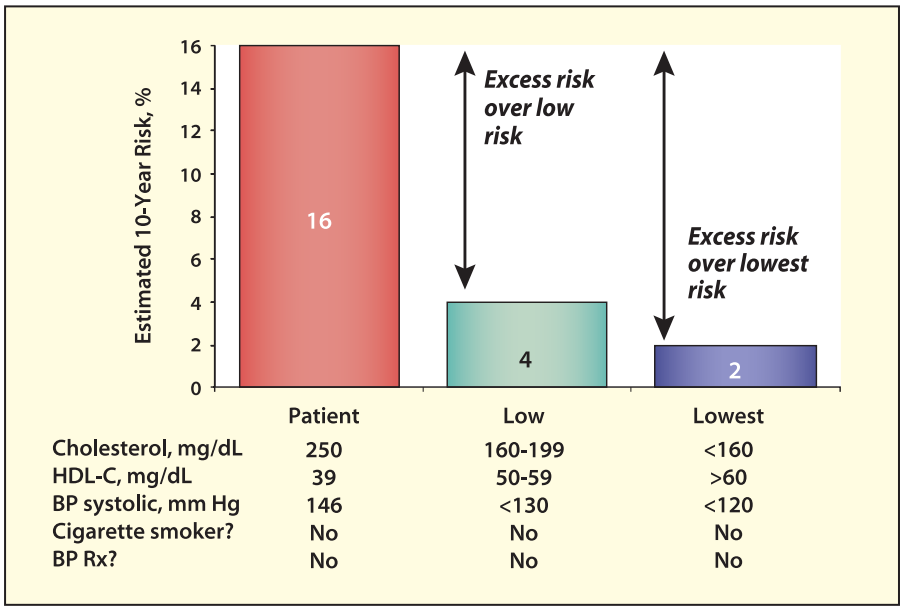

Figure 1. *Estimated 10-year hard coronary heart disease (CHD) risk in a 55-year-old man according to levels of various risk factors. For comparison, estimates are shown for a representative patient, a low-risk individual, and a lowest-risk individual. BP, blood pressure; HDL-C, high-density lipoprotein cholesterol.*

Examples of absolute and relative risk estimates from the Framingham CHD experience are shown in Figure 1. The left bar in the figure represents the estimated 10-year hard CHD risk for a 55-year-old Framingham man. For the risk factors displayed, the individual has a 16% risk of developing a first hard CHD event (myocardial infarction or CHD death) over a 10-year interval. For comparison purposes, a low-risk 55-year-old man would be expected to have a 4% risk over 10 years, as shown in the middle bar. The bar at the right shows the risk estimate of 2% over 10 years for a 55-year-old man with optimal risk factor levels. The excess risks are shown as the difference between the risk estimates. On the other hand, relative risks are derived from the ratio of the absolute estimates. For example, a 16%:4% ratio implies a relative risk of 4 when comparing the test subject to a low-risk individual, and a 16%:2% ratio implies a relative risk of 8 when comparing the test subject to an individual at the lowest risk.

In 1999, the National Heart, Lung, and Blood Institute convened a CHD Prediction Workshop to address the use of Framingham CHD risk functions in other populations. Validation of the Framingham CHD prediction scores was shown for a large number of observational data sources, representing multiple ethnic groups.[4] This workshop was restricted to American studies, and most of the data came from observational studies of Whites, including the Atherosclerosis Risk in Communities [ARIC] (3 white cohorts, 1 African American cohort), the Physicians Health Study, the Honolulu Heart Program (Japanese American men), the Puerto Rican Heart Study (Puerto Rican residents), the Strong Heart Study (Native Americans), and the Cardiovascular Health Study.

