



Differences in absolute risk of cardiovascular events using risk-refinement tests: A systematic analysis of four cardiovascular risk equations



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ABSTRACT

Background: Current cardiovascular risk assessment guidelines incorporate judicious use of C-reactive protein (CRP), carotid intima-media thickness (CIMT), and coronary artery calcium (CAC) in selected populations and describe threshold levels for higher and lower cardiovascular risk for each of the three risk refinement tests. However, the effect of these suggested thresholds of relative risk on absolute global risk remains uncertain.

Methods: Systematic permutation of risk factors provided 10-year risk estimates using the Framingham risk score, equations derived from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Atherosclerosis Risk in Communities (ARIC) study, and the Reynolds risk score. Low-, high-, and very-high-risk values of CAC, CIMT, and hsCRP were defined as: 0, 100, 400 Agatston units; 25th percentile without plaque, 75th percentile without plaque, 75th percentile with plaque; and 1.0, 3.0, 7.0 mg/L.

Results: Incorporation of low-, high-, and very-high-risk CAC values using the MESA risk score resulted in greater changes in absolute risk from the Framingham risk score than the addition of either CIMT or hsCRP values using the ARIC or Reynolds risk scores.

Conclusions: Although certain values of CAC, CIMT, and hsCRP have been similarly designated as low, high, or very-high risk, incorporation of these thresholds into validated risk equations yielded substantially different levels of absolute cardiovascular risk. Use of available risk equations may be advisable to calculate absolute risk rather than relying on risk-marker thresholds derived from relative risk estimates.

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1. Introduction

The National Cholesterol Education Program's Adult Treatment Panel III (ATP-III) report recommends assessing the patient's 10-year absolute risk of coronary heart disease (CHD) events based on readily available clinical risk factors, and matching the intensity of CHD prevention efforts to prognosis for CHD events [1]. The ATP-III approach is based on 'hard' CHD events: CHD death and non-fatal myocardial infarction (MI). Accordingly, ATP-III used a set of risk-prediction equations derived from the Framingham cohort to

inform risk categories for 10-year incidence of hard CHD events: low risk (<10%), intermediate risk (10–20%), and high risk (>20%).

Increasingly, physicians have access to more sophisticated tests in addition to those clinical risk factors included in the Framingham risk equation, fueling interest in augmenting the ATP-III risk categories with novel risk markers to refine CHD prognosis. For example, coronary artery calcium (CAC) by computed tomography provides a direct assessment of subclinical CHD, and has been shown to accurately predict CHD events [2]. Atherosclerosis outside the coronary system, as quantified by carotid intima-media thickness (CIMT) and the presence of carotid plaque, also predicts CHD events [3]. In addition, novel biomarkers, such as high-sensitivity C-reactive protein (hsCRP), may offer a low-cost and low-intensity improvement in CHD risk assessment [4].

Subsequent clinical guidelines incorporate judicious use of CAC, CIMT, or hsCRP in selected populations and describe threshold levels for higher and lower cardiovascular risk [5]. Discrete

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thresholds for novel risk markers offer a practical simplification of continuous variables and facilitate clinical decision-making. However, overreliance on thresholds for novel risk markers outside the context of the ATP-III risk factors may divert attention from the fundamental goal of CHD risk assessment: evaluation of *absolute* risk. For example, a lower-risk hsCRP value alone, defined as a level below 1.0 mg/L, does not imply low risk in absolute terms (i.e. 10-year hard CHD risk below 10% per ATP-III); nor does a higher-risk hsCRP alone imply high absolute risk. Rather, clinical management recommendations are derived from near-term, absolute risk as defined by comprehensive assessment of the ATP-III risk factors and, in selected individuals, further risk-refinement testing. Fortunately, equations have been derived from large prospective cohort studies that calculate absolute risk by ATP-III risk factors as well as novel risk markers: the Multi-Ethnic Study of Atherosclerosis (MESA) [6] incorporates CAC; the Atherosclerosis Risk in Communities (ARIC) study [7,8] incorporates CIMT; and the Reynolds risk score, derived from the Women's Health Study [9] and the Physician's Health Study [10], incorporates hsCRP.

The purpose of the present study is to examine differences in absolute 10-year cardiovascular risk between alternative risk-refinement equations by systematically varying the clinical and laboratory variables to those equations across a full range of plausible values. Our goal is to determine the extent to which differences in novel risk markers could impact CHD prognosis and clinical decision-making. Systematically varying risk-equation inputs was used to clarify the properties of the Framingham 10-year risk equation, revealing the paucity of combinations that yield a high risk score among women [11]. We applied similar methods to compare the Framingham CHD risk score to the absolute risks associated with suggested risk thresholds for CAC by MESA, CIMT by ARIC, and hsCRP by Reynolds risk equations. Because this approach does not depend on sampling individuals from a specific population, it evaluates the effects of all permutations of individual risk markers and how aggregate risk-marker burden impacts 10-year CHD risk predictions. We hypothesized that, for a given combination of ATP-III risk factors, low-, high-, and very-high-risk CAC, CIMT, and hsCRP values would yield different results in terms of absolute risk.

