Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, including in the United States. Fortunately, the major risk factors contributing to the development of atherosclerotic CVD have been detailed in epidemiological studies, and randomized clinical trials have demonstrated the benefits of lowering elevated levels of risk factors. Yet, one of the most challenging questions in clinical medicine remains: if and when to treat levels of risk factors. Yet, one of the most challenging trials have demonstrated the benefits of lowering elevated tailed in epidemiological studies, and randomized clinical to the development of atherosclerotic CVD have been de-

Central Tenets of CVD Risk Prediction

A few concepts have helped us in identifying strategies to answer the question posed above. First, CVD risk develops over the entire life course as a result of the combined influences of lifestyle-related factors, environmental triggers, and genetic susceptibility. Second, clinically overt CVD usually is antedated by the presence of ≥1 risk factors and subclinical atherosclerosis. Such a time course of evolution provides us with a window of opportunity for prevention/intervention. The long latency of CVD means that preventive approaches also may vary over the life course. Third, CVD prevention is best thought of as a combination of “population-based” prevention, primary prevention in high-risk individuals, and secondary prevention in those with established clinical CVD. The exact proportion allocated to each of these 3 approaches varies, depending on the mean absolute CVD risk (and its distribution) in a given community and the healthcare resources available at hand. Fourth, with regard to the “high-risk individuals” approach, rates of CVD vary among people with identical levels of any particular risk factor based on the levels of other risk factors, emphasizing the multifactorial origin of CVD. Therefore, combining information about levels of different CVD risk factors in an individual using 1 or more risk prediction algorithms is the best approach for assessing the likelihood that he or she will experience a CVD event in the short or long run; the estimated probability of developing CVD is referred to as the absolute risk of developing an event over a given time period. Fifth, for the most efficient use of healthcare resources, the intensity of risk factor reduction in a given individual over a given time frame should be aligned with the absolute risk of developing CVD events over that time frame. Accordingly, the choice of interventions over different time frames in different people may vary. This strategy, referred to as risk stratification, facilitates identification of high-risk candidates for CVD who have multiple marginal risk factors and quantifies absolute risk in persons with only a single risk factor, thereby mitigating needless alarm. It also informs about the number needed to treat to prevent 1 CVD event with a specific therapeutic option, thereby facilitating informed choice among various treatment alternatives. In addition, the approach could potentially aid serial monitoring of an individual’s response to treatment/preventive measures as reflected by improvement in their multivariable risk scores. Sixth, CVD risk assessment is one of several key steps in risk management and is critical for risk communication. The ultimate decision of whether to treat a given individual and how best to treat that individual also is based on factors other than the multivariable risk score such as clinical judgment, the views and preferences of the individual in whom treatment is contemplated, and the practical realities of the healthcare system in which the individual lives and the physician practices. Seventh, an evolving consensus among experts is the notion that individuals are better served if absolute CVD risk is the focus of treatment rather than the prevalent “silo” approach of treating individual risk factors.

The Framingham General CVD Risk Profile

Several CVD risk assessment instruments have been developed sequentially, each seeking to address the limitations of prior tools. The Framingham general CVD risk profile1 sought to address some of the criticisms of its precursors. First, because practitioners intend to prevent all CVD events and not just coronary heart disease events, the latest tool chose the composite end point of atherosclerotic CVD (coronary heart disease, stroke, transient ischemic attack, intermittent claudication, and heart failure). This is specifically...
important because the case mix of CVD varies across populations, with greater rates of non–coronary heart disease atherosclerotic events (such as strokes) in some populations. The performance of this general CVD risk profile also was good for predicting its individual CVD events, allowing, with simple adjustments, an estimation of the risks of each CVD component. Second, 2 new risk assessment scores were formulated: one based on standard risk factors (including laboratory variables) and another based on nonlaboratory predictors in which body mass index was substituted for the laboratory tests. Third, to enhance risk communication, Framingham Heart Study investigators translated the estimated CVD risk into a notion of “vascular age,” comparing a given individual with one who has optimal levels of CVD risk factors. This concept is analogous to the notion of rate advancement (how many years earlier a disease occurs in exposed compared with unexposed) used in epidemiological literature and has the potential advantage of being more easily understood by laypersons.