As part of the CHD workshop proceedings, D'Agostino and associates[4] showed that the effects of most CHD risk factors were similar across

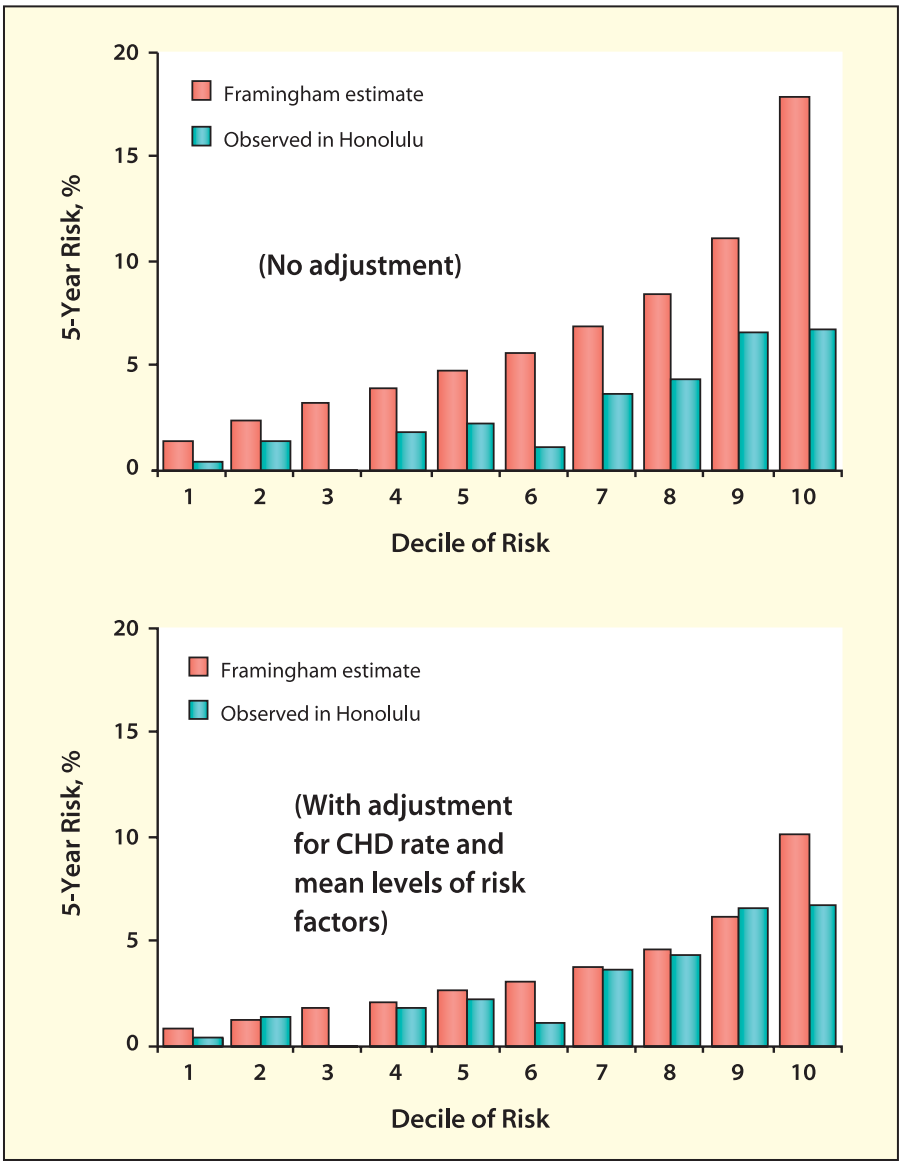

Figure 2. *Predicted versus actual estimates of hard coronary heart disease (CHD) events in men enrolled in the Honolulu Heart Study, using Framingham CHD risk equations for men. Adapted with permission from D'Agostino et al.*[4]

the different study groups. The first step undertaken in this process was discrimination of future CHD cases from noncases, with each study using its own data. The area under the receiver operating characteristic (ROC) curve was used to assess the discriminatory capabilities of these risk predictions. By this approach, an area of 0.50 indicates no predictive capability and an area of 1.00 indicates complete discrimination. Prediction algorithms for heart disease that use traditional CHD risk variables have typically provided an ROC area of approximately 0.70. External calibration was the second step in testing the CHD risk estimation. This analysis tested whether equations developed from an individual site could reliably predict CHD outcomes in other locales. The equations derived in Framingham were tested in each site and showed good predictive capabilities for CHD outcomes in the various ethnic groups and ages represented, with some exceptions.

