Cardiovascular Disease Risk Prediction in Women: Is There a Role for Novel Biomarkers?

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BACKGROUND: Risk prediction is an integral part of the current US guidelines for cardiovascular disease in women. Although current risk prediction algorithms exist to identify women at increased 10-year risk of cardiovascular disease (CVD), clinicians and researchers have been interested in developing novel biomarkers that might improve predictive accuracy further. These biomarkers have led to important insights into the pathophysiology of CVD, but results for their ability to improve prediction or guide preventive therapy have been mixed. The incidence of CVD is lower in women than men, and the effects of a number of traditional biomarkers on CVD risk differ in women compared to men. Both of these factors influence the ability to accurately predict CVD risk.

CONTENT: We review the distinctive aspects of CVD risk prediction in women, discuss the statistical challenges to improved risk prediction, and discuss a number of biomarkers in varying stages of development with a range of performance in prediction.

SUMMARY: A variety of biomarkers from different pathophysiologic pathways have been evaluated for improving CVD risk. While many have been incompletely studied or have not been shown to improve risk prediction in women, others, such as high-sensitivity troponin T, have shown promise in improving risk prediction. Increasing inclusion of women in CVD studies will be crucial to providing opportunities to evaluate future biomarkers.

CVD in Women: Relationships with Traditional Risk Factors

In addition to differences in the timing of CVD for women and men, there are also differences in the relationships between risk factors and CVD incidence. The traditional risk factors of blood pressure, total and HDL cholesterol, diabetes, and smoking predict CVD in both women and men. However, data from the Emerging Risk Factors Collaboration suggest a significantly higher CHD risk associated with diabetes in women than in men [hazard ratio (HR) for women, 2.59; HR for men, 1.89; P for interaction, <0.0001].

Cardiovascular disease (CVD) is the leading cause of death for both men and women (1). However, CVD occurs later in life in women, with an incidence of approximately 20 per 1000 person years in women between the ages of 65 to 74 years, which is similar to the rate in men who are 10 years younger (55–64 years) (2). This discrepancy is driven largely by the difference in the rate of coronary heart disease (CHD), which is approximately 17 per 1000 person years in 75–84-year-old women and equals the rate in 55–64-year-old men. The incidence of stroke in women is only slightly lower than men before age 80 and exceeds the incidence in men after age 80. The lifetime risk of CVD has also been reported to be lower in women, with a 31% risk of CVD events in a 45-year-old woman with at least 2 major risk factors compared to a 50% risk of CVD events in a man with similar characteristics (3). However, the reported lifetime risk estimates include only risk until age 75 years and so are likely to underestimate the true lifetime risk for women, owing to their longer life expectancy and delayed disease.

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2 Nonstandard abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; HR, hazard ratio; MI, myocardial infarction; NRI, net reclassification improvement; IDI, integrated discrimination improvement; AUC, area under the ROC curve; AROC, Atherosclerosis Risk in Communities; ORX, odds ratio for x; ORY, odds ratio for y; Lp-PLA2, Lipoprotein-associated phospholipase A2; Lp(a), lipoprotein a; ApoA1, apolipoprotein A-I; ApoB, apolipoprotein B-100; apo(a), apolipoprotein(a); WHS, Women’s Health Study; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone of BNP; CHS, Cardiovascular Health Study; DHS, Dallas Heart Study; SNP, single-nucleotide polymorphism; CAC, coronary artery calcification.
smoking compared to not smoking was 25% higher in women than men \( (P \text{ for interaction}, <0.0001) \) \( (5) \).

In contrast to the results for diabetes and smoking, the Emerging Risk Factors Collaboration found no evidence of a difference in the relationship between HDL or non-HDL cholesterol and CVD risk between men and women in a study using individual data from 102 prospective cohort studies \( (6) \). Results of other studies have shown no evidence of a difference in the risk associated with CVD from blood pressure for men and women \( (7) \).

