Endothelial Vascular Function as a Surrogate of Vascular Risk and Aging in Women

Peter Collins, MA, MD; Angela Maas, MD, PhD; Megha Prasad, MD, MS; Louise Schierbeck, MD, PhD; and Amir Lerman, MD

Abstract

Cardiovascular disease is the leading cause of morbidity and mortality in women. We suggest the need to develop a paradigm that connects sex- and age-specific nontraditional risk factors that serve as a common mechanism ultimately leading to an increased risk of cardiovascular events. Vascular injury with abnormal repair leading to functional, rather than structural, abnormalities can be regarded as accelerated vascular aging. It emerges as a common feature that can trigger the early diagnosis and risk stratification for cardiovascular disease in women. We discuss sex-specific risk factors that can contribute to vascular injury with age, and these might not always be considered by cardiovascular physicians. It is important for the primary physician to be aware of these risk factors to enable more intensified management of this at-risk population. Novel technologies that allow the assessment of vascular function noninvasively can serve as key diagnostic and therapeutic tools with which we can identify such individuals and target therapy to manage this important patient population appropriately and effectively. We hope that this article will stimulate interest in this field and encourage further research in these important areas.
establish obstructive CAD in female patients in middle age, this method is not sufficiently sensitive or specific to detect the majority of the mechanisms of symptoms in this population. Furthermore, once a patient has obstructive CAD, they are resigned to the existing treatments to manage the atherosclerotic process. Ideally, increased focus on preventing the atherosclerotic process can result in identifying abnormal vascular health early, and addressing this will be the key to reducing overall cardiovascular burden. In women, there are a sex-specific risk factors that must be understood and considered by the primary provider in an effort to both assess vascular health and to prevent accelerated vascular aging and future cardiovascular events. Estrogen itself plays a key role that is important for understanding the vascular process, as early in life it can be protective and can improve endothelial function because of the upregulation of nitric oxide; however, as estrogen production slows and halts in women, they can become prone to accelerated vascular aging.6-9

It is estimated that at least half of women with chest pain but no evidence of CAD have coronary microvascular dysfunction causing characteristic symptoms of ischemia. We propose that additional vascular function testing should be included in this patient population, and even before the onset of symptoms, to improve risk stratification and to potentially enable intensification of primary and secondary prevention interventions (Figure 1). Among traditional risk factors, hypertension is generally underdiagnosed and undertreated in women. As CAD is affected by hormonal status and other common comorbidities, a more sex-specific approach is justified for optimal prevention and treatment in aging women. Men and women require dedicated attention to detail and assessment of vascular function and traditional and nontraditional risk factors to help better understand an individual’s cardiovascular risk. We have chosen to focus on sex-specific risk factors in women that predispose to increased vascular age, atherosclerosis, and cardiovascular risk; this can be challenging because menopausal status and estrogen levels are directly associated with age. With this article, we hope to stimulate physicians to engage in more intensive risk assessment and management for middle-aged women who have traditionally received poor management.

ASSESSMENT OF ENDOTHELIAL FUNCTION
Angina or ischemia-induced breathlessness (angina equivalent) is the result of myocardial ischemia occurring because of an imbalance between oxygen supply and demand.8,9 The coronary microcirculation is the main regulator of myocardial perfusion. Thus, even in the absence of occlusive epicardial disease, coronary microvascular dysfunction can lead to angina, myocardial ischemia, myocardial infarction, and heart failure. Moreover, vascular reactivity and arterial function are important markers of vascular aging that may be the first step of the atherosclerotic process, and early identification of abnormal vascular reactivity can help to stratify patients according to risk more effectively.