The third step in the validation assessment of CHD risk equations in the 1999 CHD Risk Workshop was estimation of absolute risk in different population groups. Results for the Honolulu men using the Framingham risk equations are shown in Figure 2. Study participants were ranked according to estimated sex-specific decile of CHD risk over 5 years, each estimated decile was matched with the actual CHD experience, and accuracy of fit was determined with the Hosmer-Lemeshow chi-square test.[4] The unadjusted results were significantly different, and the Framingham equations systematically overestimated CHD risk in the Hawaiian men. It was possible, however, to markedly improve the estimation if the Framingham CHD risk equations were adjusted for the overall CHD rates in Hawaii and if the estimating equations were modified to use the mean risk factor levels from the Hawaiian participants. The full details of these adjustments are provided by D'Agostino and coworkers.[4] On the other hand, the Framingham Heart Study equations were able to reliably predict CHD risk in African American men and white men who participated in the ARIC study (Figure 3). No additional corrections were needed to provide accurate CHD risk estimates for the ARIC men. Good predictive capability was also shown for the ARIC white women and African American women, without any need for adjustments (not shown). Overall, these results suggested that Framingham CHD equations provided reasonable estimates for CHD risk in African American population groups.

The National Cholesterol Education Program (NCEP) published new guidelines in 2001 that included using the Framingham risk approach to estimate the absolute risk for initial CHD events in some individuals. People with diabetes mellitus were considered to be at a very high risk for an initial CHD event, and the committee recommended aggressive risk factor management of those with type 2 diabetes, treating them as if they had already developed CHD.[3] A new CHD risk equation based on the Framingham experience was developed for the NCEP report. In this algorithm, people with diabetes were not included and hard CHD risk was estimated, and the algorithm included interaction terms for age × cholesterol, age × smoking, and blood pressure level × blood pressure treatment.

European CHD Risk Estimation Approach

By the late 1990s, concern had risen among European scientists as to how well Framingham algorithms predicted CHD risk in their region. A prospective study in Munster, Germany, provided data for CHD risk estimation;[5] however, data were sparse for women, and European scientists did not believe that equations derived from German men were adequate to estimate risk in all sectors of Europe. A large-scale, multinational European effort was undertaken to address this issue. This consortium, called the System for Cardiac Operative Risk Evaluation (SCORE) Project, included data from 12 European countries, and most of the participants were white. The investigators analyzed data sets from several observational studies, more than 200,000 men and women were represented, and the experience included 2.7 million person-years of follow-up. The large number of countries, different collection methods, and difficulty in assuring accuracy in CHD events across the different regions led to some limitations. Fatal cardiovascular disease (CVD) was the vascular disease outcome that was estimated, as there were not enough data to assess CHD morbidity.