**PREDICTION**

The most widely used risk prediction model is the original Framingham CHD risk score \( (8) \) and the simplified version used in the Adult Treatment Panel III guidelines \( (9) \). This model includes smoking, blood pressure, use of antihypertensive treatments, total and HDL cholesterol, age, and sex. Diabetes status is included in the original model and classified as a high-risk equivalent in the guidelines. More recently, the Framingham cohort was used to create a total CVD risk score, which used the same risk factors to predict a combined outcome including CHD, stroke, peripheral artery disease, or heart failure \( (10) \). The same risk factors were also used in an additional Framingham score developed to predict 30-year risk of CVD \( (11) \). The risk model used in the European guidelines, the SCORE (Systematic COronary Risk Evaluation) model, includes age, blood pressure, smoking, and cholesterol and provides the risk for men with a note that it will be an overestimate for women \( (12) \).

The Reynolds Risk Score, which was developed in a cohort of women, includes smoking, blood pressure, total and HDL cholesterol, age, and sex, plus family history of myocardial infarction (MI), high-sensitivity C-reactive protein, and hemoglobin A1c for women with diabetes \( (13) \). Family history is a strong and consistent risk factor for CVD, with parental history of a premature heart attack increasing risk by 70% in women \( (14) \). C-Reactive protein, a marker of inflammation, has been shown to be associated with an increased risk of CVD in multiple cohorts and in men and women, though the association was slightly stronger in men than women \( (P \text{ for interaction}, 0.015) \) \( (15) \). Hemoglobin A1c values provide additional information beyond diagnosed diabetes, improving CVD prediction for women with diabetes \( (16) \). As a whole, the Reynolds Risk Score has been shown to improve risk prediction compared to the Framingham risk score in men \( (17) \) as well as in an independent cohort of women \( (18) \). Although the Framingham risk score is recommended in the treatment guidelines, the Reynolds Risk Score is also accepted \( (19) \).

**Statistical Considerations in Improving Prediction**

The effects of the addition of new biomarkers on the predictive ability of a model depends on many factors in addition to the relationship between the marker and the development of the disease, including the strength of the base model and the incidence (or prevalence) of disease in the population under consideration. Because many of these are different in women and men, the evaluation of model performance can vary by sex as well, depending on the measure of predictive ability being evaluated. Below we describe several measures of predictive ability typically reported, including the \( c \)-statistic, the categorical net reclassification improvement (NRI), the continuous NRI, and the integrated discrimination improvement (IDI), and examine the challenges for showing improvement in CVD prediction for women related to each measure.

**IMPORTANT BASELINE DIFFERENCES BETWEEN MEN AND WOMEN**

As described above, given the same age distribution, the incidence of CVD is much lower in women than in men. In the Framingham data, the incidence of total CHD (including angina) over 10 years among women aged 45–49 years was 5% compared to 11% among men in the same age range \( (8) \). The strength of the baseline model using traditional risk factors, however, is often somewhat stronger in women. Despite having lower absolute risk of disease, the discrimination ability of CVD risk prediction scores, as measured by the area under the ROC curve (AUC) or \( c \)-statistic, has been observed to be higher in women than men. In the Framingham risk score \( (8) \), the \( c \)-statistic for women is 0.77 for women and 0.74 for men. The same is true for the Framingham risk score for “hard” CHD \( (0.83 \text{ in women and 0.79 in men}) \), a model that has been validated in multiple cohorts \( (20) \) and in the Atherosclerosis Risk in Communities (ARIC) study for both white and black women and men \( (21) \). The Reynolds Risk Score had a \( c \)-statistic of 0.81 in the original population validation set \( (13) \) and 0.76 in an independent cohort of healthy women \( (18) \). This effectively leaves less room for improvement in prediction with novel biomarkers. In addition, the size of effects of various new markers may be somewhat different in women and men, as for many of the biomarkers described below.

**c-STATISTIC**

The \( c \)-statistic is the probability that the predicted risk for a randomly selected case is higher than for a randomly selected control and is based on ranks only. This measure is thus not affected by the incidence of disease or by the calibration of the model, defined as how well the predicted and observed risks agree \( (22) \). It is, how-
ever, affected by the strength of the baseline model as well as the effect size of the new predictor.