Assessment of the Framingham General CVD Risk Profile

The National Cholesterol Education Program Adult Treatment Panel III proposed a risk assessment instrument (based on Framingham data) for estimating the absolute risk of “hard” coronary heart disease events over a 10-year period. Investigators have previously highlighted the propensity of the Adult Treatment Panel III algorithm to categorize women and younger men as having a low short-term absolute CVD risk (<10%) even when they have elevated levels of several risk factors. In this issue of Circulation, Marma and Lloyd-Jones critique the latest Framingham general CVD risk prediction tool by assessing which risk factor combinations result in reaching an absolute 10-year CVD risk of 20% and how different risk factor burdens translate into the concept of vascular age.

In their systematic examination of this latest Framingham CVD risk profile, the authors make some interesting observations. They note that the new risk assessment tool improves on prior Framingham algorithms mainly because it uses an expanded set of atherosclerotic CVD outcomes. Thus, some men and women can reach an absolute CVD risk threshold of 20% at a younger age with this general CVD risk profile (eg, men age ≥35 years and women ≥40 years of age with a specified maximal risk factor burden). However, the authors point out that even with this new assessment instrument, some younger individuals (men <55 years or women <60 years of age) with 1 CVD risk factor will not reach the 20% absolute risk threshold even if that risk factor is markedly abnormal. Other young people (men <40 years or women <50 years of age) may harbor multiple risk factors yet not be recognized as being at “high risk.” This is of concern because a modest 10-year risk in young to middle-aged individuals may evolve into a substantial lifetime CVD risk in the elderly. In addition, recent data indicate that individuals <50 years of age but with a higher burden of risk factors (and consequently greater lifetime CVD risk) have a greater prevalence of subclinical atherosclerosis and experience greater progression of subclinical disease compared with individuals with a lower risk factor burden (and lower lifetime risk). Overall, if a 20% absolute CVD risk was used as the threshold for instituting treatment, the general CVD risk assessment instrument would differentially result in treatment of older people. Such a strategy could be deemed suboptimal from a public health perspective because CVD events in young and middle-aged individuals may not be prevented.

How Best to Approach CVD Risk Estimation Over the Life Course

It is important to note that the limitations noted by Marma and Lloyd-Jones are not unique to the Framingham general CVD risk profile. Rather, these shortcomings plague any tool that assesses short-term absolute risk. Two specific scenarios generate debate: how best to approach the individual with high short-term absolute CVD risk who has levels of individual risk factors below some contemporary single factor-oriented guidelines, a situation encountered frequently in older people, and how best to treat the individual with multiple risk factors (exceeding levels that are “treatable” in some single-factor guidelines) but low short-term absolute CVD risk, typically seen in younger people.

Absolute CVD risk escalates with age, and it is important to keep in mind that currently available risk prediction tools are valid up to 75 years of age. Use of an absolute risk threshold of 20% beyond this age carries the risk of labeling most older people as high risk and therefore as candidates for treatment of CVD risk factors even with “average” levels of risk factors. It has been noted that beyond this age treatment sometimes simply “changes the cause of death rather than prolonging life.” The notion of absolute risk also raises ethical issues about the appropriateness of risk-based versus time-based allocations of preventive resources. A time-based approach uses differences in the absolute numbers of life-years gained and deaths averted, directing more treatment at younger people (leading to the so-called Matthew effect). Risk-based strategies direct greater treatment at elderly, leading to more deaths averted (mostly among those ≥70 years of age) but fewer life-years gained relative to the time-based approach. Such risk-based approaches are “age blind” in that the social role and productivity of individuals at different ages are not factored into cost-effectiveness estimates. As noted by Bonneaux, “Absolute risk scores also label male sex, old age, and risky lifestyles as diseases to be treated, while denying life extending drugs to women, younger people, and those living healthily.”

How does one reconcile the issue of to treat or not to treat (especially with drugs) in the short run young individuals who have a low short-term but higher long-term CVD risk? Several caveats must be remembered before one ventures to answer this question. Jackson has underscored the different perspectives of short-term prediction and lifetime risk assessment. Short-term prediction has a clinical focus of intervening over the next 5 to 10 years with the expectation of direct benefit to patients in the short run. Lifetime risk is more important in terms of public health, while at an individual level it emphasizes the need for implementing lifestyle-related measures to lower risk in the long run over which the
heightened risk is experienced. There is some evidence that if levels of risk factors in such individuals are lowered at a later age (assuming failure to lower them with nonpharmacological means in the short run), CVD risk is often reversed rapidly, so waiting to treat a single elevated risk factor in a person with low absolute risk may not necessarily be a hazardous strategy (with some exceptions, as noted below).\textsuperscript{9,12} In addition, it is important to remember that most CVD risk factor intervention trials have been of relatively short duration (typically <6 years). It is unclear whether the results of these trials can be extrapolated to initiate long-term pharmacological treatment of individuals with currently low absolute risk but higher long-term risk. Most such individuals would not benefit from treatment in the short run, and estimation of the number needed to treat to prevent a CVD event would confirm the limited cost-effectiveness of such an approach.\textsuperscript{2}

