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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.

Keywords

acute coronary syndromes; biomarkers; cardiovascular disease; coronary heart disease; epidemiologic studies; metabolic syndrome; stroke; cardiovascular risk factors; risk prediction; sex differences; women

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 y later in life. Before age 75, stroke occurs more commonly than CHD in women, whereas the opposite pattern holds for men (2).

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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 y, 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 y; women: >39 v. 31 y). 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.

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-y 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-y (7) or 30-y 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-y 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 y 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 8,000 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 y. (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 y, 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 ($\text{NRI}=4.9\%$; $p=0.02$), and a positive integrated discrimination improvement ($\text{IDI}=4.1\%$; $p<0.0001$). In race-specific analyses, the model showed improved classification in both white ($\text{NRI}=4.3\%$; $p=0.04$) and black ($\text{NRI}=11.4\%$; $p=0.13$) women. Analyses of the 2013 ACC/AHA risk models show that they do not yield significantly better calibration or discrimination than earlier models (11). Risk was overestimated when the 2013 ACC/AHA risk models were applied to the WHS and WHI-OS cohorts (15).

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).

Statistical and practical considerations

Various statistical approaches assess whether a novel biomarker improves risk prediction in epidemiologic settings (16). Besides showing that such a biomarker is independently associated with CVD risk as indicated by a significant multivariable-adjusted relative risk (RR), researchers must also demonstrate that adding the biomarker to a base model improves model performance as assessed by parameters such as risk discrimination and event reclassification. The usual measure of risk discrimination reported in the literature is the c-statistic, also known as the area under the receiver operating curve, is the probability that the predicted risk for a randomly selected case is higher than that for a randomly selected control, based on ranks. Commonly reported measures of reclassification include the net reclassification index (NRI), which is the net increase v. decrease in risk factor categories among the cases minus those among the controls after a novel biomarker is added

to a model, and the integrated discrimination index (IDI), which is the difference in the mean predicted risks among cases and controls for the new v. old model. These parameters increase when novel biomarkers correctly assign individuals to higher or lower probabilities of having events. As a rough guideline, a change in c-statistic of >0.01 and an NRI $>10\%$ generally indicate meaningful improvement in risk prediction when a novel biomarker is added to a traditional model (17). However, there is debate about the appropriate clinical interpretation of the size of these metrics.

From a practical standpoint, a novel biomarker must also have an accurate, reproducible, safe, cost-effective, and time-sensitive method of measurement if it is to be incorporated into risk prediction algorithms for clinical decision making on a national level (16).

Lipid-related markers

Apolipoproteins B-100 (ApoB) and A-I (ApoA1) are the primary surface proteins on proatherogenic lipoproteins ($>90\%$ in LDL) and HDL, respectively. A 2006 meta-analysis of study-level data from 23 prospective cohorts found that ApoA1, ApoB, and the ratio of ApoB to ApoA1 each showed moderately strong associations with CHD risk; the associations were of similar magnitude in women and men (18). For Apo A1, the RR for persons in the bottom third compared with those in the top third of the baseline distribution was 1.62 (1.43–1.83); for Apo B-100, the corresponding statistic was 1.99 (1.65–2.39). However, in analyses limited to those studies that adjusted for highly correlated lipids (i.e., HDL cholesterol for ApoA1; LDL cholesterol and total cholesterol for Apo B), the associations were substantially weaker. A 2012 meta-analysis of individual-level data from 26 prospective studies in primary and secondary prevention settings with a total of 140,000 participants found that the simultaneous addition of Apo A1 and ApoB to prognostic models containing traditional risk factors yielded a statistically significant though modest improvement in risk discrimination (change in c-statistic=0.0006) but a nonsignificant worsening in reclassification (19). In exploratory sex-stratified analyses, the combination of ApoA1 and ApoB preferentially improved risk discrimination in men compared with women (p, interaction=0.01). The 2013 ACC/AHA guidelines conclude that the contribution of ApoB to risk assessment in primary prevention setting is “uncertain” (9).