An example can be used to illustrate the importance of the strength of the baseline model and the effect size of the new predictor on risk estimation. We can think of the baseline model as a single variable, $x$, which is a linear combination of all the traditional risk factors. The effect size for $x$, or the odds ratio for $x$ (ORX), may be as low as 2 for diseases with few predictors, or as high as 16 or even 25 for models as strong as the Framingham risk score. We can then, using an additional assumption of normality for our single marker, relate the ORX to the $c$-statistic. For example, a model with a $c$-statistic of 0.80 would correspond to an ORX of 10.8 per 2 SD units, similar to comparing the top to the bottom tertiles of a risk marker. A $c$-statistic of 0.7 would correspond to an ORX of 4.4 per 2 SD.

As shown in Fig. 1A, the change in the $c$-statistic is affected by both the strength of the baseline model (ORX) and the strength of a new predictor, $y$, represented by the OR for $y$ (ORY) per 2 SD units. This figure applies for both men and women because the difference in incidence rates does not affect the $c$-statistic. If the baseline model (ORX) is stronger, as in women, then the change in the $c$-statistic will be smaller, even with the same effect size for $y$. For example, if the baseline model has an ORX of 16 per 2 SD (corresponding to a $c$-statistic of 0.84), then a novel risk marker with an ORY as high as 3 would exhibit a change in $c$-statistic of only 0.02. Alternatively, if the base model has an ORX of only 3 per 2 SD (with a $c$-statistic of 0.65), then the same ORY of 3 would lead to a larger increase of 0.06. If the OR for a novel marker is 1.5, which is more similar to those typically seen, including for traditional risk factors, then the change in $c$-statistic would be only 0.003 for an ORX of 16. Thus, the change in $c$-statistic can appear small even for new markers that are strongly associated with outcome (23).

CONTINUOUS NRI
The continuous NRI is used to examine whether the estimated risk for cases is higher in the new model than in the old and whether the estimated risk is lower for
controls (24). Because it is not affected by disease incidence nor by the strength of the baseline model (Fig. 1B), this figure is the same for men and women and is a function only of ORY, the effect size of the new marker. Consequently, the continuous NRI behaves more as a measure of effect than a measure of model improvement (25). The continuous NRI would thus be similar in women and men for markers with the same strengths of association. A test of the continuous NRI is similar to a test of the OR itself, though it is based solely on ranks and may thus be less powerful (26). Although it has been suggested as an alternative to assess improvement (24), it does not appear to add much new information to the test of association (27).

INTEGRATED DISCRIMINATION IMPROVEMENT

The IDI is the difference in the mean predicted risks among cases and controls for the new minus the old model (25). It measures how much higher the estimated risk is in cases vs controls and whether this difference is increased in the new model. The IDI is affected slightly by the strength of the baseline model, but is also affected by the disease incidence. Fig. 1, C and D, represent the effect of adding a predictor to models with overall disease incidences of 5% and 10%, roughly representing the different CVD incidence rates in men and women. As shown, given the same ORX and ORY, the IDI is higher when disease incidence is higher. This is because when risk is higher, the risk differences are also higher. Thus, a new marker for CVD would generally have a lower impact on the IDI in women than in men when evaluated at the same ages.

CATEGORICAL NRI

When risk strata and categorical measures of risk reclassification are used, as is the case for CVD, disease incidence and the strength of the baseline model are both determinants of the influence of novel markers. For example, if 3 risk strata, defined as 10-year predicted risk of 0% to <5%, 5 to <20%, and ≥20% are used, then for a marker with the same ORY, the percentage of individuals who are reclassified into new risk strata will differ for men and women (Fig. 2, A and B). This is because the distribution in risk categories for the baseline model depends on the overall incidence. If risk is very low in the group under consideration, then most individuals will fall into the lowest stratum, whereas if the risk is very high, then many will fall into the highest risk stratum. Unless the new marker is very strong, there may be little ability to change strata under these circumstances. When the risk strata straddle the overall incidence, as in the examples here, then there will be more reclassification. The categorical NRI based on these risk strata, which measures whether cases are reclassified upward, into higher risk strata, and controls downward, also differs by all 3 characteristics, as shown in Fig. 2, C and D. The NRI may be lower for women if the overall incidence is lower and fewer are reclassified. Although these results depend very much on the particular risk strata used, if they are carefully chosen to correspond to risks and benefits of treatment, then they will have different clinical implications for treatment decisions in women and men.