The endothelium is a single-cell layer that separates the blood and vascular supply from other tissues and is important in maintaining hemostatic balance between thrombosis and anticoagulation, regulating
vascular tone, and regulating angiogenesis at the level of the epicardium and microcirculation. Shear stress causes vasodilation owing to endothelium-dependent release of nitric oxide. Endothelial dysfunction occurs at an early stage of atherosclerosis, and it is characterized by an imbalance in vasodilation and vasoconstriction. It has also been linked to traditional cardiovascular risk factors such as hypertension, hyperglycemia, smoking, advancing age, and nontraditional risk factors particularly in women, such as polycystic ovaries, preeclampsia of pregnancy and autoimmune diseases. Endothelial dysfunction is a significant independent risk factor for future cardiovascular events, and this has often been attributed to the relationship between arterial function and vascular aging. A number of modalities are available to assess vascular aging, and they will be useful as we further establish the role of screening in the management of patients with increased risk of cardiovascular disease.

Endothelial function can be measured both invasively and noninvasively. The gold standard of assessing coronary endothelial function involves the responses of both the epicardial arteries and the microcirculation to an endothelium-dependent vasodilator such as acetylcholine (a “functional angiogram”). Epicardial coronary artery diameter is measured using quantitative coronary angiography or intravascular ultrasound. The assessment of the microvasculature is done with a Doppler or pressure wire that measures microvascular endothelial coronary flow reserve. The main limitation of these techniques is their invasive nature, making them less applicable in daily clinical practice. Therefore, in a wide range of clinical settings, noninvasive testing can be used and would be preferable to assess endothelial function.

Endothelial function can be measured through various clinically validated techniques in a noninvasive fashion as well. This approach is ideal for screening and is a good adjunct to consider when seeing women with risk factors for cardiovascular disease. Noninvasive means of measurement of endothelial function include the use of dedicated algorithms designed to assess vascular reactivity and function using cardiac magnetic resonance imaging (MRI), or the use of positron emission tomography to measure coronary flow reserve. In addition, a peripheral technique using venous plethysmography of the forearm, ultrasound of the brachial artery or radial artery, or digital arterial tonometry using flow-mediated vasodilatation or infusion of vasoactive agents, such as acetylcholine or nitroglycerin, can also be used to quantify endothelium-dependent and nondependent vasodilation. The main and common principles for the noninvasive assessment of endothelial function are based on the seminal role of the endothelium in reactive hyperemia as a response to ischemia. This process involves placement of a pressure cuff on the arm and inflation for 5-10 minutes to induce absence of flow and local ischemia. The release of the cuff induces the endothelium-dependent process of reactive hyperemia that can be quantified, and it serves as a subsequent assessment of peripheral endothelial function. Importantly, measurements of peripheral endothelial function correlate with coronary artery
endothelial function.\textsuperscript{20,21} Even noninvasively assessed impaired endothelial function has been shown to be independently predictive of future cardiovascular events, as the function of the endothelium may be a marker of vascular aging.\textsuperscript{13,20,22-25}

**Sex Differences in Endothelial Function**

In middle-aged women, functional rather than structural coronary abnormalities are a main cause of chest pain syndromes.\textsuperscript{1,26} It has been shown that coronary flow reserve is lower in women than in men, suggesting possible sex-specific mechanisms contributing to microvascular dysfunction. In women without obstructive CAD, the presence of endothelial dysfunction has been shown to be an important predictor of ischemic heart disease.\textsuperscript{27,28} The Women's Ischemia Syndrome Evaluation study emphasized that microvascular ischemia was associated with the signs and symptoms of ischemia in women with nonobstructive CAD.\textsuperscript{29} Symptomatic women with established endothelial dysfunction should be offered medical therapy directed at improving established risk factors and endothelial function. Noninvasive endothelial function testing in sex-specific assessment could provide additional benefit in preventing future cardiac events.\textsuperscript{7} Although women might not have traditional risk factors for cardiovascular disease, further investigation into their clinical and medical history can elucidate risk factors that predispose them to cardiovascular disease. Conditions that are highly prevalent among women can contribute to accelerated atherosclerosis by inducing and promoting endothelial dysfunction. These conditions include pre-eclampsia, polycystic ovarian syndrome (PCOS), age at menopause, presence of inflammatory disorders, anemia, hyperuricemia, and stress-induced cardiomyopathy.

