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STATE-OF-THE-ART PAPER

Women and Ischemic Heart Disease

Evolving Knowledge

Leslee J. Shaw, PHD,† Raffaelle Bugiardini, MD,‡ C. Noel Bairey Merz, MD*

Los Angeles, California; Altanta, Georgia; and Bologna, Italy

Evolving knowledge regarding sex differences in coronary heart disease is emerging. Given the lower burden of obstructive coronary artery disease (CAD) and preserved systolic function in women, which contrasts with greater rates of myocardial ischemia and near-term mortality compared with men, we propose the term "ischemic heart disease" as appropriate for this discussion specific to women rather than CAD or coronary heart disease (CHD). This paradoxical difference, where women have lower rates of anatomical CAD but more symptoms, ischemia, and adverse outcomes, appears linked to abnormal coronary reactivity that includes microvascular dysfunction. Novel risk factors can improve the Framingham risk score, including inflammatory markers and reproductive hormones, as well as noninvasive imaging and functional capacity measurements. Risk for women with obstructive CAD is increased compared with men, yet women are less likely to receive guideline-indicated therapies. In the setting of non–ST-segment elevation acute myocardial infarction, interventional strategies are equally effective in biomarker-positive women and men, whereas conservative management is indicated for biomarker-negative women. For women with evidence of ischemia but no obstructive CAD, antianginal and anti-ischemic therapies can improve symptoms, endothelial function, and quality of life; however, trials evaluating impact on adverse outcomes are needed. We hypothesize that women experience more adverse outcomes compared with men because obstructive CAD remains the current focus of therapeutic strategies. Continued research is indicated to devise therapeutic regimens to improve symptom burden and reduce risk in women with ischemic heart disease. (J Am Coll Cardiol 2009;54:1561–75) © 2009 by the American College of Cardiology Foundation

During the past several decades, an evolving knowledge regarding sex differences in coronary heart disease (CHD) has emerged. Prevalence, symptom manifestation, and pathophysiology for CHD vary between women and men. Annual CHD population statistics continue to report a greater number of deaths for women than men (455,000 vs. 410,000) (1). Although recent reports document decreases in CHD mortality for women, reductions lag behind those realized for men (2), including mortality increases among younger women (3). The most recent Centers for Disease Control and Prevention data reveal that 1 in 2.6 women die from CHD contrasted with 1 in 4.6 from cancer (4). Current projections indicate a continued increase in CHD, given our aging population and epidemics of obesity, diabetes, and the cardiometabolic syndrome (1,2,5,6). Notably, cardiac death remains the leading killer of women at all ages (1,7,8).

Among clinical cohorts, paradoxical sex differences are observed where women have less anatomical obstructive coronary artery disease (CAD) and relatively preserved left ventricular function yet greater rates of myocardial ischemia and mortality compared with similarly aged males (5,9–11). Accordingly, the term ischemic heart disease (IHD) is more appropriate for a discussion specific to women rather than CAD or CHD. Data from the National Institutes of Health-National Heart, Lung and Blood Institute-sponsored WISE (Women's Ischemia Syndrome Evaluation) and related studies implicate abnormal coronary reactivity (12), microvascular dysfunction (13), and plaque erosion/distal microembolization (14,15) as contributory to a female-specific IHD pathophysiology. Thus, knowledge beyond an anatomical description of

From the *Women's Heart Center, Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California; the †Emory Program in Cardiovascular Outcomes Research and Epidemiology, Emory University School of Medicine, Atlanta, Georgia; and the ‡Department of Internal Medicine, Cardio-Angiology and Hepatology, University of Bologna, Bologna, Italy. Dr. Shaw received grant support from GE Healthcare and Bracco Diagnostics. Dr. Merz has done consulting for Novartis, Karolinska Institute, Strategy Group, University of Pittsburgh, Pfizer, Biological Systems Processing, Kendle Internation, Inc., and the National Heart, Lung, and Blood Institute; received lecture honoraria for Northwestern University, University of California-Davis, Abbott Laboratories, CV Therapeutics, Boehringer Ingelheim, American College of Physicians, ProMedica, Mayo Clinic, and Merck; and owns stock in Boston Scientific, Medtronic, Johnson & Johnson, and Teva Pharmaceuticals. This work was supported by National Heart, Lung, and Blood Institute contracts N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, R01 HL090957-01A1, and R03 AG032631-01; a GCRC grant MO1-RR00425 from the National Center for Research Resources; and grants from the Gustavus and Louis Pfeiffer Research Foundation, Danville, New Jersey; the Women's Guild of Cedars-Sinai Medical Center, Los Angeles, California; the Edythe L. Broad Women's Heart Research Fellowship, Cedars-Sinai Medical Center, Los Angeles, California; and the Barbra Streisand Women's Cardiovascular Research and Education Program, Cedars-Sinai Medical Center, Los Angeles, California.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
CAC = coronary artery calcium
CAD = coronary artery disease
CCTA = coronary computed tomographic angiography
CHD = coronary heart disease
cIMT = carotid intima-media thickness
CMR = cardiac magnetic resonance
CRP = C-reactive protein
CVD = cardiovascular disease
FRS = Framingham Risk Score
hsCRP = high-sensitivity C-reactive protein
IHD = ischemic heart disease
MET = metabolic equivalent
MI = myocardial infarction
PCI = percutaneous coronary intervention
PET = positron emission tomography
STEMI = ST-segment myocardial infarction

obstructive CAD may provide important clues to IHD risk detection and treatment for women.

This review outlines our evolving knowledge of pathophysiology and mechanisms of IHD in women. We include clinical studies addressing sex-specific issues in IHD prevalence and prognosis, traditional and novel risk factors, screening and diagnostic testing, as well as therapeutic management strategies. We propose models for application of our emerging knowledge on IHD in women to clinical practice, as well as forward novel hypotheses for investigation. Finally, although it is unknown to what extent the described issues are specific or simply more prevalent in women, it is likely that the outlined concepts should also be applicable for men.