IMPLICATIONS FOR EVALUATING RISK PREDICTION IN WOMEN

As shown above, measures of model improvement may be very different in men and women. Given the same effect size for a new marker, the change in the c-statistic would be expected to be smaller in women, due to the stronger baseline model, whereas the continuous NRI would generally be expected to be similar in men and women. The IDI would be lower in women because it is a function of differences in absolute risk, whereas the categorical NRI would depend on the particular risk strata used and how these compare to the overall disease incidence. Understanding these fundamental differences between men and women in the epidemiologic and statistical determinants of the performance of risk prediction models can help guide future investigative efforts.

Biomarkers

In order for a marker to have utility in CVD risk prediction, it must be associated with CVD risk and add to risk prediction beyond currently recommended models. An additional key feature for the use of any biomarker is the ability to measure the marker reliably, safely, at a reasonable price, and in a time frame that can inform clinical decision-making. Important determinants of each of these parameters include the type of biological specimen that must be collected, the methods of collection and requirements for sample handling before analysis, the analytic tools required to measure the biomarker of interest, and the reliability and reproducibility of the test itself. These practical challenges are sometimes addressed in parallel with epidemiologic evaluation for association and prediction.

We have selected biomarkers in different stages of evaluation to illustrate a range of challenges to and results of assessment for utility in risk prediction (Table 1). Some, such as cardiac troponin measured with a high-sensitivity assay, and coronary artery calcium scores, have been studied in multiple populations and show consistent improvements in prediction. Others, such as the natriuretic peptides, have demonstrated robust associations with incident CVD in a wide range of cohorts, but their impact on predictive accuracy has been evaluated only in a few studies, with mixed results. Also included are biomarkers that measure dif-
different aspects of traditional predictors, such as alternative lipid measures. Many promising biomarkers have not been deemed clinically useful in part because of the challenges to reliable, low-cost, accessible ascertainment. Lipoprotein-associated phospholipase A\(_2\) (Lp-PLA\(_2\)) and lipoprotein a (Lp(a)), as discussed below, may have greater utility for prediction if the variability in ascertainment can be decreased.

**Table 1. Summary of selected biomarkers.**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Evidence for effect on CVD in women</th>
<th>Improved prediction in populations of men and women</th>
<th>Improved prediction in women alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A-1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Apo B-100</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>BNP/NT-proBNP</td>
<td>Yes (but not well studied)</td>
<td>Unclear (studied but results mixed)</td>
<td>Not tested</td>
</tr>
<tr>
<td>High-sensitivity troponin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, for CHD</td>
</tr>
<tr>
<td>Genetic markers</td>
<td>Yes</td>
<td>Unclear (studied but results mixed)</td>
<td>No</td>
</tr>
<tr>
<td>CAC</td>
<td>Yes</td>
<td>Yes</td>
<td>Not tested</td>
</tr>
</tbody>
</table>
ALTERNATIVE LIPID MEASURES

