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Biomarkers of cardiovascular disease risk in women

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ABSTRACT

Cardiovascular disease (CVD), including coronary heart disease and stroke, is the leading cause of death among U.S. women and men. Established cardiovascular risk factors such as smoking, diabetes, hypertension, and elevated total cholesterol, and risk prediction models based on such factors, perform well but do not perfectly predict future risk of CVD. Thus, there has been much recent interest among cardiovascular researchers in identifying novel biomarkers to aid in risk prediction. Such markers include alternative lipids, B-type natriuretic peptides, high-sensitivity troponin, coronary artery calcium, and genetic markers. This article reviews the role of traditional cardiovascular risk factors, risk prediction tools, and selected novel biomarkers and other exposures in predicting risk of developing CVD in women. The predictive role of novel cardiovascular biomarkers for women in primary prevention settings requires additional study, as does the diagnostic and prognostic utility of cardiac troponins for acute coronary syndromes in clinical settings. Sex differences in the clinical expression and physiology of metabolic syndrome may have implications for cardiovascular outcomes. Consideration of exposures that are unique to, or more prevalent in, women may also help to refine cardiovascular risk estimates in this group.

Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is the leading cause of death for both men and women in the United States [1]. The incidence of first cardiovascular events in men is 3/1000 person-years at age 35–44, rising to 74/1000 person-years at age 85–94. Comparable rates occur in women 10 years later in life. Before age 75, stroke occurs more commonly than CHD in women, whereas the opposite pattern holds for men [2].

1. Role of traditional risk factors in predicting CVD risk

A 2006 analysis of data from ~8000 white participants in the Framingham Heart Study highlights the importance of traditional risk factors – diabetes, smoking, unfavorable total and high-density lipoprotein (HDL) cholesterol levels, hypertension, and overweight/obesity – in the prediction of CVD risk in both sexes [3]. At age 50, lifetime risks (to age 95) of CVD were 52% for men and 39% for women, with median survivals of 30 and 36 years, respectively. Men and women without risk factors had a much lower risk of developing CVD than their counterparts with ≥2 risk factors (men: 5% *v.* 69%; women: 8% *v.* 50%); they also had longer median survivals (men: >39 *v.* 28 years; women: >39 *v.* 31 years). Similarly, a 2012 meta-analysis of data from 18 cohorts with a total of 257,000 adults found that men and women with an optimal risk-factor profile at age 55 – no diabetes, nonsmoking, total cholesterol <180 mg/dL, blood pressure <120/80 mm Hg – had much lower risks for incident CHD (men: 3.6% *v.* 37.5%; women: <1% *v.* 18.3%), stroke (men: 2.3% *v.* 8.3%; women, 5.3% *v.* 10.7%), and cardiovascular death before age 80 (men: 4.7% *v.* 29.6%; women: 6.4% *v.* 20.5%) than those with ≥2 risk factors [4]. The presence of traditional risk factors predicted cardiovascular risk in black as well as white individuals and in multiple birth cohorts.

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2. Risk prediction models

Several algorithms have been developed to predict an individual's absolute risk of CVD. Assessment of such risk is used to set thresholds for treatment of hyperlipidemia. The original Framingham Risk Score for CHD [5] and the simplified version included in the Adult Treatment Panel-III (ATP-III) guidelines [6] use smoking, blood pressure, antihypertensive medication use, total and HDL cholesterol, diabetes status, age, and sex to predict 10-year risk of developing CHD. Framingham investigators subsequently used these variables to predict risk of total CVD – i.e., CHD, stroke, peripheral artery disease, or heart failure – over a 10-year [7] or 30-year period [8]. In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) introduced a prediction model based on data not only from the all-white Framingham Study but also from three more diverse U.S. cohorts to provide sex-specific and race-specific equations for calculating 10-year risks of the combined outcome of CHD and stroke [9]. However, the ACC/AHA estimator, which is based on the same variables as the earlier Framingham algorithms, has been criticized for failing to incorporate other known risk factors [10,11], **including family history of premature myocardial infarction** (MI); **high-sensitivity C-reactive protein** (hsCRP); and, in individuals with diabetes, **hemoglobin A1c**. In contrast, the Reynolds Risk Score, which was developed in 2007 using data from a subsample of 16,000 initially healthy U.S. women aged ≥45 who were followed for 10 years in the Women's Health Study (WHS), adds these variables (hemoglobin A1c only for those with diabetes) to the Framingham risk factors to produce a single quantitative estimate of CVD risk [12].