Some strategies are available to guide risk reduction in younger individuals with multiple risk factors in whom absolute short-term absolute CVD risk may be below the threshold of 20%. For one, presentation of both the relative risk (comparing a given individual’s risk with that of someone with an optimal risk factor profile) and the absolute risk of CVD, as suggested by some European guidelines,\textsuperscript{4} may motivate such individuals to adopt lifestyle-related measures aggressively. Another risk communication strategy that could be explored to motivate younger individuals to modify their risk profile in the short run and eventually over the life course is one in which the short-term risks,\textsuperscript{9} the recently formulated 30-year absolute CVD risks,\textsuperscript{13} and the associated relative risks (comparison with corresponding risks experienced by individuals with a more favorable risk factor profile) are juxtaposed (the Figure).

It is also pertinent to note that there may be clear situations in which single risk factors are targeted even when the absolute CVD risk is <20% because some risk factors have consequences well beyond CVD. The 2 risk factors worth noting in this context are smoking (which causes cancers) and diabetes (which if uncontrolled can result in multiple end-organ damage). In these cases, one should not be guided by the absolute CVD risk estimates alone. In addition, marked elevations of single risk factors (eg, hypertensive urgency) must be treated regardless of short-term absolute risk because of the imminent danger to people in these situations.

### Moving Beyond the Framingham General CVD Risk Profile: Some Contemporary Issues

It is critical to note that the absolute CVD risk is likely influenced by several factors that are not part of the Framingham general CVD risk profile. At least 4 sets of such factors have been highlighted in the contemporary literature.\textsuperscript{14} They include family history of CVD, socioeconomic position, ethnicity, and newer risk factors (genetic, circulating, and imaging biomarkers). Some guidelines (such as the recent UK lipid-lowering guidelines\textsuperscript{14}) suggest that absolute risk estimated with an earlier version of the Framingham CVD prediction instrument be multiplied by 1.5 to 2 (for 1 or >1 first-degree relative with premature CVD, respectively) and by 1.4 for men of South Asian origin. It is clear that Framingham equations may underestimate risk in people with a lower socioeconomic position, although it is less clear by what factor absolute risk should be multiplied in such an individual\textsuperscript{14}; some risk scores formally incorporate socioeconomic position into CVD risk prediction.\textsuperscript{15,16} Overall, it is conceivable that physicians could exercise their clinical judgment and choose to treat younger people with multiple risk factors but a low absolute CVD risk in the presence of family history of premature CVD, a lower socioeconomic position, and select ethnicities.
Another evolving area is more controversial. Some experts have advocated that treatment goals for individual risk factors (such as levels of blood lipids\textsuperscript{14} or blood pressure\textsuperscript{17}) may be less important when treating individuals with a high absolute CVD risk. It is also worth noting that additional clinical trial–based evidence is needed to demonstrate the efficacy of a strategy of treating multiple risk factors guided solely by absolute CVD risk and not according to the levels of the individual risk factors themselves.

The last decade also has seen intense debate on some other key issues related to CVD risk assessment: what is the optimal time frame for CVD risk assessment (5 years, 10 years, or long term); what absolute risk thresholds should be used to determine eligibility for pharmacological treatments; who should choose these thresholds and how does one balance a societal perspective against that of physicians and individuals; whether use of CVD risk assessment changes physician prescription habits, patient behavior, or patient outcomes and whether such risk assessment is cost-effective; and how such risk assessment and communication are incorporated into the offices of busy primary care physicians. A discussion of these issues is beyond the scope of this editorial, but these questions are important to ponder.

Conclusions
CVD risk prediction has evolved considerably in recent times. The Framingham general CVD risk profile and the 30-year CVD risk scoring tool are examples of such progress. However, as noted above, refinements in CVD risk prediction continue to be contemplated because none of the currently available tools is perfect. It is important to remember that such “perfection is the child of time” (to quote Joseph Hall, the English satirist).

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