Prevalence of IHD in Women

In addition to an absolute greater number of women dying from IHD, a greater proportion of women die of sudden cardiac death before their arrival at a hospital (52%) contrasted with 42% of men (16,17). Recent data (18) report significant decreases in sudden cardiac death in men with essentially no change in women. Symptomatic women more often have persistent symptoms requiring more hospitalizations compared with men, accompanied by lower ratings of general well-being and limitations in their abilities to perform activities of daily living (19,20). Notably, these adverse outcomes are experienced by women of all ages despite a lesser extent and severity of obstructive CAD and better systolic function compared to men (11). Relatively greater CAD health care costs are incurred in women where resource consumption patterns are characterized by: 1) more frequent diagnoses of angina, office visits, and hospitalizations; 2) greater myocardial infarction (MI) mortality; and 3) greater rates of heart failure hospitalization as compared with men (22–24). Thus, IHD in women presents a unique and difficult challenge for clinicians as the result of a greater symptom burden, functional disability, greater health care needs, and more adverse outcomes as compared with men despite a lower prevalence and severity of anatomical CAD.

Risk Factors for IHD in Women

More than 80% of midlife women have 1 or more traditional cardiac risk factors (25). Women have, on average, greater blood cholesterol levels than men after their 5th decade of life (10) and exhibit mild decreases in high-density lipoprotein cholesterol after menopause (1,26). Obesity is prevalent in one-third of women, including 7% having a body mass index $\geq$40 kg/m^2 with associated increased mortality (27,28). Hypertriglyceridemia is a more potent independent risk factor for women as compared with men (26,29). Diabetic women have significantly greater rates of IHD mortality compared with diabetic men (30,31) and an elevated 3.3-fold IHD risk compared with nondiabetic women (32). Importantly, 30-year trends reveal marked cardiovascular disease (CVD) mortality reduction for diabetic men but not for diabetic women (33).

The rate of IHD mortality increases with the number of traditional cardiac risk factors, with 30-year death rates (per 10,000 person-years) ranging from 1.5 to 9.1 for women with 0 to $\geq$2 risk factors (34). Clustering of risk factors is common after menopause, notably the combination of obesity, hypertension, and dyslipidemia (35–39); this phenomenon is potentially related to hormonally-mediated metabolic disturbances.

Novel Risk Factors for IHD in Women

Traditional risk factors and the Framingham risk score (FRS) underestimate IHD risk in women (40–45), whereas novel risk markers improve risk detection (13,46,48,49). Women have, on average, greater mean C-reactive protein (CRP) measures compared with men, a sex difference apparent at the time of puberty (50). This difference in CRP is consistent with the 2- to 50-fold greater frequency of inflammatory-mediated autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus, in women as compared with men (51), suggesting a prominent role for inflammation in IHD sex differences. Indeed, the relative risk of future IHD events increases proportionally with increasing levels of high-sensitivity C-reactive protein (hsCRP), acting synergistically with other risk factors to accelerate IHD risk in women (47,48,52–55). A number of inflammatory measures, including hsCRP, are related to other IHD risk markers such as the cardiometabolic syndrome, type 2 diabetes, and heart failure (53,56,57). The use of multiple biomarkers improves IHD risk assessment in women (58–60).

We and others have further demonstrated that disruption of ovulatory cycling, indicated by estrogen deficiency and hypothalamic dysfunction (61) or irregular menstrual cycling (62) in premenopausal women is associated with an increased risk of coronary atherosclerosis and adverse CVD events. Polycystic ovary syndrome is prevalent in 10% to 13% of women and is linked with a clustering of risk factors, incident type 2 diabetes mellitus (63), and adverse IHD

events post-menopausally (64). The cardiometabolic syndrome is a clustering of risk factors, including at least 3 of the following: insulin resistance, dyslipidemia (increased levels of triglycerides, decreased levels of high-density lipoprotein cholesterol), hypertension, or abdominal obesity and is frequently associated with alterations in endogenous estrogens and androgens in women (36,62,65). Investigation into the optimal utilization of novel risk factors for IHD risk stratification in women is needed.

Risk Assessment in Women by the Use of Traditional Risk Factors and Scores

The FRS is used to classify patients' 10-year risk of CAD death or MI to determine the appropriate level of therapeutic intervention for both low-density lipoprotein cholesterol and hypertension (66,67). Patients at the greatest risk should receive the most intensive therapeutic and lifestyle recommendations (i.e., secondary prevention goals). However, the FRS classifies >90% of women as low risk, with very few assigned a high-risk status before the age of 70 (41). The FRS is best used to risk stratify populations and underestimates individual patient risk, notably for women (43–45).

The Reynolds risk score is a sex-specific tool recently devised from large derivation (n = 24,588) and validation (n = 8,158) cohorts of women (68). This score uses the following equation: 0.0799 × age + 3.137 × natural logarithm (systolic blood pressure) + 0.180 × natural logarithm (hsCRP) + 1.382 × natural logarithm (total cholesterol) −1.172 × natural logarithm (high-density lipoprotein cholesterol) + 0.134 × hemoglobin A_{1c} (%) (if diabetic) + 0.818 (if current smoker) + 0.438 (if family history of premature MI). When compared with the FRS, use of the Reynold's score resulted in risk reclassification in >40% of intermediate FRS women (68).

The authors of a few recent reports (43,44) also have examined the prevalence of subclinical atherosclerosis within female FRS subsets. In a recent cross-sectional study of 2,447 consecutive, clinically referred asymptomatic, nondiabetic women, 84% of those with significant coronary artery calcification (CAC) were classified with a low FRS (43). These data underscore the imprecision of FRS estimates in women and the prevalent, undetected burden of atherosclerosis in females.