Lipoprotein(a) [Lp(a)] is an LDL particle bound to the glycoprotein apolipoprotein(a). A 2009 meta-analysis of data from 36 prospective studies found that Lp(a) was associated with incident CHD and ischemic stroke after adjustment for traditional risk factors, including lipids (20). For CHD, the risk ratio per 3.5-fold higher usual Lp(a) level (i.e., 1 SD increase) was 1.16 (1.09–1.26) in women and 1.13 (1.07–1.16) in men (p, interaction=0.45). In a 2012 meta-analysis of data from 24 prospective studies with a total of 134,000 participants, the addition of Lp(a) to prognostic models containing traditional risk factors produced a statistically significant but modest improvement in risk discrimination (c-statistic change=0.0016) and a nonsignificant reclassification statistic (NRI $<1\%$) (19). Lp(a) may become more useful for prediction if greater uniformity in assessment can be achieved (16).

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is an enzyme secreted by inflammatory cells that circulates bound mainly to LDL. It is expressed in the diseased vessel and is thought to indicate plaque instability. In a meta-analysis of data from 32

prospective studies with a total of 79,000 participants (some healthy and some with stable vascular disease), higher Lp-PLA₂ mass (1 SD increase) was associated with an increased risk for CHD [RR=1.11 (1.07–1.16)] and ischemic stroke [RR=1.14 (1.02–1.27)] after adjustment for conventional risk factors; for Lp-PLA₂ activity, the corresponding RRs were 1.10 (1.05–1.16) and 1.08 (0.97–1.20) (21). Although Lp-PLA₂ activity and mass were lower in women than men, the associations between Lp-PLA₂ and CVD risk were similar for both sexes. Results generally appeared stronger for secondary prevention than for primary prevention. Improvement in risk prediction was not assessed. A 2012 meta-analysis of data from 8 prospective studies with a total of 29,000 participants found that, in a pattern similar to that for Lp(a), adding Lp-PLA₂ mass to prognostic models containing traditional risk factors yielded a statistically significant but modest improvement in risk discrimination (c-statistic change=0.0018) and a nonsignificant reclassification statistic (NRI<1%) (19).

Recent data from the WHI-OS are of interest. In a case-cohort sample that included 1821 incident CVD cases, Lp-PLA₂ mass, but not Lp-PLA₂ activity, was associated with risk for major CVD events after adjusting for traditional risk factors (per 1-SD increase: RR=1.24 [1.14–1.35], $p<0.0001$; top vs. bottom quartile: RR=1.84 [1.45–2.34], p for trend <0.0001) (22). There was no effect modification by race, use of menopausal hormone therapy (Lp-PLA₂ levels are typically lower with such use), diabetes, statin use, or levels of total or HDL cholesterol, BMI, or high-sensitivity CRP. Reclassification statistics did not suggest improvement in risk prediction, however. The utility of Lp-PLA₂ may increase if variability in assessment can be reduced (16).

Natriuretic peptides

B-type natriuretic peptide (BNP) and its precursor, N-terminal prohormone of BNP (NT-proBNP), are biomarkers that reflect left ventricular dysfunction. Assessment of B-type BNP or NT-proBNP is recommended in patients with suspected heart failure (see below), but these markers have also been examined as predictors of MI, stroke, and cardiovascular death in general populations. In a 2009 meta-analysis of study-level data from 40 prospective studies with a total of 87,000 participants, individuals with BNP or NT-proBNP values in the top tertile were >2.5 times more likely to develop CVD than those in the bottom tertile, after adjustment for age, sex, smoking, diabetes, blood pressure, and lipids (23). RRs were similar in general population cohorts comprised either of healthy individuals or persons unselected for CVD risk; individuals at high risk of CVD by virtue of their risk-factor profile; and patients with stable CVD. Whether there was effect modification by sex was not examined. Fourteen studies—three in general populations—reported changes in measures of risk discrimination or classification after BNP or NT-proBNP (often in combination with other nontraditional risk factors) was added to a risk prediction model containing established risk factors. In the three general population studies, the change in c-statistic or NRI generally indicated either no or only modest improvement in risk discrimination or classification. Risk discrimination was slightly better in studies of high-risk individuals and patients with preexisting CVD.

In healthy populations, women tend to have higher levels of natriuretic peptides than do men, perhaps as a result of estrogen-mediated stimulation and androgen-mediated

suppression (24). Establishing sex-specific reference cut-offs may increase the utility of BNP or NT-proBNP for CVD risk prediction in general populations.

Studies of patients with acute or chronic heart failure have not found significant differences in BNP or NT-proBNP levels between the sexes (24). Indeed, women show slightly lower values in clinical settings, likely because heart failure in women as compared with men is more often accompanied by preserved ejection fraction, a combination associated with lower natriuretic peptide levels. Despite this sex difference, natriuretic peptides show similar diagnostic utility for heart failure in women and men presenting with dyspnea in the emergency room (24).

