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Systematic Examination of the Updated Framingham Heart Study General Cardiovascular Risk Profile

Amanda K. Marma, MD; Donald M. Lloyd-Jones, MD, ScM

Background—An updated Framingham risk prediction tool was recently published. It features an expanded end point of general cardiovascular disease and a “vascular age” risk communication analogy.

Methods and Results—We systematically examined the tool to determine which risk factor combinations allow risk thresholds to be reached and how different risk factor burdens translate into vascular age. We varied risk factor levels in isolation and combination and observed risk output patterns, with high risk defined as ≥20% 10-year predicted risk. As expected, we found that age is the major determinant of 10-year predicted risk for both men and women. Younger individuals tend not to exceed 20% 10-year risk even with multiple risk factors, although with marked risk factor burden, including both smoking and diabetes mellitus, men as young as 35 years of age and women as young as 40 years of age can be classified as high risk. For the risk factor levels we entered, predicted risk ranges from 3.1% to 46.8% for a 45-year-old man and 2.4% to 42.7% for a 55-year-old woman. Likewise, vascular age ranges from 37 to >80 years for a 45-year-old man and 39 to >80 years for a 55-year-old woman.

Conclusions—The inclusion of noncoronary end points in this tool expands the range of predicted risks for men and women at all ages studied. Nevertheless, many younger individuals with high risk factor burden have low 10-year predicted risk. Wide ranges of “vascular age” are available for most chronological ages to assist with risk communication. (Circulation. 2009;120:384-390.)

Key Words: cardiovascular disease ■ risk assessment ■ risk factors

In primary prevention of cardiovascular disease (CVD), it is generally accepted that the intensity of risk factor treatment should be guided by the magnitude of absolute risk.1–3 Estimation of absolute risk is preferably done with multivariable risk functions because studies show that subjective estimation by physicians is inaccurate, with both systematic underestimation and overestimation observed.4,5 Likewise, risk factor counting alone may misclassify a large number of individuals compared with multivariable risk equations.6 Furthermore, it has been observed that even when provided with risk calculation tools, clinicians sometimes apply them inappropriately.7 A better understanding of the intrinsic properties of multivariable risk prediction tools would be useful to clinicians to improve their recognition of patients with those risk factor combinations that will place them at high or low estimated risk and to help them appreciate the inherent limitations of the tools so that they may be used most effectively.

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We previously investigated the intrinsic properties of the National Cholesterol Education Program Adult Treatment Panel III (ATP III) risk assessment tool for 10-year risk of hard coronary heart disease (CHD; myocardial infarction or coronary death) and systematically demonstrated the levels of risk factors required to exceed clinical threshold values of predicted risk.8 This work highlighted the inherent limitations of that approach when applying it to individuals using clinical risk thresholds, given its tendency to classify younger men and large proportions of women as low risk on the basis of age and sex despite significant risk factor burden.9–11 D’Agostino et al12 recently published a multivariable risk factor algorithm for the assessment of general CVD risk and risk of individual CVD events, as well as a method for describing the predicted risk as a “vascular age” (ie, the age of a person with the same predicted 10-year risk but with all normal risk factor levels) to improve risk communication. Before widespread clinical application of this tool, it would be useful to understand its intrinsic properties both to compare it with the ATP III risk assessment tool and to understand how it may be useful to clinicians in its own right. For example, if the expanded end point or vascular age analogy of the new tool was found to result in more relevant and motivating risk messages for women or younger men, this...
could help motivate further investigation of the tool for standard use. Therefore, the objective of the present study was to systematically evaluate the risk prediction tool developed by D’Agostino et al to determine which risk factor combinations allow risk thresholds to be reached and how different risk factor burdens translate into vascular age.