In addition to traditional measures of cholesterol, alternative lipid measures have been linked to CVD, including apolipoproteins A-I (ApoA1) and B-100 (ApoB) and Lp(a). Each LDL, intermediate-density lipoprotein, and VLDL particle carries 1 ApoB protein, and ApoA1 is the major apolipoprotein associated with HDL. These apolipoproteins have been advocated as superior to the standard lipids for CVD risk prediction (28). AMORIS (Apolipoprotein-Related Mortality Risk), one of the largest prospective studies to examine these measures, found that ApoB was a stronger predictor of fatal MI than LDL in both sexes (29). A quantitative review of 23 prospective studies in 2006 found that ApoA1, ApoB, and the ApoB/ApoA1 ratio each had moderately strong associations with risk of CHD, with little difference in effect between men and women for either ApoA1 or ApoB (30). While non-HDL cholesterol was found to be as predictive as ApoB when considered singly in the Women’s Health Study (WHS), both ApoA1 and ApoB were included in the best-fitting Reynolds model (13). Given their strong correlation with traditional measures of cholesterol, however, addition of these measures to risk prediction models are unlikely to improve risk prediction.

Lp(a) is an ApoB particle bound to an apolipoprotein(a) [apo(a)] component. Although epidemiologic studies have shown conflicting results, some of the variations may be due to the assessment in different assays. Using an assay that is independent of the apo(a) isoform size and kringle IV type-2 repeats, the WHS found that extremely high concentrations of Lp(a) were associated with increased cardiovascular risk, particularly in women with high concentrations of LDL cholesterol (31). The same was seen in the Reynolds Risk Score, albeit developed in the same cohort, in which Lp(a) was predictive among those with ApoB higher that 100 mg/dL. A subsequent Danish study, however, found a stepwise increase in risk of MI with increasing concentrations of Lp(a) that was not limited to those with high cholesterol (32). A later meta-analysis of 126,634 participants in 36 prospective studies found associations with both CHD and ischemic stroke (33), with similar effects in women and men for CHD, with a risk ratio of 1.16 per SD unit in women (95% CI, 1.07–1.26) and of 1.13 (95% CI, 1.07–1.19) in men (P for interaction, 0.45).

Despite the promise of these lipid-related markers, studies do not generally support their incremental utility over standard lipids. In a metaanalysis of individual data from 37 prospective cohorts, none of these, including ApoA1, ApoB, and Lp(a), added to risk prediction in women or men (34).

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2

Lp-PLA2 is an enzyme produced by inflammatory cells and is associated with circulating atherogenic proteins (35). About 80% of the enzyme is bound to LDL and the remaining 20% is linked to HDL and VLDL. Lp-PLA2 activity, but not enzyme mass, has been linked to small dense LDL particles in human plasma (36). Lp-PLA2 is thought to play a dual role in atherosclerosis, with both proatherogenic and antiinflammatory properties (37). Lp-PLA2 concentrations positively correlate with age and total and LDL cholesterol and negatively correlate with HDL among those without coronary artery disease. However, Lp-PLA2 does not correlate with body mass index or inflammatory markers such as C-reactive protein and interleukin-6 (38, 39).

Epidemiologic data have largely supported a role for Lp-PLA2 in predicting both CHD and stroke. In a metaanalysis examining 14 studies, including a total of 20,549 patients, the estimated adjusted OR for elevated Lp-PLA2 and CVD was 1.60 (95% CI, 1.36–1.89) (40). There was no significant evidence of heterogeneity by type of assay, presence of CVD at baseline, or inclusion of stroke by outcome definition; however, the association between Lp-PLA2 and CVD appeared to be weaker in primary vs secondary prevention (OR, 1.37; 95% CI, 1.10–1.70 vs OR, 2.12; 95% CI, 1.28–3.52). The analysis did find modest inconsistencies between studies; however, these were partially due to differing results by measure of association. The Lp-PLA2 Studies Collaboration (41) found that whereas Lp-PLA2 activity and mass were both lower among women than men, there was no evidence of a difference by sex in the relationship between Lp-PLA2 and CHD or stroke.