2. Methods

ATP-III clinical risk factors were systematically permuted for all covariate values shown in [Supplementary Table 1](#). For every combination of clinical risk factors, one Framingham risk score, three MESA risk scores (low/high/very-high-risk CAC), three ARIC risk scores (low/high/very-high-risk CIMT), and three Reynolds risk scores (low/high/very-high-risk hsCRP) were calculated. As recommended by the 2006 American Heart Association consensus statement, a CAC score of 0 Agatston units was defined as low risk; CAC scores of 100 and 400 Agatston units were considered high risk and very high risk, respectively [2]. As recommended by the 2008 American Society of Echocardiogram/Society of Vascular Medicine guidelines [3], a CIMT value at the 25th percentile with no evidence of carotid plaque was defined as low risk; CIMT values at the 75th percentile without and with carotid plaque were defined as high and very high risk. CIMT thresholds adjusted for age and sex ([Supplementary Table 2](#)). As recommended by the 2003 American Heart Association/Centers for Disease Control consensus statement [4], hsCRP values of 1.0 and 3.0 mg/L were defined as low and high risk, respectively. A hsCRP value of 7.0 mg/L was defined as very high risk; 7.0 mg/L represents the 75th percentile of hsCRP in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial (JUPITER), a clinical trial of rosuvastatin among individuals free of cardiovascular

disease at baseline with elevated hsCRP [12]. Baseline characteristics of the derivation cohorts for all risk scores are provided in [Supplementary Table 3](#) [7,9,10,13,14]. All risk equations were previously validated across the range of inputs used in our analysis.

We calculated absolute 10-year risk estimates of hard CHD for the Framingham, MESA, and ARIC risk equations. The Reynolds score did not attempt to evaluate hard CHD risk, making it more challenging to evaluate in the ATP-III framework and also making it difficult to compare with the other three. While hard CHD events are included, the Reynolds risk score additionally incorporates non-CHD death and coronary revascularization, going beyond hard CHD events, and ischemic stroke, going beyond the coronary system. Nevertheless, we thought it would be helpful to include the Reynolds score in this analysis because its ease of use and low cost enhance its clinical potential. In sensitivity analyses, we compared the Reynolds risk score to two Framingham risk equations that calculate more inclusive composite endpoints: the 'all' CHD Framingham risk score, which incorporates coronary insufficiency and angina; and the 'general' cardiovascular disease (CVD) Framingham risk score, which additionally incorporates hemorrhagic stroke, peripheral artery disease, and heart failure.

Across all risk-factor combinations, graphical summaries were produced based on scatterplot smoothing splines for (1) absolute risk estimates from all risk-refinement equations vs. the Framingham risk score and (2) differences in absolute risk from all risk-refinement equations and the Framingham risk score. At levels of Framingham risk between 10% and 20%, we calculated medians and the inter-quartile ranges of absolute risk differences between very-high-, high-, and low-risk groups across all risk-factor combinations. All analyses were completed using R 2.15.1 (R Development Core Team, Vienna, Austria) including the `knitr` extension package (Xie, 2012). The [Technical Appendix](#) provides all R commands used to define the risk equations [6–10,14] and to generate the data.

3. Results

Absolute risk scores were calculated by systematically varying inputs for the Framingham, MESA, ARIC, and Reynolds risk equations ([Fig. 1](#)). Incorporation of suggested low-, high-, and very-high-risk CAC values using the MESA risk score resulted in greater changes in absolute risk from the Framingham risk score than the addition of either low-, high-, and very-high-risk CIMT or hsCRP values using the ARIC or Reynolds risk scores, respectively ([Fig. 2](#)). Among permutations of risk factors yielding Framingham risk scores of 10–20% in men, the absolute difference between MESA risk scores generated from high- and low-risk CAC values ranged 11.8–14.6% in men ([Table 1](#)). Smaller differences in absolute risk were observed for ARIC risk scores derived from high- and low-risk CIMT values (2.5–4.4%) or Reynolds risk scores calculated using high- and low-risk hsCRP values (1.0–1.9%) ([Table 1](#)). Similar findings were observed among women and for absolute differences between risk scores derived from very-high-risk and low-risk values of CAC, CIMT, and hsCRP ([Table 1](#)). Sensitivity analyses comparing the Reynolds risk score with the more inclusive Framingham all CHD and general CVD risk equations did not reveal substantial differences in changes in absolute risk.

4. Discussion

To our knowledge, this is the first study to systematically compare the absolute cardiovascular risk estimates generated by four important cardiovascular risk equations. In general, our results demonstrated that the absolute difference in risk for CIMT was more than double that of hsCRP, and in turn, CAC was

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