Noninvasive Imaging of Atherosclerosis

There is a growing body of evidence on the use of atherosclerotic imaging. In women, the prevalence of an ankle brachial index ≤0.90 increases with age (ranging <5% for <60 years to 10% to 35% for 60 to 80 years) and is more prevalent in Black and Hispanic women (69,70). The hazard for death with an ankle brachial index ≤0.90 is 2.7 (95% confidence interval [CI]: 2.0 to 3.6) for women and 3.3 (95% CI: 2.7 to 4.1) for men (71). Carotid intima-media thickness (cIMT) is another imaging marker that is a validated measure of risk for both women and men (72–74). A low-risk cIMT is associated with a ~1% 10-year IHD risk versus ~10% for a high-risk cIMT (75), with a relatively greater risk predicted for women than men (76). The CAC is another imaging measure that is highly correlated with traditional risk factors (77) but uncorrelated with hsCRP (78). It lags by nearly a decade in incidence for women, similar to obstructive CAD (49,79–84). From the NHLBI Multi-Ethnic Study of Atherosclerosis (44), women with a CAC score ≥300 had an annual IHD event rate of 2.2%, thus achieving NCEP CHD risk-equivalent status. The IHD event risk for women with a high-risk CAC score and multiple risk factors is 10% greater in women than men (49,83), supporting the notion that comorbidity disproportionately accelerates risk in women.

Symptom Assessment and Prevalence of Ischemia in Women

The evaluation of women with symptoms suggestive of IHD is hampered by the definition of "typical" angina, derived from largely male populations where exertional components are more reflective of male patterns of presentation (85,86). Women report more angina despite lower rates of obstructive CAD (11,87–89). In a recent meta-analysis (90) of 74 reports from 13,311 women and 11,511 men, angina prevalence was 11% to 27% greater for women <65 years of age yet similar in the elderly age ≥75 years. Women with typical or atypical chest pain symptoms (nonexertional or prolonged discomfort unrelieved by rest) have calculated obstructive CAD probabilities substantially less than that of men (91–93) and among those undergoing coronary angiography, as many as 50% of women do not have obstructive CAD (93,94).

More than one-half of symptomatic women without obstructive CAD continue to have signs and symptoms of ischemia, undergo repeat hospitalization and coronary angiography, with continued consumption of CAD healthcare resources that often are the result of diagnostic and therapeutic uncertainty (20,24). Data from the Women's Health Initiative document that women with nonspecific chest pain have a 2-fold greater risk for nonfatal MI (95), whereas WISE data demonstrate increased rates of mortality in women with chest pain and no obstructive CAD (96), underscoring that prognosis in these women is not benign.

"Normal" coronary angiograms, defined as no visible obstructive CAD (luminal irregularities <50% stenosis) are also reported more frequently in women with acute coronary syndromes (ACS). In a recent large series from 600 U.S. hospitals in 459,941 patients with ACS, the adjusted odds for obstructive CAD were 50% lower for women as compared with men (11). For women presenting with ACS/ST-segment elevation myocardial infarction (STEMI), 10% to 25% of women as compared with 6% to 10% of men have no obstructive CAD (97–100). Of the estimated 1.4 million patients discharged after an ACS each year, 600,000 are

women (1). Among women, the 10% to 25% rate of "normal" angiography (101) translates into 60,000 to 150,000 women with ACS/MI having nonobstructive CAD. Specific investigation is needed to understand the paradox whereby women have less obstructive CAD and less severe MIs yet worse clinical outcomes compared to men. The higher mortality compared with men has been attributed to advanced age, comorbidity (5,10,102,103), and underutilization of guideline care among women (104); yet, the largest mortality gap is observed in younger women, with several studies (105,106) demonstrating persistent sex differences despite covariate adjustment.

Exercise Electrocardiography (ECG) in Women

Clinicians often rely on exercise ECG to assess the risk of IHD. The exercise ECG has a lower sensitivity and specificity (≥1 mm ST-segment depression ≅65%) for detection of obstructive CAD in women compared with men (107), in part as the result of lower obstructive CAD prevalence (i.e., Bayesian theory). In several large female cohorts, significant exertional ST-segment depression did not differ between survivors and nonsurvivors (108,109), although marked ST-segment changes (≥2 mm horizontal or downsloping) occurring at low workloads or persisting into recovery confirm high-risk status for women (110). Combining variables such as exercise duration and ST-segment changes into the Duke Treadmill Score accurately predicts IHD mortality in women (111,112). From the St. James Women Take Heart Study of 5,392 asymptomatic women, the risk of death decreased by 9% for every unit increase in the Duke Treadmill Score, whereas each metabolic equivalent (MET) increase in exercise capacity decreased mortality by 17% ($p < 0.001$) (111). Women undergoing exercise testing that use common treadmill protocols are often incapable of performing >5 METs (112), a level equivalent to performing routine activities of daily living (113), elevating their risk of IHD death or MI by ~3-fold (108–110,114). Reduced functional capacity (≤7 METs) portends worsening outcome equally among lean and obese women (115). A female sex-specific nomogram of exercise capacity (in METs) has been devised and can be applied to estimate average functional abilities for women of diverse ages (116).

Noninvasive Cardiac Imaging in Women

Stress-induced changes in regional myocardial perfusion or wall motion are accurate markers of IHD risk in women (110,117–120). Although the sensitivity of echocardiographic wall motion abnormalities is diminished in the setting of an intermediate stenosis or single-vessel obstructive CAD, the test's high negative predictive value renders it useful for younger women (110). Stress-induced changes in myocardial perfusion have been extensively evaluated in women by the use of SPECT imaging with more recent use of positron emission tomography (PET) and cardiovascular magnetic resonance (CMR) techniques (110).

The evidence is substantial that myocardial perfusion imaging effectively risk stratifies women (110,119,120). Pooled myocardial perfusion data in >7,500 women reveal a low annual IHD event rate of 0.6% in the setting of a normal study (119). Survival worsens for women with multivessel ischemia (120) or moderate-to-severe perfusion abnormalities, yielding a 5% annual IHD mortality for women (121). Because SPECT flow is comparatively assessed across the myocardium, it can appear normal in the setting of global reductions in perfusion attributable to severe multivessel CAD but also to endothelial or microvascular dysfunction, left ventricular hypertrophy, or cardiomyopathy. Additional challenges for SPECT in women include the following: 1) limited spatial resolution where minor perfusion abnormalities may go undetected in smaller hearts; and 2) breast tissue artifact. With regards to the latter, contemporary techniques that use Tc-99m agents, prone imaging, and/or attenuation correction algorithms diminish the frequency of artifact (110). Thus, it is no longer appropriate to label perfusion abnormalities in the setting of nonobstructive CAD as "false positives" in women if accompanied by objective signs of ischemia, such as chest pain, electrocardiographic abnormalities, or reduced functional capacity caused by the elevated IHD risk (52,106). The use of 82Rb PET has several advantages in women, including quantification of absolute values of regional and global myocardial blood flow to assess microvascular disease (flow reserve) and integrated attenuation correction along with improved image quality compared with SPECT. The use of PET has notable advantages for obese women; however, there is limited prognostic data with no sex-specific reports (122,123). On the basis of recent estimates, effective radiation dose appears slightly greater for PET when compared with single-isotope rest-stress SPECT imaging (12.6 to 13.5 for 82Rb PET vs. 11.3 to 11.4 for rest-stress Tc-99m SPECT) (124).

