Although the Framingham Risk Score forms the bedrock of coronary heart disease (CHD) risk prediction, it has several limitations that have been well documented. The clinician is left to manage a significant proportion of patients who have “low to intermediate” estimated risk but accrue the majority of CHD events because they form the majority (~65%) of the population.

The concept of lifetime risk was highlighted in the National Cholesterol Education Program Adult Treatment Panel (ATP) III guidelines and is an important one, especially for individuals who are young to middle-aged. Traditional risk factors become manifest more often in the 4th and 5th decades of life when the estimated lifespan based on national averages is at least another 4 to 5 decades. Hence, estimating a 10-year risk may give individuals a false sense of security that they have a low risk for CHD, when in reality, this may not be true when their entire lifetime is considered.

In the current issue of Circulation, Berry et al further demonstrate the importance of the concept of lifetime risk by observing that among individuals <50 years of age who have low risk by the Framingham Risk Score, equal numbers of individuals have a low lifetime risk and a high lifetime risk. Furthermore, they show that those with a low short-term (10-year) and a high lifetime risk have a greater burden and progression of subclinical atherosclerosis measured by imaging tests (carotid intima-media thickness and coronary calcium score) than those with low short-term and lifetime risks.

To test their hypothesis, they used 2 population-based studies, the Coronary Artery Risk Development in Young Adults (CARDIA) study and the Multi-Ethnic Study of Atherosclerosis (MESA). Although this analysis provides important proof that not everybody with low risk is similar, certain limitations must be mentioned. The authors have already pointed out that they used the Framingham Risk Score in ethnicities in which it has not been well validated. Furthermore, it is unclear what therapy, if any, these individuals had over the course of the follow-up. Finally, it is unclear whether the individuals with low short-term and low lifetime risk remained the same throughout the course of the study or how many of them progressed to a higher lifetime risk on subsequent examinations.

There clearly are limitations with the concept of lifetime risk as well. If one has a single elevated risk factor, one could have a high lifetime risk. For example, a 40-year-old man with a blood pressure of 118/78 mm Hg who is a nonsmoker and has a total cholesterol of 178 mg/dL has a lifetime CHD risk of 5%, whereas the same man with a total cholesterol of 201 mg/dL has a lifetime CHD risk of 46%. Clearly, as clinicians, we see such fluctuations in measurements of total cholesterol. Furthermore, given that the presence of any one elevated risk factor can confer a high lifetime risk, do we treat everybody with a high lifetime risk more aggressively? Primary prevention statin trials, such as the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), have already shown that treatment with statins in an individual with hypertension, a traditional risk factor, decreases the risk of CHD events, which supports the concept that perhaps treating individuals with a high lifetime risk would be of value. Added to this are the results from another recent primary prevention trial, Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), which showed the efficacy of statins in individuals with low-density lipoprotein cholesterol (LDL-C) <130 mg/dL but with hs-CRP levels >2 mg/L. The economic burden of
the expanding use of statins must also be considered if individuals with a single traditional risk factor and high lifetime risk are treated with drugs to lower LDL-C level. The ATP IV report will need to take into account several key aspects: (1) the stronger evidence that has accumulated for primary prevention; (2) the differences in the short-term and lifetime risks in the population; (3) the additive value of other biomarkers, imaging tests, and genetic information; and (4) the current costs and safety of statin therapy.

Suggested New Risk-Stratification Schema

The management of individuals in the highest-risk group (estimated 10-year CHD risk >20%) is fairly straightforward: They require aggressive risk factor modification. Traditionally, we have considered the management of low risk (estimated 10-year CHD risk of 0% to 10%) to be straightforward as well. However, emerging data such as those presented by Berry et al suggest that not everyone with “low” 10-year risk has low long-term risk. In our own analysis of the Atherosclerosis Risk In Communities study, we found that when the low-risk group was divided into 0% to 5% and 5% to 10% categories, a significant difference in observed risk was seen over a follow-up of ~14 years. Hence, for more effective risk assessment and prevention of CHD, the definition of low risk and targets for therapy in these patients may need to be reconsidered.

Currently, ATP III guidelines recommend counting the number of risk factors and estimating the Framingham Risk Score in individuals with 2 or more risk factors; however, on the basis of data that have suggested a potential for a high lifetime risk in the presence of even 1 traditional risk factor, this strategy needs to be reconsidered. One alternative approach (Figure) is to estimate the Framingham Risk Score in any individual who has any risk factor other than age. Once the Framingham Risk Score is estimated, for those who have an estimated short-term (10-year) risk of 0% to 10%, the lifetime risk should be evaluated to refine risk stratification. In individuals with low short-term risk but high lifetime risk, and in individuals at intermediate risk, additional imaging or biomarker assessments may help to further refine risk. TLC indicates therapeutic lifestyle changes; CIMT, carotid intima-media thickness.

Figure. Alternative approach to risk assessment. For any individual with risk factors other than age, Framingham Risk Score should be estimated to determine short-term (10-year) risk, and lifetime risk should be evaluated to refine risk stratification. In individuals with low short-term risk but high lifetime risk, and in individuals at intermediate risk, additional imaging or biomarker assessments may help to further refine risk. TLC indicates therapeutic lifestyle changes; CIMT, carotid intima-media thickness.
mg/dL. In individuals with an estimated short-term risk of 0% to 10% and an increased lifetime risk, an additional risk marker such as hs-CRP or an imaging test such as coronary artery calcium score or carotid intima-media thickness may be considered. For individuals reclassified to a higher-risk group, the goal for LDL-C should be <130 mg/dL, with an optional goal of <100 mg/dL. For those individuals with no evidence of subclinical atherosclerosis or inflammation and low short-term (10-year) risk, the goal for LDL-C would remain <160 mg/dL, with an optional goal of <130 mg/dL. Finally, in the intermediate-risk group (10% to 20% estimated 10-year risk), the goal for LDL-C would be <130 mg/dL, with an optional goal of <100 mg/dL. In these individuals, additional imaging and biomarkers as suggested above could be used as an adjunct to guide intensity of therapy, ie, to identify individuals in whom the optional goal of LDL-C <100 mg/dL should be targeted. Prospective clinical trials should be designed to test new strategies for risk assessment using imaging tests, just as they have recently been conducted using hs-CRP.

Evidence is mounting that the LDL-C levels present in most humans at birth (ie, ≈50 to 60 mg/dL) may be optimal. Overall, the benefit of incremental LDL-C reduction with statins appears to extend until these LDL-C levels are achieved. With the current availability of $4 generic statins, and given that more efficacious statins such as atorvastatin will become generic in the near future, the cost-effectiveness of statins will improve, which would allow more aggressive LDL-C targets in primary CHD prevention settings. Even before ATP IV guidelines are issued, the clinician will do well to understand that 10 years is definitely not a lifetime in CHD risk prevention.

Disclosure
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References

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