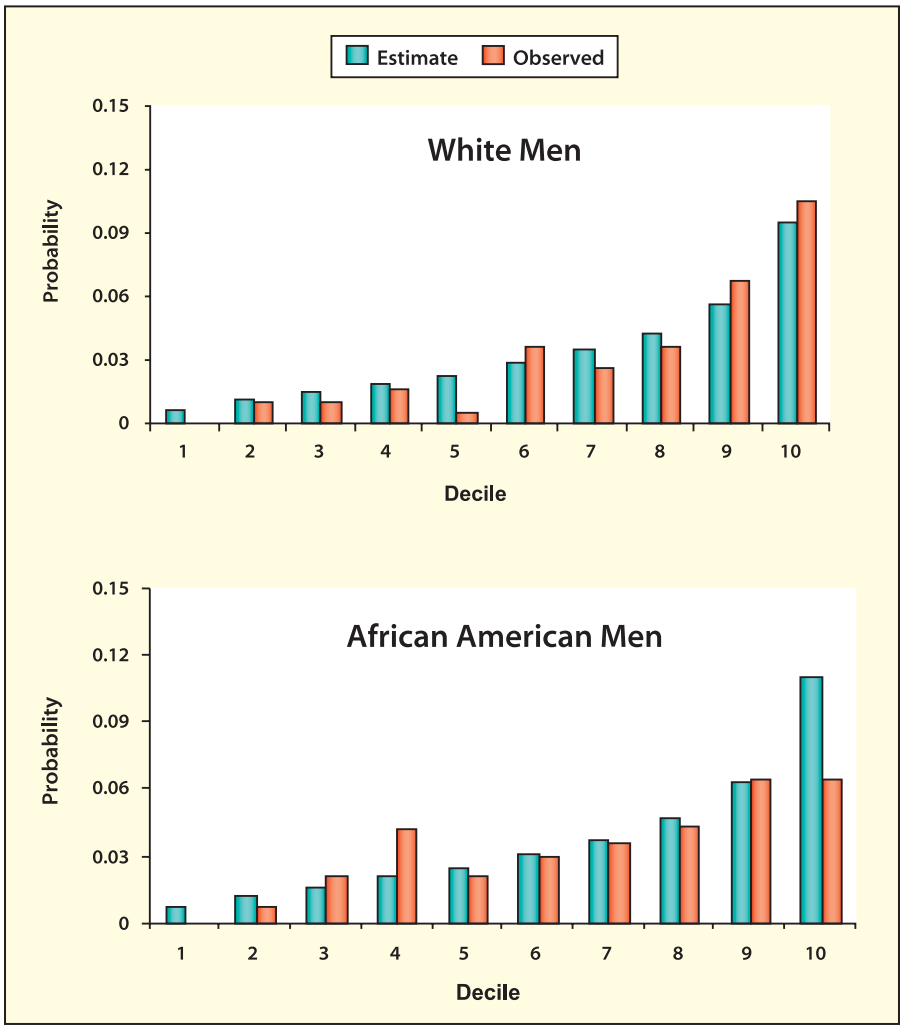

Figure 3. *Predicted versus actual estimates of hard coronary heart disease (CHD) events in men enrolled in the Atherosclerosis Risk in Communities study, according to decile of CHD risk. Adapted with permission from D'Agostino et al.*[4]

The SCORE Project undertook validation efforts within the participating groups, and the investigators reported that risk of CVD death could be estimated with good discrimination. The area under the ROC curve ranged from 0.71 to 0.84 for the participating countries. The SCORE scientists also reported that HDL cholesterol information did not markedly improve the capability of CHD risk estimation in their data, a result that differed from the North American experience. They showed that CHD mortality risk varied considerably across Europe and population samples from higher latitudes typically experienced greater risk than those closer to the equator. Because of these differences, they provided 2 CVD death risk–estimating