Stress CMR imaging uniquely allows the measurement of subendocardial perfusion. In an initial report in 19 symptomatic women with abnormal stress tests and normal coronaries, subendocardial ischemia frequently was observed (125). These findings have been validated in a larger cohort reporting a strong correlation between subendocardial ischemia and abnormal coronary reactivity testing (126), although population heterogeneity has resulted in varying results (127). Investigation into the prognostic implications of CMR subendocardial ischemia with regard to IHD events and its association with future chest pain frequency and stability is needed.

Coronary computed tomographic angiography (CCTA) is a noninvasive anatomic technique with a reported high diagnostic accuracy for obstructive CAD (128,129). In a series of 51 women and 52 men, diagnostic sensitivity and specificity was similar by sex at 85% and 99% (130); although a recent larger controlled trial demonstrated a lower specificity of 90% (131). An important limitation for CCTA, and all tests of ionizing radiation exposure, is that

imaging should be used cautiously in younger women due to a heightened lifetime cancer risk. CCTA is associated with effective radiation doses that average 11.3 mSv for men and 12.7 mSv for women (124). Test protocols emphasizing reductions in radiation exposure, including ECG-controlled tube current modulation, prospective gating, minimization of scan length, and optimization of tube current and voltage, should be emphasized in women. Moreover, especially for younger women, caution should be applied to use of testing that involves ionizing radiation and, in some cases, use of stress echocardiography or magnetic resonance imaging techniques may be favorable, in particular for younger women.

Importantly, women with angina and confirmatory ischemia have an elevated IHD mortality (106). In a recent report from an ambulatory population (n = 56,441 women and 34,885 men), the coronary standardized mortality ratio was ~2-fold greater for women 55 to 74 years and increased to 12-fold greater for those aged 45 to 54 years (132). In summary, abnormalities in functional capacity and noninvasive imaging are valuable IHD risk predictors in symptomatic women. Further work is needed to integrate the use of existing and novel strategies to optimize IHD risk detection in women.

Coronary Reactivity in Women

Women suffer disproportionately from a variety of generalized vascular disorders, including migraine headaches, Raynaud's phenomenon, and autoimmune arteritis. These observations support the influence of lifelong, varying reproductive hormone levels related to ovarian cycling, pregnancy, peripartum, and menopause are likely related to vascular function in health and disease (133). Although knowledge regarding the role of coronary reactivity was historically confined to Prinzemetal's angina, characterized by abnormal proximal epicardial coronary artery vasospasm modulated by smooth muscle dysfunction (134), it is now clear that intramyocardial microvascular arteries (135) mediated by endothelial (136) and autonomic nervous system adrenergic pathways (137) are involved.

Microvascular dysfunction. Recent data support a sex-specific role for coronary microvascular dysfunction in IHD pathophysiology. Autopsy data from sudden cardiac death victims suggest that women have a greater frequency of coronary plaque erosion and distal embolization compared with men (14,15,138–141). Retinal arterial narrowing, a measure of microvascular disease, is related to CVD events in women but not men (13). Additional important sex differences in the arterial remodeling/repair response to injury/atherosclerosis may prove etiologic for the development of microvascular dysfunction in women. Although the onset of atherosclerosis for women temporally lags behind that of men, evidence that the combination of smaller arterial size and more prominent positive remodeling (49,83,142) may lead to a greater role of microvascular dysfunction in IHD in women compared with men (143). Recently, Han et al. (144) studied patients with obstructive CAD who underwent simultaneous intravascular ultrasound and coronary reactivity assessment and demonstrated that men have a greater atheroma burden and more diffuse epicardial endothelial dysfunction while women have more disease of the microcirculation. These factors may influence the higher rates of angina, ischemia, and ACS in the absence of obstructive CAD in women supporting coronary microvascular dysfunction as a prominent disorder in women compared to men (113,143).

Endothelial dysfunction. Endothelial function (measured centrally in the coronary or distally in the peripheral circulation) contributes to IHD pathophysiology in women. Brachial artery flow-mediated dilation, a peripheral measure of endothelial function, is impaired in hyperlipidemic, hypertensive, smoking, and diabetic and women (145) and exacerbated after the advent of menopause (146). Abnormal flow mediated dilation in a large cohort of 2,264 postmenopausal women was associated with a 1.3- to 4.4-fold increased IHD risk ($p < 0.0001$) (147). Whether endothelial dysfunction mechanistically is a precursor to the development of hypertension, a marker for subclinical atherosclerosis, a measure of obstructive CAD severity, or related to left ventricular remodeling and diastolic dysfunction is unknown (5,148,149).

In the coronary circulation, both endothelial-dependent epicardial (endothelial dysfunction) and endothelial-independent (microvascular dysfunction) dysfunction predict adverse IHD events in patients undergoing diagnostic angiography, single-vessel percutaneous coronary angioplasty (PCI), or post ACS/MI (150–153). These results are important because restoration of endothelial function is associated with improved outcome. In a study of 400 hypertensive postmenopausal women, improved endothelial function was associated with a 7.3-fold lower rate of IHD events when compared with women with no improvement (154).

The role that abnormal coronary reactivity plays in ischemia in women without obstructive CAD has only now been described, and the relative importance of endothelial and microvascular dysfunction has been insufficiently explored. An integrated working understanding of the cascade of mechanisms and manifestations of ischemia impacting IHD risk in women is reviewed in Figure 1.

