

## Improving Cardiovascular Risk Prediction for Women

Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;297:611–9.

### Study Overview

**Objective.** To develop and validate new cardiovascular disease (CVD) risk prediction algorithms for women based on traditional and novel risk factors.

**Design.** Prospective cohort study.

**Setting and participants.** The study cohort consisted of 24,558 women (aged  $\geq 45$  years) enrolled in the Women's Health Study. All women were followed for a median of 10.2 years (through April 2004) for incident myocardial infarction (MI), ischemic stroke, coronary revascularization, and cardiovascular death. Two thirds of participants were randomly assigned to the derivation cohort ( $n = 16,400$ ) to develop new cardiovascular risk algorithms, and the remaining one third ( $n = 8158$ ) were used to validate the algorithms.

**Main outcome measures.** For the derivation cohort, minimization of the Bayes Information Criterion was used to develop a best-fitting prediction model (model A) and a clinically simplified model (model B; the Reynolds Risk Score [RRS]). 35 potential variables were evaluated for model inclusion, and, of these, 9 were included in model A: age, systolic blood pressure, current smoking, apolipoprotein B-100, high-sensitivity C-reactive protein (hsCRP), apolipoprotein A-I, parental history of MI before age 60 years, hemoglobin A<sub>1c</sub> (if patient had diabetes), and lipoprotein(a) level (if apolipoprotein B-100  $\geq 100$  mg/dL). Variables included in model B were similar to model A, with the exception of total cholesterol and high-density lipoprotein (HDL) cholesterol substituted for apolipoproteins B-100 and A-I and eliminating measurement of lipoprotein(a). In the validation cohort, the predicted versus actual 10-year cardiovascular event rates were computed for models A and B and compared with the National Cholesterol Education Program Adult Treatment Panel III (ATP III) risk prediction algorithm.

**Main results.** In the derivation cohort, model A and model B (the RRS) demonstrated lower Bayes Information Criterion scores as compared with the ATP III risk score. In the validation cohort, the statistical measures of fit, discrimination, and calibration were improved with both model A and the RRS as compared with the ATP III. In women classified as

intermediate risk according to ATP III risk score (10-year risk of CVD, 10% to  $< 20\%$ ), model A reclassified 43% of nondiabetic patients and 50% of diabetic patients, whereas the RRS reclassified 30% of nondiabetic patients and 45% of diabetic patients into higher- or lower-risk groups. Women at very low risk based on the ATP III classification were not significantly reclassified by either algorithm.

**Conclusion.** Two clinical algorithms for global CVD risk prediction in women were developed and validated. Both algorithms reclassified 40% to 50% of women who were classified at intermediate risk per ATP III risk score into higher- or lower-risk categories.

### Commentary

CVD accounted for more than 650,000 deaths in the United States in 2004 and is currently the leading cause of death for both men and women [1]. Primary care physicians have a key role in identifying and treating CVD risk factors in asymptomatic individuals, which can in turn prevent MIs, strokes, and death. The risk assessment tool contained in the ATP III guidelines is currently used to identify individuals at risk for CVD. It makes use of the Framingham risk score, an algorithm that uses age, total cholesterol level, HDL level, smoking status, and systolic blood pressure to predict 10-year risk for MI or cardiovascular-related death. However, recent studies have shown that the Framingham risk score underestimates CVD risk in asymptomatic and symptomatic women [2,3]. Thus, Ridker and colleagues sought to determine if the inclusion of any of the recently identified biomarkers, such as apolipoproteins, hsCRP, plasma homocysteine, fibrinogen, or hemoglobin A<sub>1c</sub>, can improve the accuracy of CVD risk prediction algorithms.

Notably, the RRS is a simple modification of the current variables used in the ATP III risk score. The new algorithms included family history of early MI and hsCRP, which have both been verified to be independently associated with increased risk of CVD [4,5]. In addition, the endpoints in this study were broad and included stroke and coronary revascularization, which were not included in the ATP III score. The study population was comprised of women, most of whom were white and well educated, and these findings may not be generalizable to women in minority groups and/or men

(although many of these risk factors have been verified in men and minority populations as well). Further, this study does not incorporate imaging or stress testing, which may contribute substantially to better risk stratification. Finally, both the ATP III risk score and RRS predict only 10-year risk of CVD, and prediction of lifetime risk would be ideal.

**Applications for Clinical Practice**

Providers should include family history of early MI when assessing CVD risk factors in women and may want to use the RRS calculator to help predict CVD risk, which is available at [www.reynoldsriskscore.org](http://www.reynoldsriskscore.org).

—Review by Mark S. Horng, MD, MPH

**References**

1. Centers for Disease Control and Prevention; National Center for Health Statistics. Deaths: final data for 2004. Available at [www.cdc.gov/nchs/products/pubs/pubd/hestats/finaldeaths04/finaldeaths04.htm](http://www.cdc.gov/nchs/products/pubs/pubd/hestats/finaldeaths04/finaldeaths04.htm). Accessed 7 Mar 2007.
2. Michos ED, Nasir K, Braunstein JB, et al. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. *Atherosclerosis* 2006;184:201–6.
3. Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? *J Am Coll Cardiol* 2003;41:1475–9.
4. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA* 2004;291:2204–11.
5. Rost NS, Wolf PA, Kase CS, et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham Study. *Stroke* 2001;32:2575–9.

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