**Methods**

**Risk Prediction Model**
The sex-specific risk prediction model formulated by D’Agostino et al incorporates age, total and high-density lipoprotein (HDL) cholesterol levels, systolic blood pressure, use of antihypertensive medication, smoking status, and diabetes status into multivariable Cox proportional-hazards regression equations to estimate the 10-year absolute risk for CVD events, including CHD (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral vascular disease (intermittent claudication), and heart failure. The model was based on 12 years of follow-up of 8491 members of the Framingham cohorts who were 30 to 74 years of age and free of symptomatic CVD at baseline examination in 1968 to 1975 or 1984 to 1987.

We created spreadsheets for each of 4 risk functions, including separate functions by sex and antihypertensive therapy status, based on the weighted coefficients in the published formulas. We entered data directly into these spreadsheets for a hypothetical man or woman from 30 to 74 years of age in increments of 5 years. Our approach did not involve examining risks for specific individuals or a specific population; rather, we varied risk factor burden systematically in the model to examine the characteristics of the output of the tool for 10-year CVD risk prediction. Special attention was paid to predicted risks ≥20% in 10 years. This level is the threshold for “high global CVD risk,” which requires more aggressive risk factor modification as presented by D’Agostino et al. ATP III does not address global CVD risk, but support for this threshold was found in the Joint British Societies’ guidelines, which define a predicted risk of ≥20% in 10 years for all CVD as high risk requiring professional intervention.

**Risk Calculation Procedure for Multiple Risk Factors**
To examine the effects of risk factor combinations on 10-year predicted risk, we varied the levels of all risk factors to values around the national means in ranges chosen to be inclusive of an “optimal” value and a “modestly abnormal” value at intervals roughly equal to the SDs observed in the population of US adults. For total cholesterol, we included values of 160 mg/dL (≈1 SD below the mean), 200 mg/dL (approximate national mean), and 240 mg/dL (≈1 SD above the mean). For HDL cholesterol in a man, we included 58, 48, and 38 mg/dL; for a woman, we included 68, 58, and 48 mg/dL. For systolic blood pressure, we included 110, 130, and 150 mm Hg. We also varied smoking status, diabetes status, and antihypertensive therapy use for all risk factor combinations. Whereas we report results for the full range of ages (30 to 74 years in 5-year intervals), we chose to graphically display the results for a 45-year-old man and a 55-year-old woman. These ages were chosen for their relevance as the point at which age itself becomes a categorical risk factor in ATP III; thus, it was thought that they would offer the most representative patterns of predicted risk for risk factor combinations without undue influence of age in either direction, with the understanding that the absolute predicted risks vary directly and substantially with age.

**Vascular Age**
D’Agostino et al define vascular age as the chronological age of a person with the same predicted risk but all risk factors at the normal levels (ie, total cholesterol of 180 mg/dL, HDL cholesterol of 45 mg/dL, untreated systolic blood pressure of 125 mm Hg, nonsmoker, nondiabetic). Given the novelty of the use of risk factors to predict vascular age, we examined this measure. For precision, our analyses of predicted risk above were done using the continuous risk functions rather than the points system presented by D’Agostino et al; similarly, we used vascular ages calculated directly through these risk functions rather than vascular ages calculated from the points system. To do this, we entered the normal levels of risk factors (defined above) into the published sex-specific risk functions and then solved for age, leaving risk probability as an independent variable. This resulted in sex-specific vascular age functions (see the Appendix in the online-only Data Supplement). Risk probability output from the D’Agostino et al risk functions for a hypothetical individual with particular risk factor levels was then entered into the appropriate vascular age function, and the resulting vascular age was read to the nearest year. In keeping with the limitations of reported vascular age used by D’Agostino et al, vascular ages at the extremes are simply reported as <30 or >80 years.

**Results**

**Effect of Varying a Single Risk Factor With Other Risk Factors Held Constant**
With all risk factors held constant at national means, 10-year predicted risk is substantially greater with increasing age (Figure 1). An accelerated rate of increase in risk with age is observed beginning at 60 years of age; this is due to the use of age-specific systolic blood pressure values and represents the elevation of that risk factor level that tends to accompany the normative aging process. As expected, predicted risk is higher for a man than for a woman at all ages, with absolute age-associated risk diverging further between a man and a woman at older ages. Of note, a 10-year risk estimate of ≥20% is not predicted by the tool for a man with average risk
factor values until 70 years of age and is never predicted (through 74 years of age, even with treated blood pressure) for a woman with average risk factor values (Figure 1).