Unifying Novel Hypotheses of IHD in Women

We propose that coronary microvascular dysfunction is more prevalent in women than men as the result of risk factor clustering, vascular inflammation and remodeling, and hormonal alterations and is etiologic for the observed paradoxical frequent (atypical) symptoms, evidence of ischemia, and adverse outcomes. We propose that symptoms occurring as the result of coronary microvascular dysfunction that result in myocardial ischemia should be called

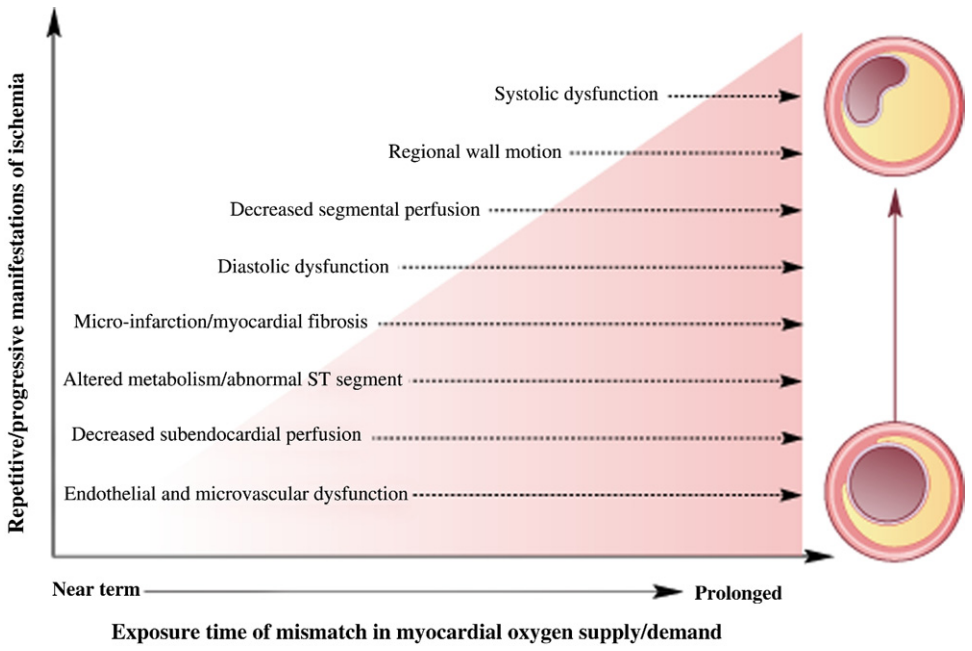

Figure 1 Cascade of Mechanisms and Manifestations of Ischemia Having an Impact on Ischemic Heart Disease Risk in Women

Figure illustration by Rob Flewell.

microvascular angina. A hypothetical model of microvascular angina in women is depicted in Figure 2. This model provides a rationale for why current approaches for detection of focal obstructive coronary lesions are less effective in women with a greater prevalence of nonobstructive CAD. Abnormal coronary reactivity occurs in the setting of underlying atheroma vulnerable to clinical instability and more progressive disease states. It is for this reason that identifying nonobstructive atheroma may provide greater risk stratification in women. An overarching working model of this proposed female-specific IHD pathophysiology is depicted in Figure 3. Although the relationship between microvascular dysfunction and epicardial atherosclerosis is not fully understood, a leading hypothesis is that it is a single disease process, where response to intimal injury may vary related to sex differences in vascular remodeling and vascular reactivity.

Prognosis in Women With IHD

A consistent pattern in the literature is a greater mortality in women compared with men with acute MI (155–157). In the Thrombolysis In Myocardial Infarction-II trial, significantly greater rates of death and reinfarction were observed in women compared with men at 6 weeks and 1 year, even after adjustment for age and comorbidity (158,159). The authors of National Registry of Myocardial Infarction-2 (105) analyzed data from 384,878 patients and found that among younger patients (<50 years of age) adjusted mortality for women was more than twice that of men. The results of the PAMI (Primary Angioplasty in Myocardial Infarction) trial demonstrated that primary PCI after MI reduced the risk of intracranial bleeding resulting in comparable survival by sex, in contrast to patients treated with tissue plasminogen activator where in-hospital mortality from acute MI was 3.3-fold greater in women than men (160). Although absolute mortality reduction in MI patients treated with fibrinolytic therapy is similar by sex, there is a greater rate of mortality after reperfusion with fibrinolytic therapy in women of all ages (161).

Prognosis in women with obstructive CAD. In women undergoing invasive coronary angiography, those with obstructive CAD have a 1.7- to 2.0-fold greater odds of in-hospital mortality as compared with nonobstructive CAD ($p = 0.013$) (11). In-hospital mortality is greatest for ACS women ranging from 22% to 38% for those with 1- to 3-vessel CAD ($p < 0.0001$). The greater short-term mortality includes more frequent complications of reinfarction and greater procedural complications, with older age, more diabetes, and greater comorbidity considered to contribute (5,103,113,162,163). In a recent postinfarction trial, there was a borderline increased risk of sudden cardiac arrest and resuscitated cardiac arrest that occurred within the first week after MI in women ($p = 0.08$), suggesting a greater acute post-MI instability in women (164).

Prognosis in women with nonobstructive CAD. The prognosis with "normal" coronary arteries co-occurring with signs and symptoms of myocardial ischemia has historically been interpreted as benign (165–167). More recent prog-