**Effect of Menopause on Endothelial Function**

As women age and reach menopause, hormonal changes can play a role in overall vascular health. Postmenopausal women have a greater than 3-fold risk of atherosclerosis when compared with premenopausal women, even after adjustment for age and other potential confounders; however, this theory remains controversial because several randomized controlled trials have suggested otherwise, and it could be attributed to age according to some theories.\textsuperscript{30,31} The decline in endothelial function starts in the early menopause or early menopausal transition and increases after menopause or any period of prolonged estrogen deficiency, although it is naturally difficult to separate postmenopausal status from age, as these two risk factors go hand in hand.\textsuperscript{31,32} Signs of endothelial dysfunction precede the appearance of plaques in the carotid arteries. Vascular health and aging in women is dependent on the hormonal status, and it can be detected by assessing endothelial function, as endothelial function can serve as marker of vascular aging.\textsuperscript{33} This suggestion is supported by data showing that women who have undergone ovariectomy have reduced endothelial dependent dilation.\textsuperscript{34,35} Women transitioning through menopause should be screened with noninvasive assessment of endothelial function for early risk stratification in addition to traditional comprehensive laboratory assessment, to manage and screen for vascular disease that might otherwise go undetected.

Vasomotor symptoms could be related to oxidative stress and adverse cardiovascular disease (CVD) risk profile.\textsuperscript{36} Severe menopausal symptoms have been associated with hypertension, elevated total cholesterol levels, and increased CVD events compared with female patients with no or few symptoms.\textsuperscript{37,38} Several studies have suggested that subclinical atherosclerosis is more prevalent in female patients with severe vasomotor symptoms.\textsuperscript{39,40} Menopausal vasomotor symptoms are associated with increased sympathetic and decreased parasympathetic function,\textsuperscript{41,42} which could enhance the risk of cardiovascular events. This increased risk could be important during a hot flush episode, particularly in women who are prone to severe arrhythmia.\textsuperscript{42,43} Vasomotor symptoms are also exacerbated by an increase in insulin resistance and inflammatory factors derived from visceral adipose tissue, which has increased activity after menopause. In
addition, there remains the need for further investigation to better understand the role of timing of hormonal replacement therapy in women who have reached menopause, as there are some data that support the effect of timing on the role of hormonal therapy in modulating cardiovascular risk.44

**Polycystic Ovary Syndrome and Endothelial Function**

Polycystic ovary syndrome (PCOS) is a complex disorder characterized by oligomenorrhea, amenorrhea, hyperandrogenism, and polycystic appearance of the ovaries. It is the most common hormonal imbalance among women of reproductive age, affecting up to 10% of women. Endothelial dysfunction has been shown to be prevalent among women with PCOS, independent of obesity, age, and other risk factors.45-48 The mechanism responsible for this association is not known, although many studies suggest a direct vascular effect. Reduced nitric oxide bioavailability and hyperandrogenism are both potential contributing etiologies.49 The hyperandrogenic state has been associated with reduced endothelium and smooth muscle—dependent vasodilatation and vascular constriction with loss of nitric oxide dependent relaxation in the rat model.50 Over time, such hormonal imbalance can play a significant role in impairing vascular function and accelerating vascular aging.

From a clinical standpoint, when evaluating female patients for cardiovascular risk, it is important to consider a history of PCOS and inquire about irregular menses. Because obesity is prevalent in patients with PCOS, weight loss should be integral to risk factor management. We suggest that patients with PCOS should undergo noninvasive assessment of endothelial function and the results can be used to guide therapy. Adequate treatment of PCOS early could play a role in reducing associating cardiovascular morbidity as a woman ages.