As shown in Figure 2, risk varies linearly with total cholesterol but curvilinearly with HDL cholesterol (Figure 2A, 2B, 2E, and 2F). Systolic blood pressure variations produce a linear risk distribution with particularly prominent effects for a woman, so that at extremes of systolic blood pressure, a woman reaches 20% risk by 60 years of age (Figure 2C and 2G). A requirement for antihypertensive therapy independently increases risk (eg, allows a man to reach 20% risk at 65 years of age even if he is treated to an optimal systolic blood pressure) (Figure 2D and 2H).

Smoking and diabetes mellitus both have prominent effects on 10-year predicted absolute risk but with differential influence for a man versus a woman (Figure 3A and 3B). Either smoking or diabetes mellitus alone produces ≥20% risk for a man >55 years of age, but risks associated with smoking (Figure 3A) are somewhat more prominent than those associated with diabetes mellitus (Figure 3B). In contrast, a woman can reach 20% predicted risk at >65 years of age with diabetes mellitus alone but not until 74 years of age with smoking alone.

**Effect of Varying Multiple Risk Factors Simultaneously**

Figure 4 displays 10-year risks predicted by the tool with varying levels of risk factors (but no antihypertensive use) for a 45-year-old man and a 55-year-old woman. For the risk factor levels we entered, the range of predicted risk observed for a 45-year-old man is 3.1% to 36.5% (reaching 46.8% if blood pressure is treated but uncontrolled), and that for a 55-year-old woman is 2.4% to 33.6% (reaching 42.7% if blood pressure is treated but uncontrolled). The full range of predicted risk observed for a 30-year-old individual with the risk factor levels we entered is 0.9% to 16.7% for a man and

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**Figure 1.** Ten-year predicted risk for CVD for a hypothetical man and woman at selected ages, with risk factors held constant at approximate age-adjusted national means (including nondiabetic, nonsmoking, and no antihypertensive use). A change in the slope of each line is observed between 55 and 60 years of age; this is an artifact of the use of average systolic blood pressure by age categories, with different values for <60 vs ≥60 years of age.

**Figure 2.** Ten-year predicted risks for CVD by varying levels of single risk factors in a hypothetical man and woman at selected ages, with other risk factors held constant at approximate age-adjusted national means (including nondiabetic, nonsmoking, and no antihypertensive use). A more marked separation is observed between the lines for 55 and 60 years of age in A, B, E, and F; this is an artifact of the use of average systolic blood pressure (SBP) by age categories, with different values for <60 vs ≥60 years of age.
0.6% to 12.7% for a woman; the range for a 74-year-old individual is 13.3% to 94.4% for a man and 4.8% to 67.1% for a woman.

With optimal levels of all risk factors (indicated by total cholesterol of 160 mg/dL, HDL cholesterol of 58 mg/dL for a man or 68 mg/dL for a woman, systolic blood pressure of 110 mm Hg, nonsmoking, nondiabetic), no man or woman, through 74 years of age, reaches the 20% threshold of 10-year predicted risk with this tool. Even with risk factor levels all modestly abnormal (indicated by total cholesterol of 240 mg/dL, HDL cholesterol of 38 mg/dL for a man or 48 mg/dL for a woman, and systolic blood pressure of 150 mm Hg), 20% risk is not reached until 55 years of age for a man or 74 years of age for a woman without the presence of smoking or diabetes mellitus.

Figure 3. Ten-year predicted risks for CVD by presence or absence of smoking (A) and diabetes mellitus (B) in a hypothetical man or woman at selected ages, with other risk factors held constant at approximate age-adjusted national means. A change in the slope of each line is observed between 55 and 60 years of age; this is an artifact of the use of average systolic blood pressure by age categories, with different values for <60 vs ≥60 years of age.