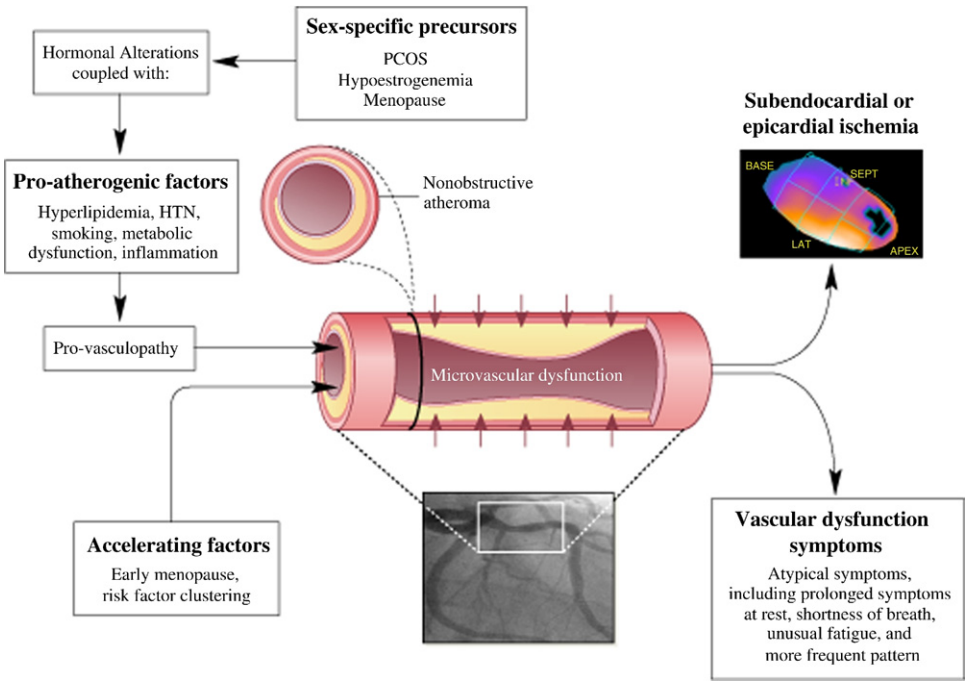

Figure 2 Model of Microvascular Angina in Women

Figure illustration by Rob Flewell. HTN = hypertension; PCOS = polycystic ovary syndrome.

nostic data in patients with ACS and nonobstructive CAD do not appear to be consistent with these historical findings, and the authors note a 2% risk of death and myocardial infarction at 30 days of follow-up (168). Notably, although a majority of these subjects were women, these datasets include men with nonobstructive CAD and comparative analyses by sex are needed.

A recent investigation demonstrated that 30% of women with chest pain, "normal" angiograms, and endothelial dysfunction developed obstructive CAD during a 10-year follow-up (169). A pooled analysis of women from recent, large randomized trials reveals that women with mild CAD have a worsening prognosis as compared with those with normal coronaries (170). Recently, Gulati et al. (96) reported 5-year CVD event rates of 16.0% for those with mild CAD (stenosis 1% to 49%), 7.9% for those with no coronary stenosis, and 2.4% in asymptomatic women ($p \leq 0.002$) after adjustment of cardiac risk factors. Despite these compelling findings, treatment for women with open coronary arteries remains often reassurance, sedative-hypnotic prescriptions, and/or repeated hospitalization and coronary angiography in response to refractory symptoms (97).

Given the sizeable gap in IHD prognosis between women and men, further research into sex-specific pathophysiology is needed. A model summarizing the factors known to contribute to the prognostic risk of IHD events in women with and without obstructive CAD is depicted in Figure 4.

Treatment of Women With IHD

Invasive strategies for ACS in women. For women with ACS, existing evidence-based guidelines support a stratified invasive versus conservative strategy for high- and low-risk women (171). Data from a recent meta-analysis of 8 ACS trials (3,075 women and 7,075 men) were used to compare risk reduction when an invasive compared versus a conservative strategy was implemented (172). For both women and men, an invasive strategy resulted in an equivalent 19% to 27% relative risk reduction by the use of a composite end point of death, MI, or repeat ACS. There were, however, important differences in risk reduction between biomarker-positive and -negative women. The invasive strategy was associated with a 33% lower risk of the composite end point in biomarker-positive women in contrast to a greater risk in biomarker-negative women, a difference that was not evident in men. Similarly, although women and men with ACS derive similar benefit from drug-eluting stents (174), women have an overall greater mortality with PCI for STEMI and non-STEMI (173).

Conservative strategies for ACS in women. After fibrinolysis, the 30-day incidence of death or nonfatal MI was significantly lower in women compared with men in the enoxaparin group compared with unfractionated heparin (161), suggesting that sex differences may beneficially impact outcomes in women for specific therapies. For both women and men undergoing PCI, despite greater bleeding

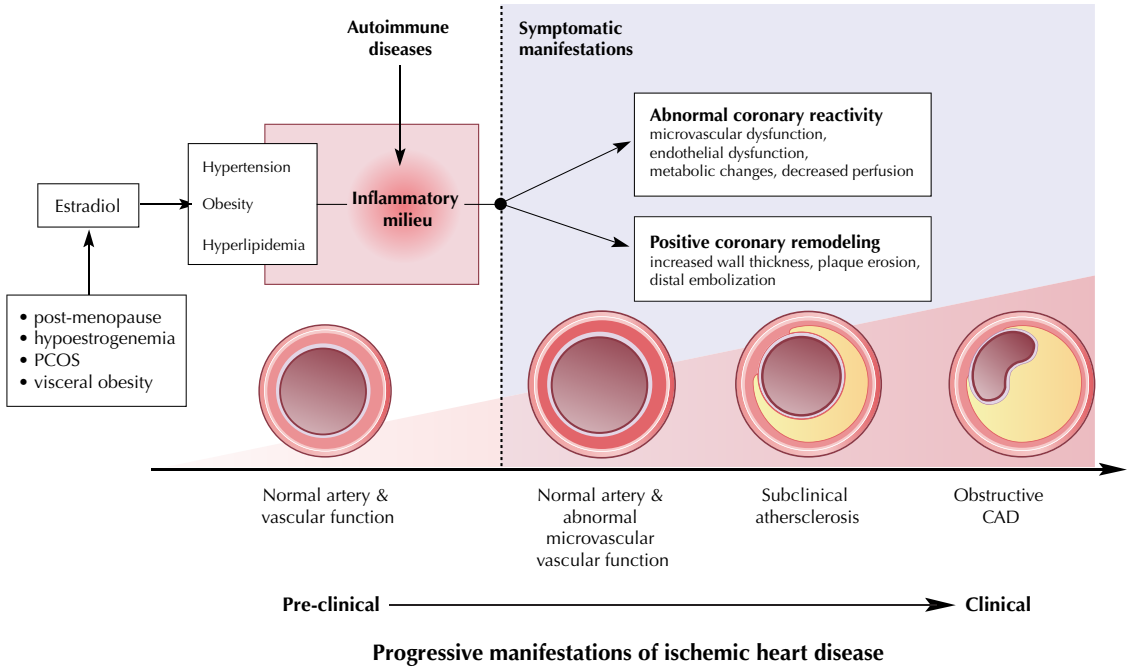

Figure 3 Overarching Working Model of Ischemic Heart Disease Pathophysiology in Women