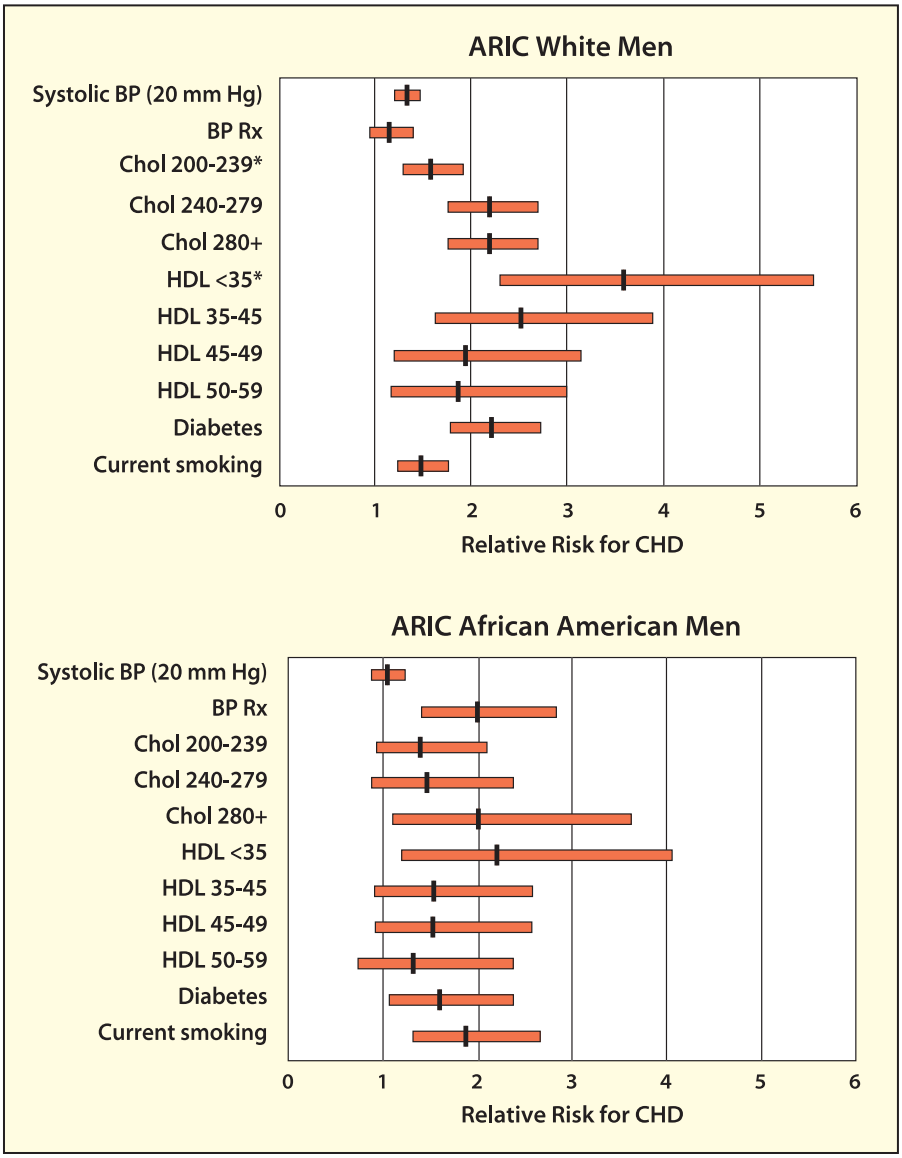

Figure 4. *Age-adjusted relative risks for coronary heart disease (CHD) in men enrolled in the Atherosclerosis Risk in Communities (ARIC) study. *Figures for cholesterol and high-density lipoprotein are given in milligrams per deciliter. BP, blood pressure; Chol, cholesterol; HDL, high-density lipoprotein. Data from Chambless et al.*[13]

algorithms and recommended that the high-risk algorithm be used for persons from high-CVD risk countries (eg, Russia, Scotland, Sweden, and the United Kingdom) and a different CVD risk algorithm be used for regions where CVD risk was lower (eg, France, Southern Germany).

The SCORE investigators noted limitations in vascular disease risk estimation, including the error related to use of measurements from a single clinic visit, the potential effects of a regression-dilution bias, the use of principal risk factors only, and absence of information such as family history of premature vascular CHD. Unfortunately, SCORE had only CVD mortality experience, provided low estimates of risk that needed to be extrapolated to estimate CHD morbidity, and included few minority participants, which may limit its utility.

CHD Risk Estimation in the African American Population

A variety of issues relating to CHD risk estimation are of particular importance to high-risk population groups such as African Americans. Most of the standard CHD risk variables exhibit differences in effects, prevalence, or treatment in African Americans, and these differences may affect the accuracy of prediction.

For example, in comparisons of the relative risks for CHD in the ARIC participants, the relative risk for CHD in people with diabetes was significantly increased in men (2.19, Whites; 1.60, African Americans) and women (2.95, Whites; 1.86, African Americans) (Figures 4 and 5). Different results were evident for the effects of blood pressure on CHD risk in white versus African American participants. The relative risk for CHD associated with a 20 mm Hg difference in systolic pressure was 1.31 in white men, a relative risk that was statistically greater than 1.00. On the other hand, the relative risk for a 20 mm Hg difference in African American men was only 1.05, and not statistically significant. The lower relative risk in African American men might lead a reader to conclude that systolic pressure exerted a less important effect in African American men. However, the relative risk of CHD related to hypertension therapy was 2.00 in African American men and only 1.13 in white men, indicating that hypertension treatment in African American men was associated with a much greater risk than anticipated. A reasonable interpretation of this result is that hypertensive African American men were treated inadequately and may have received therapy later in the course of the

hypertension. These data are discouraging, as clinical trials have convincingly demonstrated beneficial effects of hypertension therapy on CHD risk in white and African American populations. These results also suggest that caution should be exercised when implementing CHD risk algorithms, especially when effects in observational studies are not congruent with the experience of controlled clinical trials.