High-sensitivity cardiac troponin

Cardiac troponins are blood biomarkers that reflect myocardial cell damage; their measurement is recommended for a definitive diagnosis of MI in clinical settings. In the past, assays were not sensitive enough to detect circulating troponin in general populations. Newer assays measure very low levels of circulating troponin that were undetectable with earlier assays. In healthy populations as well as in those with stable CAD, cardiac troponin levels are significantly higher in men than in women (24).

Several large studies have recently used high-sensitivity assays to examine the relation between troponin and CVD incidence or CVD mortality in cohorts without CHD, stroke, or heart failure at baseline. For example, in the Atherosclerosis Risk In Communities (ARIC) study, which followed 9,698 men and women aged 54–74 for 9.4 y, individuals with cardiac troponin T (cTnT) levels in the highest category ($>0.014 \mu\text{g/L}$) were more likely to develop incident CHD than those with undetectable levels ($\text{RR}=2.29$ [$1.81\text{--}2.89$]), after adjustment for traditional risk factors, kidney function, high-sensitivity CRP, and NT-proBNP (25). The RRs in women and men were 3.05 ($2.05\text{--}4.53$) and 1.92 ($1.42\text{--}2.60$), respectively. Adding cTnT to a model with traditional coronary risk factors significantly improved risk prediction parameters in the overall cohort (change in c-statistic= 0.014 [$0.008\text{--}0.024$]; $\text{NRI}=10.1\%$ [$3.8\text{--}15.9\%$]; $\text{IDI}=0.032$ [$0.021\text{--}0.048$]), in women (change in c-statistic= 0.027 [$0.014\text{--}0.046$], $\text{NRI}=19.2\%$ [$6.7\text{--}25.2\%$], $\text{IDI}=0.043$ [$0.026\text{--}0.071$]), and in men (change in c-statistic= 0.013 [$0.014\text{--}0.028$], $\text{NRI}=7.2\%$ [$1.6\text{--}19.1\%$], $\text{IDI}=0.028$ [$0.015\text{--}0.052$]). In the Cardiovascular Health Study, which followed 4,221 women and men aged ≥ 65 for a median of 11.8 y, persons with the highest cTnT levels ($>12.94 \text{ pg/mL}$) were more likely to experience cardiovascular death compared with those with undetectable levels ($\text{RR}=2.91$ [$2.37\text{--}3.58$]). There was also modest but significantly improved measures of discrimination (change in c-statistic= 0.013) and classification ($\text{NRI}=4.0\%$; $\text{IDI}=0.021$) (26). In the WHS, detectable cTnT ($>0.003 \mu\text{g/L}$) was associated with subsequent major CVD events in women with type 2 diabetes ($\text{RR}=1.79$ [$1.04\text{--}3.07$]) but not in other women, after adjustment for traditional risk factors and hemoglobin A1c (27). Most recently, in the Scottish Heart Health Extended Cohort study, a 20-y follow-up of 7,742 women and 7,598 men with a mean age of 49, cardiac troponin I (cTnI) was associated with incident CVD after adjustment for traditional risk factors. Persons with the highest levels of cTnI had a higher risk of CVD events than those without detectable levels ($\text{RR}=2.5$ [$1.60\text{--}2.61$]; $p<0.0001$) (28). Addition of cTnI to clinical variables also improved discrimination (c-statistic change, 0.0044 ;

$p < 0.0001$) and reclassification ($\text{NRI} = 3.2\%$; $p < 0.0001$). Upon examination of specific endpoints, the improvement occurred for CHD but not stroke. A secondary analysis suggested an optimal cut-off value for cTnI of 4.7 pg/mL in women and 7.0 pg/mL in men to detect individuals at high risk for future CVD events. Use of these values in risk prediction models yielded an NRI of 13.1% ($p < 0.0001$) in women and 13.4% ($p < 0.0001$) in men.

In clinical settings, women are less likely than men to have cardiac troponin levels that exceed the MI decision limit despite a presentation suggestive of acute coronary syndrome (24). The reasons for the sex difference are not well understood. It is possible that the current lack of sex-specific decision limits on troponin levels for diagnosing MI is a factor in the underdiagnosis and undertreatment of MI in women compared with men. Thus, identifying an optimal MI decision limit for this biomarker in women is critical. The prognostic ability of troponin in female v. male patients with known coronary disease also remains unclear (24).