Figure illustration by Rob Flewell. CAD = coronary artery disease; PCOS = polycystic ovary syndrome.

risk in women, the clinical benefit of glycoprotein IIb/IIIa platelet receptor blockade with abciximab for adverse events is similar (175). Overall, among patients with ACS treated with glycoprotein IIb/IIIa receptor blockade (not undergoing early coronary angiography), men experienced a benefit with an odds ratio (OR) of 0.81 (95% CI: 0.75 to 0.89) compared with a suggestion of harm in women (OR: 1.15, 95% CI: 1.01 to 1.30); although high-risk women with elevated troponins did derive a benefit (176). The authors of a previous study (177) document that women's greater risk of bleeding is attributable in part to a lack of dose adjustment to body size and renal function compared with men. A sex difference in bleeding risk was not observed when doses were adjusted for age and renal function (175). From a large international registry, women with ACS were generally treated less aggressively, including less acute heparin, angiotensin-converting enzyme inhibitors, and glycoprotein IIb/IIIa inhibitors, and had lower rates of discharge with aspirin, angiotensin-converting enzyme inhibitors, and statins as compared with men (104). Application of guideline-indicated therapy after ACS is associated with abolishment of the adverse mortality gap in women (178).

Medical therapy for IHD in women. As noted previously, one factor contributing to relatively greater IHD risk in women is less intensive use of indicated medical therapy (aspirin, beta-blocker, statin, angiotensin-converting enzyme [ACE], therapeutic lifestyle counseling) (179–183); despite specific guidelines noting their benefit (6). The Cooperative Cardiovascular Project (184) showed that women received less medical treatment after MI, including 5% that received fewer prescriptions of aspirin at discharge; although they were 5% more likely than men to receive ACE inhibitors, perhaps as the result of hypertension. A more recent registry (104) indicates that this observation has not changed, with women receiving less (indicated) aspirin at discharge (87.5% vs. 90.4%), beta-blockers (80.5% vs. 82.7%), and statins (55.9% vs. 69.4%) compared with men.

Treatment of women with obstructive CAD. Undertreatment of women has been attributed to the lower prevalence of obstructive CAD. Recent data from the Euro Heart Survey of Stable Angina reported that women with CAD less likely received coronary revascularization (OR: 0.70; 95% CI: 0.52 to 0.94, $p = 0.019$) and were less often on lipid-lowering therapy at 1-year follow-up (76% vs. 81%, $p = 0.05$), despite adjustment for an array of clinical factors (185). In contrast, the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) registry (104) revealed similar rates of PCI among women and men after accounting for the severity of angiographic CAD (adjusted OR: 0.97; 95% CI: 0.91 to 1.03). The authors of the GRACE (Gender, Race, and Clinical Experience) study investigated women with obstructive CAD and demonstrated less use of aspirin (95% vs. 96%), beta-blockers (87% vs. 89%), and statins (75% vs. 77%) compared with men (186). The recent COURAGE (Clinical Outcomes Utilizing Revascularization and Ag-

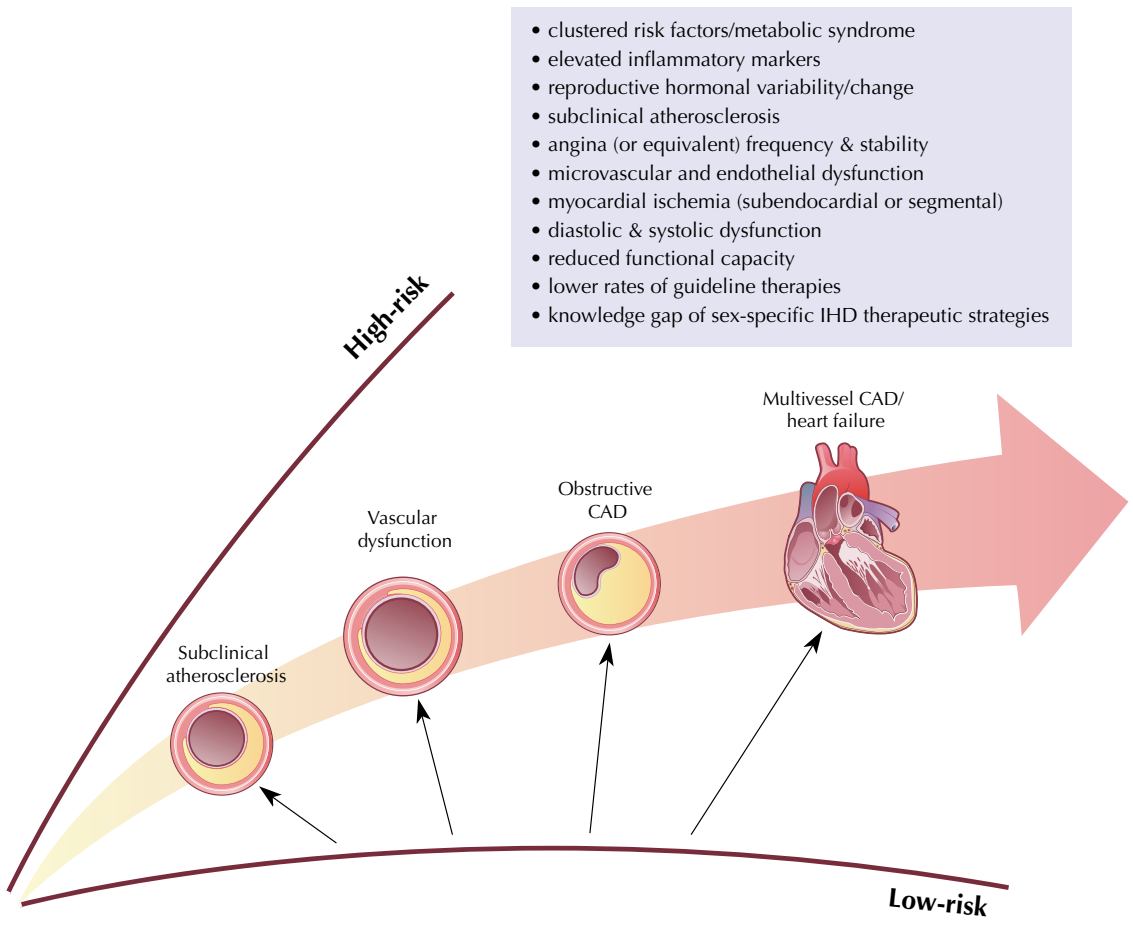

Figure 4 **Factors That Have an Impact on the Risk of IHD Events in Women**

Figure illustration by Rob Flewell. CAD = coronary artery disease; IHD = ischemic heart disease.