Blood pressure elevation has been consistently shown to be an important CHD risk predictor, and levels are typically higher in the African American population. These differences may be particularly important in higher blood pressure categories. For example, Joint National Committee Hypertension grades III and IV are uncommon in the Framingham Heart Study experience for Whites but are more frequently seen in African American population groups. A second blood pressure consideration is the role of blood pressure treatment. There may be a greater degree of no treatment, undertreatment, and late treatment of hypertension among African Americans compared with Whites in the United States.

A third element related to blood pressure is the myocardium itself, regarding left ventricular mass and electrocardiographic left ventricular hypertrophy. In the 1991 formulation of CHD risk published by the Framingham investigators, left ventricular hypertrophy on electrocardiogram (ECG-LVH) was included as a risk factor. Framingham data obtained during the 1990s showed that the prevalence of ECG-LVH was low, only a few percent, and the Joint National Committee on Blood Pressure and NCEP expert committees have not recommended ECG determinations or echocardiographic evaluations at the time of screening for CHD risk.[2,3] This recommendation may hold for white population groups, but the greater prevalence of ECG-LVH in African Americans, potentially occurring at the same blood pressure levels, suggests biological differences may be operative and more pronounced adverse effects on CHD risk are possible. Data from observational studies have consistently shown that ECG-LVH leads to a fivefold or greater risk for CHD. Overall, the data suggest that ECG-LVH is a CHD risk equivalent and should be assessed in population groups in which it is reasonably common so that aggressive therapy may be instituted and maintained.