**Endothelial Function in Pregnancy: Effects of Gestational Hypertension and Diabetes**

Pregnancy is a stress-factor that might pose an intense challenge to the cardiovascular system (Figure 2). During normal pregnancy, several metabolic factors are temporarily increased, such as insulin resistance, lipid levels, and coagulation and inflammatory factors.52-54 In women who develop hypertensive pregnancy disorders or gestational diabetes mellitus, this physiologic response is altered, leading to vascular dysfunction.

**FIGURE 2.** Identifying pregnancy as a stressor can increase awareness and identify an opportunity to institute chronic disease prevention. A, Women at high risk of future cardiovascular disease are identifiable during pregnancy, at which point subclinical vascular risk may become clinically evident. B, The risk revealed by pregnancy can be used to target high-risk women for screening and early intervention by lifestyle modification and treatment, altering their chronic disease trajectories as they enter middle age. Adapted with permission from Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ. 2002;325(7356):157-160.51
endothelial dysfunction in both the uterine and maternal circulation. Preeclampsia represents a severe form of hypertension in pregnancy that occurs after 20 weeks of gestation; it can lead to fetal growth retardation, intrauterine death, and metabolic, vascular, and thrombotic complications in the mother (HELLP-syndrome). In developed countries, hypertensive pregnancy disorders (affecting 10% of all pregnancies) are the leading cause of maternal mortality, accounting for 16% of maternal deaths. Insufficient placentation can be caused by genetic, immunologic, vascular, and environmental factors, and it has many pathophysiologic mechanisms with concomitant release of biomarkers in common with the initial process of atherosclerosis. After experiencing hypertensive pregnancy disorders, women may also have earlier ovarian aging as a sign of impaired vascular health. Women with previous hypertensive pregnancy disorders have enhanced sympathetic nervous activity associated with more disabling vasomotor symptoms.

The retrospective Cardiovascular Health After Maternal Placental Syndromes (CHAMPS) study, which included 1.03 million healthy women, demonstrated that CVD occurring at least 90 days after the delivery was twice as common (hazard ratio, 2.0) in women who had any gestational complication. A metaanalysis of 43 studies demonstrated that women with a history of preeclampsia had a 2-fold increased risk of both ischemic heart disease and cerebrovascular disease and a 4-fold increased risk of developing hypertension. The risk of chronic hypertension was found to be related to the severity of preeclampsia. After early preeclampsia, more than 40% of women clinically manifest hypertension before the age of 40 years. Other CVD risk factors, such as obesity, insulin resistance, and endothelial dysfunction, are also frequently present within several years after hypertensive pregnancies. These data suggest the prolonged effect that the state of preeclampsia might have on overall vascular health. When assessing women for cardiovascular risk, it is important to be aware of such risk factors that might have contributed to premature aging of the vasculature. Gestational diabetes mellitus occurs in 2% to 10% of pregnancies and confers a 4- to 7-fold higher risk of future type II diabetes and the development of the metabolic syndrome in midlife. These patients also have a higher risk of CAD, myocardial infarction, and stroke. Signs of subclinical atherosclerosis were already present before the onset of overt diabetes mellitus or the metabolic syndrome. Women with gestational diabetes mellitus also have a 1.5-fold greater likelihood to develop hypertensive pregnancy disorders compared with women without gestational diabetes mellitus.

Endothelial dysfunction is thought to be one of the mechanisms linking preeclampsia and gestational diabetes mellitus to the development of cardiovascular disease. Studies have suggested that vascular injury can predispose to the beginning of the atherosclerotic process in patients with history of preeclampsia. Similarly, gestational diabetes mellitus is also a marker of abnormal vascular function. Maternal vascular endothelial dysfunction is thought to contribute to the high incidence of CVD seen in women with a history of gestational diabetes. Studies in mice have suggested long-term impairment of endothelial function in animals with previous gestational diabetes.