Coronary artery calcium

Although concerns about cost, radiation exposure, and management of incidental findings may limit its routine measurement in clinical practice, coronary artery calcification (CAC), as assessed by computed tomography, is a strong predictor of CHD risk and has been shown in many epidemiologic studies to yield sizable improvements in risk discrimination and classification in primary prevention settings when added to traditional risk factor models, particularly among individuals at intermediate risk (16, 29). Few studies have conducted sex-stratified analyses. One study that did was the Rotterdam Study, which followed 5,933 Dutch adults with a mean age of 69 for 7 y (30). In this cohort, multivariable-adjusted RRs of CHD associated with elevated CAC scores (extreme quartile comparison) were 7.8 (3.3–18.4) in men and 4.8 (2.0–11.7) in women; the change in c-statistic was 0.06 in men and 0.05 in women; and the NRI was 24.1% in men and 13.4% in women. In those at intermediate risk according to their Framingham scores, the NRI was 50.9% in men and 25.2% in women. The appropriate use of CAC screening in clinical practice is a topic of vigorous debate (11, 29, 31).

Genetic markers

Researchers have identified many genetic variants associated with coronary artery disease, but effect sizes associated with individual single-nucleotide polymorphisms (SNPs) are small (16). Although there are exceptions, the addition of genetic risk scores based on multiple SNPs related either to clinical CVD events or cardiovascular risk factors to models containing traditional risk factors has failed to improve risk prediction (16).

Although not a major factor in the prediction of CHD or composite stroke outcomes, *thrombophilic abnormalities* such as presence of the gene polymorphisms prothrombin G20210A and factor V Leiden, not only increase the risk for venous thromboembolism and pulmonary embolism but also raise the risk for cerebral venous thrombosis, a stroke subtype that is far more common in women of reproductive age than in similarly aged men. The sex

differential appears to result from an interaction between clotting-factor polymorphisms and pregnancy or oral contraceptive use (32).

Metabolic syndrome

Metabolic syndrome (MetSyn) refers to a clustering of at least three of the following interrelated cardiometabolic risk factors: dysglycemia, increased blood pressure, increased triglycerides, decreased HDL cholesterol, and abdominal obesity (33). Individuals with MetSyn are 4 to 5 times more likely to develop diabetes and about twice as likely to develop CVD than those without the syndrome (33). Sex-stratified analyses are limited, but a meta-analysis of data from five cohorts with a total of 18,353 participants suggest that MetSyn is associated with similar elevations in CVD risk in women (RR=1.83 [1.53–2.20]) and men (RR=1.98 [1.71–2.28]) (33). It is unclear whether MetSyn confers additional risk beyond its individual components.

Comparative data from two U.S. National Health and Nutrition Surveys (NHANES III [1988–1994] and NHANES 1999–2006) show a striking rise in prevalence of MetSyn between the two surveys, with the relative increase larger in women (22.8%) than in men (11.2%) (34). In NHANES 1999–2006, the prevalence of MetSyn was 33% in women and 35% in men. The prevalence of specific risk factor clusters responsible for triggering the MetSyn diagnosis has not been reported for the 1999–2006 data, but such clusters differed between the sexes, at least in those under age 65, in NHANES III (35). Abdominal obesity was a dominant feature in women with MetSyn, whereas risk factor combinations were more heterogeneous in their male counterparts.

Sex affects not only the clinical expression but also the pathophysiology of MetSyn. A recent review (33) argues that that sex differences in dysglycemia, body fat, adipocyte biology, and the hormonal control of body weight, as well as the estrogen decline that occurs postmenopausally, may have implications for cardiometabolic sequelae in women and men with the syndrome.

Dysglycemia is a global term referring either to impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). However, the two conditions are physiologically distinct. IFG results from inadequate basal insulin secretion or sensitivity in the liver, whereas IGT is a consequence of insufficient insulin response or sensitivity to a carbohydrate load in not only the liver but also skeletal muscle. IGT is more common in women than in men (except at older ages), whereas IFG is more often seen in men than in women. The reasons for this pattern are unknown, but sex differences in “lean muscle mass, visceral adiposity, differential impact of aging, influence of menopausal transition, and altered susceptibility to free fatty acid induced peripheral insulin resistance” may play a role (33; pp. 46–47). Because IGT is not included in most current MetSyn definitions, it is possible that, compared with their male counterparts, dysglycemic women are underdiagnosed with the syndrome.