Blood cholesterol levels in Whites and African Americans are roughly

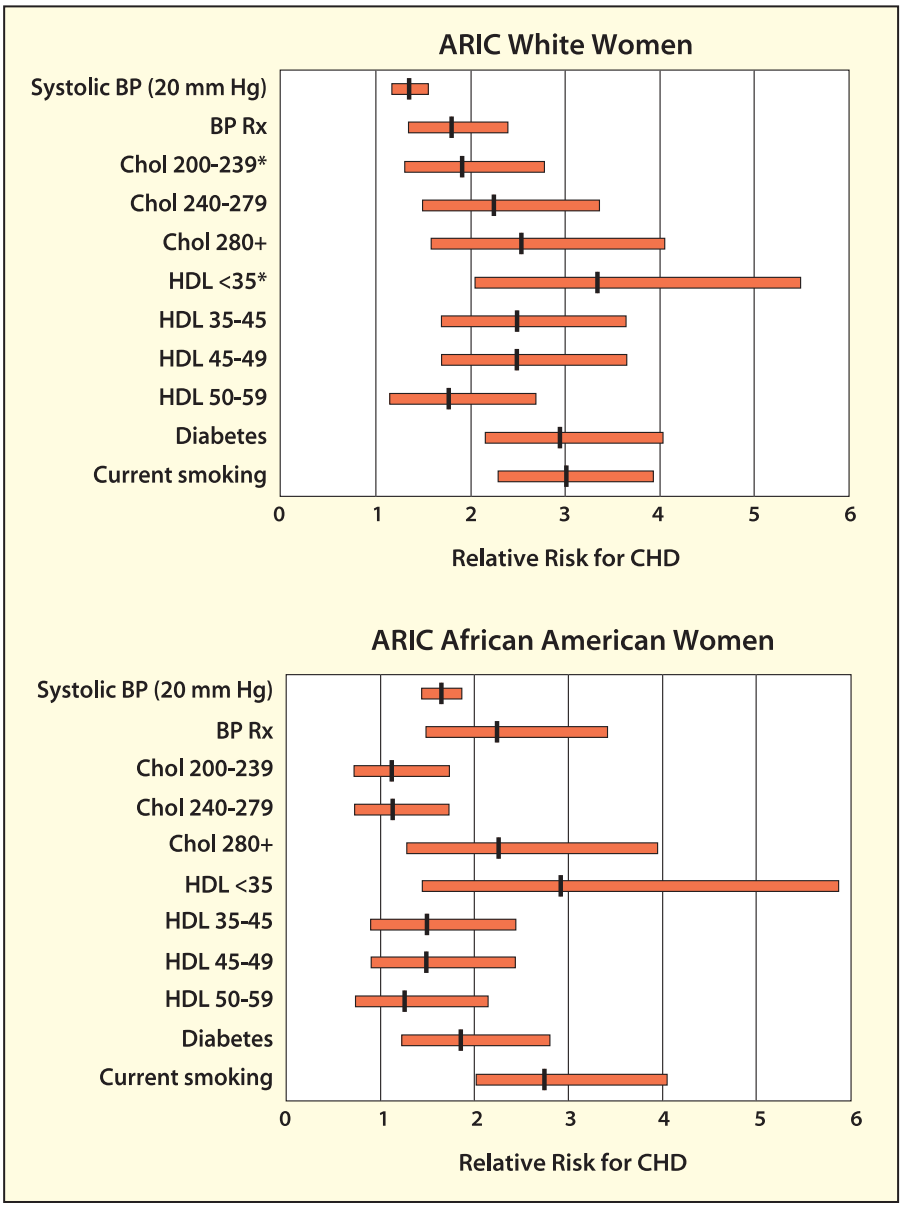

Figure 5. *Age-adjusted relative risks for coronary heart disease (CHD) in women enrolled in the Atherosclerosis Risk in Communities (ARIC) study. *Figures for cholesterol and high-density lipoprotein are given in milligrams per deciliter. BP, blood pressure; Chol, cholesterol; HDL, high-density lipoprotein. Data from Chambless et al.*[13]

similar, but a tendency toward higher HDL cholesterol levels has typically been reported for African Americans.[6] This difference may not be obtained among African Americans in a higher socioeconomic class or if obesity or type 2 diabetes mellitus is present.[7]

Additionally, levels of lipoprotein (a), a lipid particle that includes an apolipoprotein (a) linked to a low-density lipoprotein moiety, are typically greater in persons of African ancestry.[8]

Finally, obesity and type 2 diabetes mellitus are more common among African Americans, and CHD risk has not been well characterized for this group. In the African American ARIC participants from Jackson, Mississippi, most of the CHD risk factors appeared to exert effects that were similar to what was observed for white Americans. It has been reported, however, that greater duration of diabetes and microalbuminuria may augment the risk of initial CHD events in people with diabetes.[9] These issues may be particularly important to African Americans with type 2 diabetes mellitus and have not been well assessed.

The tendency toward less arterial calcification in the African American population has the potential to provide false assurances of low CHD risk for individuals who might undergo testing.

A variety of cardiovascular techniques are now available to assess subclinical arteriosclerosis. Examples of these methods include the ankle-brachial index, carotid intima-media thickness measurement, and assessment of arterial calcium with computed tomographic techniques.[10] Investigators have suggested that subclinical assessments may improve the prediction of later clinical CHD events, but many of the investigations are limited because the population groups were self-referred.[11] Caution is needed when interpreting these studies, and large-scale investigations are under way to assess the utility of this new approach, especially considering the possibility of serial testing. By this strategy, individuals would undergo a screening evaluation and selected persons would undergo additional testing to refine CHD risk estimates. A word of caution, however, is particularly appropriate for African American individuals who might undergo this sort of testing. It has been noted that African American individuals generally have less arterial calcification.[12] The tendency toward less arterial calcification in the African American population has