Pregnancy-related disorders offer a unique opportunity for increasing the awareness of increased cardiovascular risk and promoting early preventive cardiovascular measures, and have therefore been incorporated in the 2011 American Heart Association guidelines prevention in women and the 2014 American Heart Association guidelines on stroke prevention. Adherence to a healthy lifestyle and regular measures of CVD risk factors are of primary importance, also reinforcing the importance of an increasing role for self-monitoring involving modern e-Health information. It is thus apparent that pregnancy-related conditions such as preeclampsia and gestational diabetes mellitus are associated with an increased risk of future endothelial dysfunction with advancing age. Although the underlying etiology is less understood, it is
important to consider this closely when evaluating these patients, as such risk factors might call for early assessment and risk factor modification to prevent future cardiovascular morbidity and mortality.

Menarche and Menopause and Endothelial Function
Age and hormonal levels at a specific age can also play a role in development or acceleration of CVD. Conflicting data exist regarding the correlation of age at menarche and CVD risk. Genetic factors, obesity, and smoking are related to the onset of menarche and CVD risk. Worldwide, a decline in age of menarche is observed that is primarily attributed to deterioration in lifestyle factors and environmental toxic agents. The magnitude and clinical significance of age at menarche for CVD risk assessment is still undetermined.

The average age of menopause is approximately 51 years, and premature menopause (< 40 years), either natural or surgical, has been associated with an elevated risk of CVD. Because of the high proportion of Western women using oral contraceptives and hormonal uterine devices throughout menopause transition, the exact age of menopause is difficult to establish. Approximately 1% of women age 40 years receive a diagnosis of spontaneous primary ovarian insufficiency (POI). Women with POI are at increased risk for impaired endothelial function and earlier onset of ischemic heart disease. It has been suggested that early-onset vascular dysfunction may be a crucial determinant of menopausal age, either through direct effects on the ovarian vasculature or effects on the endocrine system. It is thus unclear whether vascular aging is a result of hormonal risk factors or a cause of these. This will be important to further investigate management for these patients. Still, data suggest that early risk factors could have a role in inducing vascular damage and thus adversely affect overall vascular health.

Interestingly, women who have had a prophylactic bilateral oophorectomy before the age of 40 also have an increased risk for CVD. Although long-term follow-up data are relatively scarce, a recent meta-analysis showed that POI is associated with a modest increased risk for ischemic heart disease (hazard ratio, 1.61; 95% CI, 1.22-2.12), but not for stroke. In the current guidelines of the International Menopause Society, systemic hormone replacement therapy is recommended in women with POI, at least until the average estimated age of natural menopause. Appropriate use of hormonal therapy in this younger patient population is therefore an important consideration.

BRCA1/2 mutation carriers have an elevated risk of developing breast cancer and ovarian cancer at a relatively young age. Risk-reducing salpingo-oophorectomy (RRSO) is an established strategy to reduce the risk of ovarian cancer. It is recommended that this surgery be performed during the age of 35-40 years (BRCA1) or 40-45 years (BRCA2), resulting in an early and abrupt menopause. Although temporary use of hormone therapy is not contraindicated in BRCA patients without previous breast cancer, its use is hampered by the increased susceptibility and fear of breast cancer. The decision to use hormone therapy after RRSO should be based on individual quality of life issues and not on life expectancy. Others advise consideration of the use of hormone therapy use in BRCA1/2 mutation carriers without prior breast cancer after RRSO to the age of natural menopause, and especially in women who have had risk-reducing mastectomy.