Lp-PLA2 mass and activity are both affected by the use of hormone therapy and tend to be lower among hormone users (42). Data from the WHI-OS (Women’s Health Initiative Observational Study) demonstrated that Lp-PLA2 was associated with risk of ischemic stroke, an effect that was larger among women not currently using hormone therapy (43). However, an analysis of CVD that included both stroke and CHD revealed that Lp-PLA2 mass, but not activity, was associated with CVD in women, and that the association remained among women not using hormone therapy (HR, 1.75; 95% CI, 1.20–2.54 in the highest vs lowest quartile) (42). Neither mass nor activity, however, improved predictive performance over traditional risk factors. In general, these assays also suffer from limited reproducibility, leading to a lack of calibration over different studies, which severely limits their clinical utility (44).

In a metaanalysis of individual data from 37 prospective cohorts, neither Lp-PLA2 mass nor activity added to risk prediction in women or men (34).
Natriuretic Peptides
Natriuretic peptides are hormones produced in the myocardium in response to wall stress. The peptide is produced and then cleaved to a 108 amino acid prohormone. It is then cleaved again into the biologically active B-type natriuretic peptide (BNP) and the inactive amino-terminal fragment, N-terminal prohormone of BNP (NT-proBNP). Both BNP and NT-proBNP are markedly increased in patients with heart failure and have gained widespread use in diagnosing heart failure as a cause of dyspnea in patients presenting with shortness of breath (45, 46). However, concentrations of BNP and NT-proBNP that are within the reference interval have nonetheless demonstrated strong associations with adverse cardiovascular outcomes, including MI, stroke, and cardiovascular death (47, 48). Indeed, a recent metaanalysis demonstrated that individuals in the general population with BNP or NT-proBNP concentrations in the upper third of the distribution were at more than 2.5 times the risk of incident CVD compared to those in the lowest third [relative risk, 2.68 (95% CI, 2.07–3.47)] (49). These effects were unchanged when cases of heart failure were no longer counted as incident CVD. No differences in the relative risks were observed among women, but as noted below, any differences in association with incident CVD by sex have not been well studied.

The ability of BNP and NT-proBNP to improve indices of risk prediction algorithm performance has been tested in only a few studies, and the results have been mixed. Although BNP/NT-proBNP improved risk prediction in one study of elderly men and another cohort of women, it failed to improve measures of discrimination in 2 European populations including both men and women (48, 50–52), and it improved prediction when combined with other biomarkers in a multimarker score. A minority of cardiovascular events reported in these studies occurred in women, and some studies were restricted to men (48). Furthermore, although women have a lower absolute risk of CVD than men, they also seem to have higher baseline concentrations of natriuretic peptides (53, 54). Thus, whether BNP or NT-proBNP might be used to improve cardiovascular risk stratification in women without preexisting CVD has not been well studied.

Sensitive Cardiac Troponin Assays
Cardiac troponin has become the gold standard in the diagnosis of MI, with consensus guidelines defining an “abnormal” troponin as any concentration above the 99th percentile in a healthy reference population (55). However, traditional assays for cardiac troponin I and T are not analytically sensitive enough to detect circulating troponin in most healthy individuals. Recently, a newer generation of highly sensitive assays for cardiac troponin have allowed detection of circulating troponin I concentrations in as many as 80% of healthy individuals, with acceptable analytic imprecision (<10% CV at the upper limit of the reference interval), although rates of detection are lower for cardiac troponin T (56).

In a primary prevention population of women, detectable concentrations of cardiac troponin T, as assayed with a novel high-sensitivity assay, were associated with a composite cardiovascular end point (MI, stroke, and cardiovascular death) in women with type 2 diabetes, but not in women without diabetes (57). In primary prevention and general populations, the ability of these novel, high-sensitivity cardiac troponins to improve cardiovascular risk prediction has been tested in the ARIC study, the Cardiovascular Health Study (CHS), and the Dallas Heart Study (DHS). In the ARIC study, circulating cardiac troponin T concentrations demonstrated a strong association with incident CHD, and the addition of high-sensitivity cardiac troponin T to the ARIC CHD risk prediction model significantly improved the AUC, IDI, and NRI in the overall cohort and in women specifically (58). In the CHS, DeFelippis and colleagues observed modest but significantly improved measures of classification and discrimination for cardiovascular death (59). Cardiac troponin T, again measured with a high-sensitivity assay, was also associated with all-cause and cardiovascular mortality, was reported in the DHS (60). In the only study performed in a cohort composed entirely of women, the WHS, an association with adverse cardiovascular outcome was observed among women with type 2 diabetes, but not among women without diabetes, as noted above (57). No interaction by sex was noted in the CHS, ARIC, or DHS.