Recent reports from two large national studies of women – the WHS and the Women's Health Initiative Observational Study (WHI-OS) – have compared the predictive utility of these risk prediction tools. In a validation sample of 8000 WHS participants (i.e., participants whose data were not used to develop the algorithm), the Reynolds Risk Score demonstrated a strong predictive role for CVD events. It did as well as models based on the ATP-III covariates for women in the lowest and highest risk groups, and it outperformed the ATP-III model for women in the middle two risk groups, reassigning 45% of them into higher or lower risk categories. These reclassifications better predicted whether or not these women actually had a CVD event in the next 10 years. (Clinical performance of the Reynolds Risk Score was also superior to that of the model based on ATP-III covariates in a large cohort of U.S. men aged 50–79 without diabetes [13].) In a case–cohort sample that included 1722 incident cases of major CVD from the WHI-OS, a racially/ethnically diverse cohort of >90,000 postmenopausal women followed for 10 years, investigators compared the model fit of the Framingham score used in the ATP-III guidelines, the Framingham score for total CVD, and the Reynolds Risk Score [14]. The Reynolds model was found to be better calibrated than the other models—i.e., the predicted risks more closely reflected the observed incidence of events. The Reynolds model also showed better discrimination and reclassification (see next section) than other models. Compared with the ATP-III model, the Reynolds model had a higher c-statistic (0.765 *v.* 0.757; $p = 0.03$), a positive net reclassification index (NRI = 4.9%; $p = 0.02$), and a positive integrated discrimination improvement (IDI = 4.1%; $p < 0.0001$). In race-specific analyses, the model showed improved classification in both white (NRI = 4.3%; $p = 0.04$) and black (NRI = 11.4%; $p = 0.13$) women. Analyses of the 2013 ACC/AHA risk models show that they do not yield significantly better calibration or discrimination than earlier models [11]. In preliminary analyses, risk appeared to be overestimated when the 2013 ACC/AHA risk models were applied to the WHS and WHI-OS cohorts [15].

3. Novel biomarkers for risk prediction

Traditional risk factors and existing risk prediction models are very good predictors of CVD risk in both women and men, which leaves a comparatively small space for as yet unidentified biomarkers to emerge as important factors for risk stratification. Nonetheless, cardiovascular researchers have begun to focus on identifying novel biomarkers that may prove useful for improving current risk stratification models, deepening understanding of pathophysiologic processes, and suggesting new treatment approaches. This section briefly describes statistical and practical considerations in evaluating candidate biomarkers, and then reviews selected biomarkers of interest (Table 1).

3.1. *Statistical and practical considerations*

Various statistical approaches assess whether a novel biomarker improves risk prediction in epidemiologic settings

Table 1 – Summary of selected novel biomarkers.

Biomarker	Evidence for effect on CVD in women	Improved prediction in populations of men and women	Improved prediction in women alone
Lipid-related markers			
Apo A-1	Yes	No	No
Apo B-100	Yes	No	No
Lp(a)	Yes	No	No
Lp-PLA_2	Yes	No	No
BNP or NT-proBNP	Yes (but not well studied)	Unclear (studied, but results mixed)	Not tested
High-sensitivity troponin	Yes	Yes	Yes, for CHD
Coronary artery calcium	Yes	Yes	Yes (but data are limited)
Genetic markers	Yes	Unclear (studied, but results mixed)	No

Adapted from reference [16], with permission.