BRCA1/2 mutation carriers could have excess mortality unrelated to cancerous causes. Whether the potential harmful effects of an early surgically induced menopause in BRCA1/2 mutation carriers translates to endothelial dysfunction and increased CVD risk is still unknown; however, recent evidence suggests a potential excess CVD risk. Preclinical research shows that BRCA1 is basally expressed in endothelial cells and is a modulator of endothelial cell apoptosis, endothelial dysfunction, and potentially atherogenesis. After a diagnosis of breast cancer, women with BRCA1/2 mutation have an excess risk of diabetes, particularly in overweight patients.
In addition, breast cancer therapies including chemotherapy and radiation each are associated with increased cardiovascular risk as well.99 Future research might reveal whether basal mechanisms involving BRCA genes influence the cardiovascular system and disease processes, and the role of immunomodulating therapies with limited cardiovascular risk profile. At present, however, it is still unclear whether these findings translate to increased CVD risk in women with BRCA1/2 mutations or what role therapy plays in this association. Further investigation is necessary to determine the interactions among age, CVD risk, and BRCA1/2 mutations and the role of novel chemotherapy agents and radiation protocols to better manage these patients while minimizing cardiovascular risk.

Hormonal Therapy and Vascular Function

There are substantial data to suggest that estrogen plays a role in triggering the release of nitric oxide through estrogen receptors, thus improving overall endothelial function. It is also important to consider the effects of hormonal therapy on vascular function. In a double-blinded randomized controlled trial conducted by Hurtado et al,100 the effect of conjugated equine estrogens versus placebo was studied in 64 women. Authors found that administration of estrogen for 28 days had a significant effect in improving flow-mediated dilation of the brachial artery, a marker of vascular nitric oxide–dependent dilatation.100 A separate study by Moreau et al101 exploring the effect of endurance training on endothelial function in women treated with estrogen therapy and found that estrogen status could have a role in modulating improvements in endothelial function with endurance training in postmenopausal women. There are limited data to suggest an improvement in endothelial vascular function with the use of estrogen replacement. This limitation stems from the underlying pathophysiology and that reduced estrogen is associated with a variety of factors that contribute to abnormal endothelial function, including reduced nitric oxide.102

The timing of administration of hormonal therapy in the postmenopausal period is an important consideration as well, and data have suggested that the potential benefits of estrogen are dependent on the timing of initiation relative to the onset of menopause. The timing hypothesis essentially suggests that estrogen has a time-dependent beneficial effect if administered early in menopause, because at this point a woman’s arteries are likely to be relatively healthy. On the other hand, if started late in menopause, the estrogen may be less likely to have a beneficial effect because of the higher likelihood of atherosclerotic disease later in menopause.103-105 In a study by Bassuk et al,104 oral estradiol therapy administered within 6 years of menopause was associated with reduced atherosclerotic progression when compared with patients in whom estrogen was administered 10 or more years after menopause. Thus, it is possible that the presence of abnormal vascular endothelial function in the immediate postmenopausal period may be an indication to consider estrogen therapies; however, more investigation in the form of large studies is required to better understand both the role and timing of estrogen therapy in postmenopausal women with abnormal vascular endothelial function.

PRACTICE RECOMMENDATIONS

Vascular endothelial function is a risk factor for progressive atherosclerotic disease; if recognized early, it can play a role in risk stratification and cardiovascular risk prevention. There remains substantial controversy regarding the role of noninvasive vascular function testing to guide further management of cardiovascular health. Although additional investigation is required to better understand treatment and management of abnormal endothelial function, it is important to institute aggressive lifestyle modification and risk factor management based on the results of abnormal endothelial function testing. Although risk factor management typically involves management of specific risk factors, an abnormal endothelial function test provides a comprehensive
assessment of overall cardiovascular risk, and it is a marker of subclinical atherosclerosis. As a result, a provider can tailor therapies more aggressively rather than simply basing antihypertensive, lifestyle, and statin regimens on single laboratory values.