gressive Drug Evaluation) trial demonstrated that women with CAD and chronic stable angina derive an equal benefit from intensive, long-term medical therapy and with no added benefit of PCI (Fig. 5) (187).

Thus, the weight of the evidence indicates suboptimal treatment of women with proven obstructive CAD (188), despite evidence and guidelines supporting effective risk reduction when applying acute, revascularization, and/or chronic medical therapies (6,189–191).

Treatment of women with ischemia and nonobstructive CAD. Much of the evidence of treatment in women with nonobstructive CAD has focused on improvement in symp-

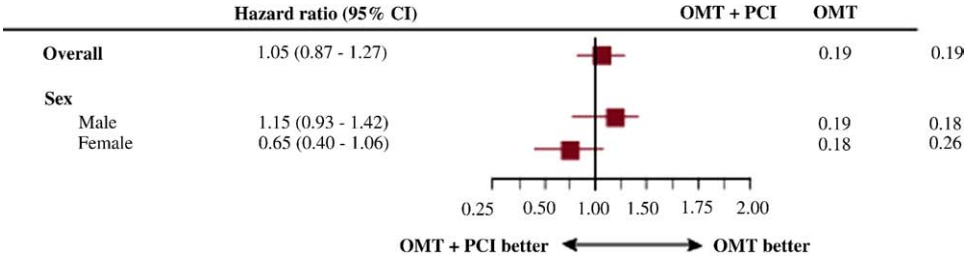

Figure 5 **Relative Hazard (95% CIs) for Death or MI for Women and Men Enrolled in the COURAGE Trial**

Reprinted with permission from Boden et al. (187). CI = confidence interval; MI = myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

toms or vascular function. Many anti-ischemic therapies have been evaluated, including data that calcium antagonists reduce coronary flow reserve and fail to improve symptoms (192). Beta-blockers, however, are highly effective for improving chest pain symptoms (193). No controlled studies are available on the effects of nitrates on health status outcomes in women. Statins and ACE inhibitors improve endothelial dysfunction (194,195) and may be of benefit in patients with nonobstructive CAD (194–196). Beneficial effects of statins on the coronary microcirculation have been documented in clinical studies (197). Combinations of drugs, specifically statins and ACE inhibitors, may amplify these benefits (194). However, combination therapy to more fully attenuate the renin-angiotensin aldosterone system has not been explored; additional work is required to determine the translational value of this treatment. The proven benefit of exercise training in this population (198) suggests that mechanisms of adrenergic modulation play a role.

Novel therapies have been evaluated in women without obstructive CAD. Imipramine improves symptoms in patients with abnormal cardiac pain perception and normal coronary angiograms; possibly through a visceral analgesic effect. It also has anticholinergic and alpha-antagonist effects demonstrated both in the coronary and peripheral circulation (199). Six-month supplementation of L-arginine improved endothelial function and symptoms in patients with nonobstructive CAD (200), although a recent post-MI trial demonstrated adverse effects of L-arginine questioning its safety (201). Menopausal hormone therapy may improve emotional well-being in postmenopausal women with angina and "normal" angiograms, yet there is no anginal symptom benefit for these patients (202).

No randomized trials comparing therapies for risk reduction and cost effectiveness in women with angina/ischemia and "normal" coronary arteries have been conducted. Future IHD research will need to specifically characterize patients as to the pathophysiologic mechanism(s) of disease, with regard to the presence or absence of coronary microvascular dysfunction, to devise optimal clinical trials aimed at improved IHD risk and health status outcomes.

Summary

Given the relatively lower prevalence of obstructive CAD yet the notably greater prevalence of ischemia, symptom burden, and mortality relative to men, we propose the use of the term IHD as more appropriate for symptomatic women in lieu of the terms CAD or CHD. Traditional risk factors contribute to accelerating risk for IHD events in women, and novel risk markers, including inflammatory markers and reproductive sex hormones, provide unique value for identifying at-risk women. More recent specific global risk scores for women, such as the Reynold's risk score, and markers of subclinical atherosclerosis improve risk detection. Routinely available diagnostic testing can be used to accurately risk stratify women; however, the identification of compromised functional capacity and evidence of ischemia as markers of an adverse prognosis are particularly important. Given the frequent paradoxical findings of angina and ischemia in women without obstructive CAD, new data support the use of the term microvascular angina to reflect the occurrence of microvascular dysfunction in IHD pathophysiology in women; models linking these findings with symptoms, ischemia, and adverse outcomes should be tested.

For ACS, new sex-specific guidelines indicate that conservative management is indicated for biomarker-negative women; however, interventional strategies are equally effective in biomarker-positive women and men. Yet, the weight of evidence documents suboptimal use of evidence-based guideline therapies in women with IHD compared with men. Antianginal and antiatherosclerotic strategies are effective for symptom and ischemia management in symptomatic women with evidence of ischemia and no obstructive CAD; however, they are used infrequently and need to be evaluated in large outcome trials. The evolving knowledge regarding sex differences in IHD appears to be at the precipice of our understanding; future investigation should identify tailored diagnostic and therapeutic strategies to optimize outcomes for women and men (203).

Reprint requests and correspondence: Dr. C. Noel Bairey Merz, Cedars-Sinai Medical Center, Department of Medicine, 444 S. San Vicente Boulevard, Suite 600, Los Angeles, California 90048. E-mail: merz@cshs.org.

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