Figure 4. Ten-year predicted risks for CVD by varying levels of multiple risk factors in a hypothetical man at 45 years of age and woman at 55 years of age. SBP indicates systolic blood pressure. HDL-c indicates HDL cholesterol.
diabetes mellitus (or 50 and 65 years of age, respectively, if blood pressure is treated to this level).

However, for a nondiabetic smoker, modest abnormalities of all risk factors are sufficient to reach 20% risk at 45 years of age for a man or 60 years of age for a woman (and 5 years earlier if blood pressure is treated). For a nonsmoking diabetic individual with modestly abnormal risk factors such as the metabolic syndrome, 20% risk is reached at 45 years of age for a man or 55 years of age for a woman (and 5 years earlier if blood pressure is treated). Finally, the combination of smoking and diabetes mellitus with modestly abnormal lipid and systolic blood pressure levels allows a man >35 years of age or a woman >40 years of age to reach 20% 10-year predicted risk, whereas treatment of blood pressure lowers the required ages further to >30 and >35 years, respectively.

Vascular Age
Regardless of chronologic age, the vascular age of a man with 20% predicted risk is 70 years, and that of a woman with 20% predicted risk is >80 years. In other words, to reach the 20% threshold despite all normal risk factor levels on the basis of age alone, a man would need to be 70 years of age and a woman would need to be >80 years of age.

Individual risk factor variations have prominent effects on the vascular age estimate. For example, every 10-mm Hg increase in systolic blood pressure increases vascular age by 1.5 to 4 years in a man and 3 to >5 years in a woman; the requirement for antihypertensive therapy increases vascular age by 3 to 8 years for a man and 4 to 11 years for a woman. The differing influences of smoking and diabetes mellitus on a man versus a woman are apparent; smoking adds 7 to 15 years to vascular age of a man and 5 to 13 years to that of a woman, whereas diabetes mellitus adds 6 to 13 years to vascular age of a man and 12 to 17 years to that of a woman.

When multiple risk factor levels are varied simultaneously, the range of vascular ages observed for a 45-year-old man is 37 to >80 years and that for a 55-year-old woman is 39 to >80 years. With optimal levels (as defined above) of all risk factors, a man can take up to 14 years off of his chronological age for a vascular age of 60 at 74 years; similarly a woman can take up to 21 years off of her chronological age for a vascular age of 53 at 74 years. In contrast, the combination of smoking, diabetes mellitus, treated blood pressure, and modest abnormalities of all risk factor levels can add up to 41 years to chronological age for a man (vascular age 76 years for a 35-year-old man) and up to >50 years for a woman (vascular age >80 years for a 30-year-old woman).

Discussion
Principal Findings
In this systematic examination of the intrinsic properties of the Framingham general CVD risk prediction tool, we had several important findings. First, men as young as 35 years of age and women as young as 40 years of age who have the maximal risk factor burden we entered can be classified as high risk (≥20% 10-year risk). However, men <55 years of age or women <60 years of age with a single adverse risk factor (no matter how extreme), as well as men <40 years of age or women <50 years of age with multiple risk factors, including either diabetes mellitus or smoking (but not both), would still be classified as having lower risk (<20%) by this tool. Finally, wide ranges of predicted vascular age can be observed with varying risk factor burdens, including possible vascular ages both decades younger and decades older than chronological age.

Implications
Various risk estimation tools for CVD have been developed over the past 4 decades, and national guidelines now routinely recommend their use in primary prevention to assist in matching intensity of therapy with absolute risk. The risk prediction tool endorsed by ATP III for the direction of cholesterol treatment goals is the Framingham Risk Score, which estimates 10-year risk for hard CHD (myocardial infarction and coronary death). However, the approach recommended by ATP III is subject to important limitations. For example, the Framingham Risk Score classifies most younger men and large proportions of women as low risk despite substantial risk factor burden. Additionally, the restriction of predicted end points to hard CHD only (to the exclusion of stroke and heart failure) also may lead to risk estimates that are unjustifiably reassuring to patients with significant risk factor burden.