We call for noninvasive vascular function testing using MRI, positron emission tomography, or venous plethysmography in all women to establish a baseline vascular health assessment during the early perimenopausal period. Although further investigation is needed in this regard to separate normal aging from pathologic endothelial dysfunction, baseline measurements of peripheral endothelial function in conjunction with the presence of traditional and nontraditional risk factors can help to alert both the patient and provider to the increased risk of cardiovascular disease and help to address this early. Such early vascular health screening can help to identify a systemic process that is not isolated to individual risk factors and could motivate the patient to address the underlying risk factors with appropriate lifestyle changes and medication. Furthermore, noninvasive vascular function testing can be used to assess the effects of such lifestyle and medical interventions to help guide therapy further. The results of peripheral endothelial function should be taken in conjunction with other traditional and nontraditional risk factors and a risk stratification strategy and appropriate therapies should be used accordingly. We recommend aggressive risk factor screening during this time as well. This screening is inclusive of but not limited to traditional risk factor profiles, including the lipid profile, blood pressure measurements, and novel risk factors including inflammatory markers such as C-reactive protein and uric acid and lipoprotein(a). Asymptomatic women with endothelial dysfunction should be managed with appropriate control of hypertension, hyperlipidemia, and exercise programs. In addition to screening, noninvasive vascular screening has a role in women who have symptomatic known coronary artery disease as well. Although vascular function testing results will likely be abnormal in patients with known obstructive coronary artery disease, baseline testing can again serve as a marker against which to measure response to treatment or lifestyle modifications. Further investigation studying the role of serial vascular function testing is required to better understand this phenomenon and its potential role in the management of patients.

Thus, this field requires additional large studies to better assess the role of noninvasive vascular screening in management of women with nonobstructive and obstructive coronary artery disease. The information provided is often a marker of underlying systemic vascular health and an important precursor to atherosclerotic disease; therefore, routine testing of vascular function and surveillance has the potential to guide treatments. We look forward to large cohort studies to better understand the role of this noninvasive testing to help guide further management. Currently, our recommendation is that providers begin to use such noninvasive testing, whether it be positron emission tomography, MRI, or plethysmography in conjunction with traditional risk factor screening in all perimenopausal women to better understand the systemic nature of a patient’s vascular health profile and to help guide therapy by performing serial measurements every 1 to 2 years. The vascular function assessment will give the provider a snapshot of the overall cardiovascular risk profile and vascular function as opposed to individual risk factors such as lipid profile or hemoglobin A1c, which is a component of the patient’s overall cardiovascular risk. The assessment of vascular function provides a measurement of subclinical atherosclerosis which may differ from patient to patient, but within the same patient can be used to guide appropriative cardiovascular risk prevention strategies. As increased research is conducted in this field, our approach to the use of such tests will continue to become more sophisticated.

CONCLUSION
Cardiovascular disease is the leading cause of morbidity and mortality in women. We
suggest the need to develop novel paradigms that can improve cardiovascular risk assessment and management in women, which might lead to improved cardiovascular outcomes. A wealth of clinical data exist, but additional preclinical studies in female animal models could play a role in elucidating unknowns in this field. Specifically, the role of both traditional and novel biomarkers, noninvasive assessment of vascular function testing and hormonal factors in predicting cardiovascular events in women will help to guide preventive management in this patient population. Management of these patients should include traditional therapies including weight loss, regular physical activity and a healthy diet, but in addition, more aggressive risk factor modulation might be necessary, depending on an individual’s comprehensive risk profile. We suggest further research and evaluation of these areas in an attempt to improve the cardiovascular health of women.

Abbreviations and Acronyms: CAD = coronary artery disease; CMD = coronary microvascular dysfunction; CVD = cardiovascular disease; MRI = magnetic resonance imaging; PCOS = polycystic ovarian syndrome; RRSO = risk-reducing salpingo-oophorectomy

Potential Compelling Interests. Dr Collins and Dr Lerman are advisers to Itamar Medical, Israel.

Correspondence. Address to Peter Collins, MA, MD, Department of Cardiology, Royal Brompton Hospital, Sydney Street, London SW3 6NP, United Kingdom (peter.collins@imperial.ac.uk).

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