Genetic Markers
Major advances have been made in finding genetic variants associated with complex diseases. Recent results from the CARDIoGRAMplusC4D [Coronary Artery Disease Genome wide Replication and Meta-analysis (CARDIoGRAM) plus the Coronary Artery Disease (C4D) Genetics] consortium identified 46 well-replicated single-nucleotide polymorphisms (SNPs) associated with coronary artery disease (61). However, with small effect sizes for the associations with individual SNPs (ORs ranging from 1.04 to 1.28), it has been suggested that many more SNPs may be needed to identify a substantial genetic risk, requiring sample sizes closer to a million (62).

Multiple studies have examined the incremental effect of adding known genetic markers to improve risk prediction using 1 of 2 approaches. The first approach examined genetic risk scores based on SNPs with pub-
lished associations with CVD. A large study in the WHS cohort showed no improvement in CVD risk prediction using a score based on 13 CVD-related SNPs, including the most consistently replicated SNP at 9p21.3 (risk allele frequency of 49% and HR 1.16) (63). Similar results were seen using a 13-SNP score in 7 European cohorts (64) and the Framingham cohort (65). In the Framingham cohort, a modest improvement was seen for CHD prediction using the 13 SNP score, whereas CVD risk prediction remained unchanged even after the addition of 16 subsequently identified SNPs (65). Another 13-SNP score was examined in the Framingham, ARIC, and Rotterdam cohorts for CHD prediction, and improvements were found only in the ARIC cohort (66).

The second approach added SNPs associated with CVD risk factors. No improvement in CVD risk prediction was seen with a score based on 102 SNPs in the WHS cohort (63) or 101 SNPs in the Framingham cohort (65). Scores based on SNPs associated with lipid concentrations did not improve CHD risk prediction in the Whitehall II and British Women’s Heart and Health Study cohorts (67).

CORONARY ARTERY CALCIFICATION
Coronary artery calcification (CAC), measured by computed tomography, is the imaging measure that has shown the most consistent effect on CVD prediction. A score of >0 indicates the presence of some calcified atherosclerotic plaque, with higher cutoffs used for clinical significance. Women have lower scores than men, with a large cohort study finding scores >0 in only 30% of women compared to 60% of men (P < 0.0001) (68). In the same study, the HR of CHD associated with a CAC score in the top tertile of detectible scores compared to a CAC score of 0 was 17.7 in men (CAC, ≥250) and 7.2 in women (CAC, ≥113). The effect of CAC score on prediction has been assessed in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, in which addition of CAC score to the Framingham risk model in the entire cohort increased the AUC from 0.76 to 0.81 (P < 0.001) (69). Prediction results stratified by sex were not shown. Additionally, concerns about cost and radiation exposure risk have also been raised (70).

Conclusions
In addition to offering insights into biological pathways, biomarkers may have utility in prediction of CVD risk for women, but there are challenges. Understanding both the unique aspects of CVD risk prediction in women, including a lower incidence of CVD due to a later age of onset, better existing risk models, and differences in effects of biomarkers, as well as the effects of those differences on evaluation of risk prediction, is critical. Several current trends may aid in identification of useful new biomarkers. First, there is growing public awareness that CVD is an important disease in women and that risk markers and predictors of CVD should be evaluated in women, resulting in increasing numbers of women included in CVD research studies. Second, development of new statistical methods for evaluation of prediction may help ascertain which are most likely to have clinical utility. Finally, promising new biomarkers and technologies offer new opportunities for both pathophysiologic insight and improved risk prediction. Taken together, these factors may lead to further improvement in the early prediction of CVD risk in women.

References
CVD Risk Prediction in Women

Reviews