The tool we study here, which estimates 10-year risk for general CVD (coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, intermittent claudication, and heart failure), avoids some of these limitations and may prove to be a valuable addition to the current array of risk prediction tools. Primarily because of the more inclusive set of outcomes, both men and women can reach risk thresholds of 10% or 20% at younger ages. For example, it has been shown with the Framingham Risk Score that most women <65 years of age have 10-year predicted risks for hard CHD of <10% even with extreme elevations in multiple risk factors; with the present tool, the 20% threshold for 10-year risk of general CVD is reached by women as young as 60 years of age with a single elevated risk factor (systolic blood pressure) and as young as 40 years of age with multiple abnormal risk factors. Of course, as noted above, if a 20% treatment threshold were adopted on the basis of this tool, the majority of those treated would be older individuals; only younger individuals with markedly elevated risk factor burden would exceed this threshold. This is problematic because a narrow focus on older individuals cannot prevent, in the short term, all events or, in the long term, nearly as many events as a more global approach could.

As a measure of CVD risk that is inclusive for end points but still focused on the near term, the particular value of this tool may be in identifying those whose marginal risk factors place them at unexpectedly high risk for noncoronary cardiovascular events and thus require timely intervention. For example, a 65-year-old female nondiabetic smoker with untreated systolic blood pressure of 138 mm Hg, total cholesterol of 200 mg/dL, and HDL cholesterol of 55 mg/dL has a 10-year risk for general CVD of 16% with this tool, although her 10-year risk for hard CHD is only 5% with the ATP III risk assessment tool. The impressive disparity in risk
exists largely because this woman’s prehypertension, in addition to her age and smoking, likely places her at substantial risk for stroke and heart failure, end points not included in the ATP III tool. Certainly, smoking cessation is paramount to decrease her risk, but in the absence of prompt success in that regard, consideration of the general CVD risk should lead to efforts to reduce blood pressure. In the same example, decreasing her systolic blood pressure to 120 mm Hg would yield an improved 10-year general CVD risk of 11% (versus a minimally decreased 10-year hard CHD risk of 4% with the ATP III tool).

However, with this new tool arise new issues. First, at present, national guidelines do not address general CVD risk. Therefore, although the threshold used here of 20% predicted risk in 10 years to indicate high risk is supported by the Joint British Societies’ guidelines,13 the appropriateness of this threshold in the United States should be discussed before widespread clinical use. Moreover, there are currently no established protocols for the care of US adults based on general CVD risk, which means that clinicians still need to calculate risk for hard CHD to provide best care according to ATP III. Although D’Agostino et al12 provide a calibration factor (a multiplier to adjust for a particular end point, which is equal to the observed proportion of events of that subtype) for CHD, the inclusion of angina in their CHD category makes the factor potentially less useful.

Furthermore, the proper use of the calibration factors and vascular age calculations in particular has the potential to be problematic. The static calibration factors predict an unvarying distribution of end points, but in reality, which risk factors are abnormal, how abnormal they are, and what kind of patient they occur in all have important implications for which CVD event is likely to occur first in an individual and thus for how preventive therapy should be targeted.20 The simple fact is that even with improved risk estimation tools, the information must still be individualized to the context of a given patient. Vascular age is appealing as a presentation of risk that sounds more personalized than abstract probabilities or population-based event rates, and data from focus groups21 and health psychology studies22 indicate that such an analogy for probability, paired with counseling about how to improve risk, may increase the perception of threat and self-efficacy to motivate behavioral changes. However, the vascular age provided by this tool is still the product of a risk function with the limitations of population-based calculations and should not be misunderstood by clinicians as a definite characterization of the true state of an individual’s vasculature. In other words, the calculated vascular age lacks any underlying determination of actual vascular components such as endothelial function or atherosclerotic burden and has no incremental value over the predicted risk level apart from a potential for improved communication of that risk level.