Main Points

- In 1998, the Framingham coronary heart disease (CHD) risk approach was simplified, a step that increased interest in using risk prediction algorithms in clinical care. The 1998 formulation used categories for blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, smoking, and diabetes mellitus to assess CHD risk.
- In 1999, the National Heart, Lung, and Blood Institute convened a CHD Prediction Workshop to address the use of Framingham CHD risk functions in other populations. Overall, the results suggested that Framingham CHD equations provided reasonable estimates for CHD risk in African American population groups.
- The System for Cardiac Operative Risk Evaluation (SCORE) Project undertook validation efforts within participating groups, and the investigators reported that risk of CVD death could be estimated with good discrimination.
- A variety of issues relating to CHD risk estimation are of particular importance to high-risk population groups such as African Americans. Most of the standard CHD risk variables exhibit differences in effects, prevalence, or treatment in African Americans, and these differences may affect the accuracy of prediction. Caution should be exercised when implementing CHD risk algorithms, especially when effects in observational studies are not congruent with the experience of controlled clinical trials.
- Blood pressure elevation has been consistently shown to be an important CHD risk predictor, and levels are typically higher in the African American population. These differences may be particularly important at higher blood pressure categories.
- Blood cholesterol levels in Whites and African Americans are roughly similar, but a tendency toward higher HDL cholesterol levels has typically been reported for African Americans.
- Obesity and type 2 diabetes mellitus are more common among African Americans, and CHD risk has not been well characterized for this group.

the potential to provide false assurances of low CHD risk for individuals who might undergo testing.

Future Directions for CHD Risk Estimation

Estimation of risk for cardiovascular events is a dynamic field, and it is expected that approaches will undergo modification as newer information is obtained. There is tremendous enthusiasm for the incorporation of novel factors into CHD and CVD risk estimation, but a variety of issues require examination. A primary consideration is that more clinical data may provide only small improvements in risk estimates. Novel risk factors stimulate interest in the pathophysiology of disease, but their use may be limited by lack of standardized testing, large variability in the measurements, high correlation with existing risk factors, and lack of validation across multiple studies. In addition, cost and benefit for any new test must be considered. It is more likely that low-cost tests that are easy to standardize will be incorporated into CHD and CVD risk estimation more rapidly than expensive tests that may require technical expertise, specialized equipment, and have limited availability.

Summary

In summary, data from African American population groups suggest that Framingham risk estimations are reasonably predictive of cardiovascular outcomes in this segment of the population. As mentioned above, however, a variety of factors may be operative in African Americans that could lead to a greater degree of misclassification than might have been anticipated. These include differences in blood pressure treatment, predilection toward left ventricular hypertrophy and greater left ventricular mass, different distributions of HDL cholesterol and lipoprotein (a), a greater tendency toward end-organ kidney damage, and less arterial calcification. ■

References

1. Anderson KM, Wilson PWF, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. *Circulation*. 1991;83:357-363.
2. Lenfant C, Chobanian AV, Jones DW, Roccella EJ. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension*. 2003;41:1178-1179.
3. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
4. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham Coronary Heart Disease Prediction Scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180-187.
5. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. *Circulation*. 2002;105:310-315.
6. Watkins LO, Neaton JD, Kuller LH, for the MRFIT Research Group. High density lipoprotein cholesterol and coronary heart disease incidence in black and white MRFIT usual care men. *Circulation*. 1985;71:417a.
7. Wilson PW, Savage DD, Castelli WP, et al. HDL-cholesterol in a sample of black adults: the Framingham Minority Study. *Metabolism*. 1983;32:328-332.
8. Mooser V, Seabra MC, Abedin M, et al. Apolipoprotein(a) kringle 4-containing fragments in human urine. Relationship to plasma levels of lipoprotein(a). *J Clin Invest*. 1996; 97:858-864.
9. Stevens RJ, Coleman RL, Adler AI, et al. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. *Diabetes Care*. 2004;27:201-207.
10. Wilson PW, Smith SC Jr, Blumenthal RS, et al. 34th Bethesda Conference: Task force #4—How do we select patients for atherosclerosis imaging? *J Am Coll Cardiol*. 2003;41:1898-1906.
11. Raggi P, Cooil B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. *Am Heart J*. 2001;141:375-382.
12. Bild DE, Folsom AR, Lowe LP, et al. Prevalence and correlates of coronary calcification in black and white young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Arterioscler Thromb Vasc Biol*. 2001; 21:852-857.
13. Chambless LE, Folsom AR, Sharrett AR. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Epidemiol*. 2003;56:880-890.