The sex difference in the **distribution of body fat** is well known, with adipose tissue accrual in the upper body (trunk and abdomen) and lower body (hips and thighs) more prominent in men and women, respectively. Visceral adipose tissue (VAT) in the abdomen is a stronger

correlate than subcutaneous adipose tissue (SAT) of metabolic disturbances and cardiovascular risk. The amount of VAT, as well as the ratio of VAT to total body fat, is lower in premenopausal women than in men. Also, given the same waist circumference, women have less VAT than men. In addition, changes in VAT are less tightly linked to changes in total body fat in premenopausal women than in men. These findings imply that BMI and waist circumference—two commonly used measures in epidemiologic settings—are less accurate indicators of visceral obesity in women and may thus underestimate the impact of VAT on cardiometabolic risk in this group.

Sex affects *adipocyte size* in certain anatomic locations. For example, in men, omental adipocytes (a type of intraperitoneal VAT) and abdominal subcutaneous adipocytes are approximately equal in diameter, and show only minimal size increases with increasing BMI. In contrast, in women, omental adipocytes are 20–30% smaller than abdominal subcutaneous adipocytes, and show larger size increases as BMI increases. Adipocyte size, in turn, affects adipocyte function and metabolic activity, independent of obesity level. Larger adipocytes show higher lipolysis rates and proinflammatory adipokine secretions, for example. Thus, sex differences in adipocyte size may affect the cardiometabolic risk associated with MetSyn in women and men.

Sex differences in *hormonal control of body weight* may also contribute to the clinical expression and sequelae of MetSyn. The hormones leptin, insulin, and estrogen play a role in weight control via “adiposity signals” to the brain. Leptin, which has the effect of inhibiting food intake, suppressing insulin secretion, and increasing lipolysis, is released from adipose tissue in direct proportion to fat mass; its expression is greater in subcutaneous than in visceral adipocytes. On the other hand, insulin, which is secreted from pancreatic beta-cells in response to rising glucose levels, is a better marker of visceral than subcutaneous fat. Given the aforementioned sex differences in visceral vs. subcutaneous fat, it seems likely that hormonal control of body weight varies in women and men. Accumulating data also suggest that estrogen affects adipocyte biology, as well as glucose and lipid metabolism. It has been suggested that estrogen stimulates leptin-mediated mobilization from visceral to subcutaneous fat depots. At menopause, a time of fluctuating and ultimately falling estrogen levels, an increase in visceral adiposity occurs, along with atherogenic lipid changes characteristic of MetSyn.

Other Risk Factors in Women

Other conditions/exposures unique to, or more common in, women may warrant special consideration for CVD risk prediction in female populations. Although a review of risk factors other than biomarkers is beyond the scope of this article, a brief listing of such factors is instructive. Current AHA guidelines for CVD prevention in women classify a history of *pregnancy complications* (preeclampsia, gestational diabetes, or pregnancy-induced hypertension) and *systemic autoimmune collagen vascular diseases* (such as lupus erythematosus and rheumatoid arthritis) as “major” CVD risk factors, on par with traditional risk factors included in prediction models (2). The *use of hormonal contraceptives or menopausal hormone therapy* is also associated with adverse cardiovascular outcomes,

particularly in women at high baseline risk. AHA guidelines also recommend screening for *depression*, a risk factor for poor prognosis, in female CVD patients (2).

Conclusion

Risk prediction models for CVD that rely on traditional cardiovascular risk factors are useful for estimating a woman's risk for developing CVD, but there is room for improvement. Alternative lipids, B-type natriuretic peptides, high-sensitivity troponin, CAC, and genetic markers have been proposed as novel risk factors that may improve risk prediction. Of these markers, CAC appears to yield the most substantial improvement, but concerns about cost and radiation exposure may limit its routine use in general populations. Sex differences in the predictive role of novel cardiovascular biomarkers for primary prevention require additional study, as do the diagnostic and prognostic utility of cardiac troponins in acute coronary syndromes. Sex differences in the clinical expression and physiology of metabolic syndrome may be important in refining sex-specific predictions of cardiovascular risk. Consideration of other exposures that are unique to or more prevalent in females, such as history of pregnancy complications or autoimmune disease, may also help improve accuracy of risk estimates in women.

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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 (data are limited)
Genetic markers	Yes	Unclear (studied, but results mixed)	No

Adapted from Paynter NP et al., *Clin Chem* 2014; 60:88–97. Permission pending.