Finally, although the present tool for prediction of 10-year general CVD risk differs from the Framingham Risk Score in important ways, they have common limitations that impair clinical decision making and risk communication and necessitate supplemental strategies. First, the 10-year time frame underestimates long-term risk.23 For example, the present tool indicates that a 50-year-old nonsmoking, nondiabetic man with total cholesterol of 240 mg/dL, HDL cholesterol of 58 mg/dL, and untreated systolic blood pressure of 160 mm Hg has an estimated 10-year risk for general CVD of 13%. In contrast, we have previously demonstrated that such a man has an average lifetime risk for CVD of nearly 70%, a forecast that may be more useful in motivating adherence to therapeutic plans.24 Second, the inclusion in the tool of only traditional risk factors excludes a multitude of other modifiers of risk (some as yet undiscovered) that may act in any individual patient.

Potential Limitations
Our methods may have been limiting in some ways. The precision of our findings was limited by the increments of age and risk factor levels we used, but we believe that our findings nonetheless provide useful information about general characteristics of the tool across a wide spectrum of potential risk. We varied a single risk factor at a time to illustrate the impact of that factor on risk; however, we acknowledge that many risk factors are correlated and thus that some combinations we studied would be rare in the general population. In addition, the tool itself presented some limitations. One relates to the nature of the Framingham cohorts from which the risk functions were developed and may limit the generalizability of our findings. The Framingham cohorts consist almost exclusively of white individuals, and the use of data from particular examination cycles (eg, those coincident with the peak of the cardiovascular epidemic) to develop the risk functions could lead to birth cohort effects and potential miscalibration of risks. However, application of Framingham functions in more contemporary US cohorts indicates overall good calibration and discrimination for whites and blacks.25 The other lies in the fact that the tool includes diabetes mellitus as a variable in the equation despite the fact that ATP III guidelines consider diabetes mellitus a coronary risk equivalent (therefore indicating the need for lipid-lowering therapy regardless of predicted risk). Finally, it should be noted that along with the model we studied, D’Agostino et al12 published a simplified risk model using body mass index in place of cholesterol values. Because national guidelines recommend routine screening of cholesterol levels for all adults in the United States, we did not examine the simplified model in the present study and cannot offer insight into its properties.

Disclosures
None.

References
CLINICAL PERSPECTIVE

An updated Framingham multivariable risk function with the expanded end point of general cardiovascular disease is now available. The published tool includes a “vascular age” analogy (providing the chronological age of a person with the same 10-year predicted risk but all normal risk factor levels) for risk communication. Here, we examined the risk output of the tool and its “vascular age” analogy to determine the levels of risk factors required to exceed clinical treatment thresholds. We found that the more inclusive end point expands the range of 10-year predicted risks for all ages and enables the tool to identify some individuals with unexpectedly high predicted risk as a result of risk for noncoronary end points (such as stroke and heart failure) associated with particular risk factor combinations (such as female sex and hypertension). However, the majority of individuals reaching a 20% risk threshold with this tool would be older individuals. Despite significant risk factor burden, many younger individuals would not exceed the 20% threshold simply because of their younger age. The vascular age analogy provides an alternative means for risk communication, so we believe that this tool may merit further investigation. However, the short 10-year time frame of this updated general cardiovascular disease risk prediction tool leads to an underestimation of long-term risk and therefore necessitates supplemental strategies of risk estimation.

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SUPPLEMENTAL MATERIAL
APPENDIX

The sex-specific vascular age functions we derived are as follows:

For women,

\[
Vascular\ age = 192.51644 \times (-\ln(-\hat{p} - 1)))^{0.42941},
\]

and for men,

\[
Vascular\ age = 114.25792 \times (-\ln(-\hat{p} - 1)))^{0.32667},
\]

where \( \hat{p} \) is the 10-year risk for general CVD as calculated with the sex-specific risk functions published by D’Agostino et al.\(^{12}\)

For example, a 55 year-old woman with a calculated risk of 14% would have a vascular age of

\[
192.51644 \times (-\ln(-0.14 - 1)))^{0.42941} = >80\ years.
\]