

STATE-OF-THE-ART PAPER

Women and Ischemic Heart Disease

Evolving Knowledge

Leslee J. Shaw, PhD,[†] Raffaele Bugiardini, MD,[‡] C. Noel Bairey Merz, MD*

Los Angeles, California; Atlanta, 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).

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 International, 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.

Manuscript received February 13, 2009; revised manuscript received April 20, 2009, accepted April 27, 2009.

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

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

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.

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

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 ≥ 40 kg/m² 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 ≥ 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: $0.0799 \times \text{age} + 3.137 \times \text{natural logarithm (systolic blood pressure)} + 0.180 \times \text{natural logarithm (hsCRP)} + 1.382 \times \text{natural logarithm (total cholesterol)} - 1.172 \times \text{natural logarithm (high-density lipoprotein cholesterol)} + 0.134 \times \text{hemoglobin A}_{1c} (\%)$ (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, non-diabetic 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 $\sim 1\%$ 10-year IHD risk versus $\sim 10\%$ 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 health-care 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 $\cong 65\%$) 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 Prinzmetal'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).

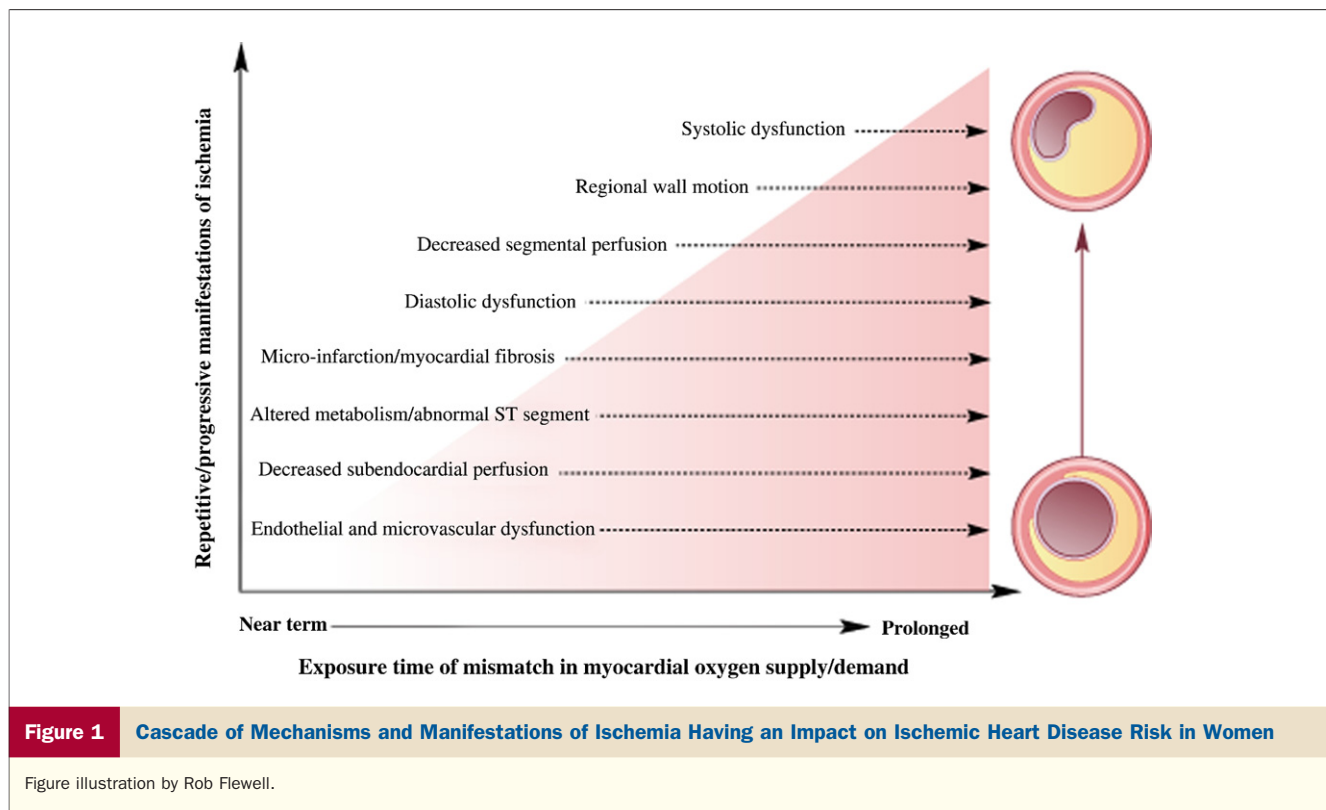
Endothelial dysfunction. Endothelial function (measured centrally in the coronary or distally in the peripheral circulation) contributes to IHD pathophysiology in women. Brachial artery flow-mediated dilation, a peripheral measure of endothelial function, is impaired in hyperlipidemic, hypertensive, 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



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.

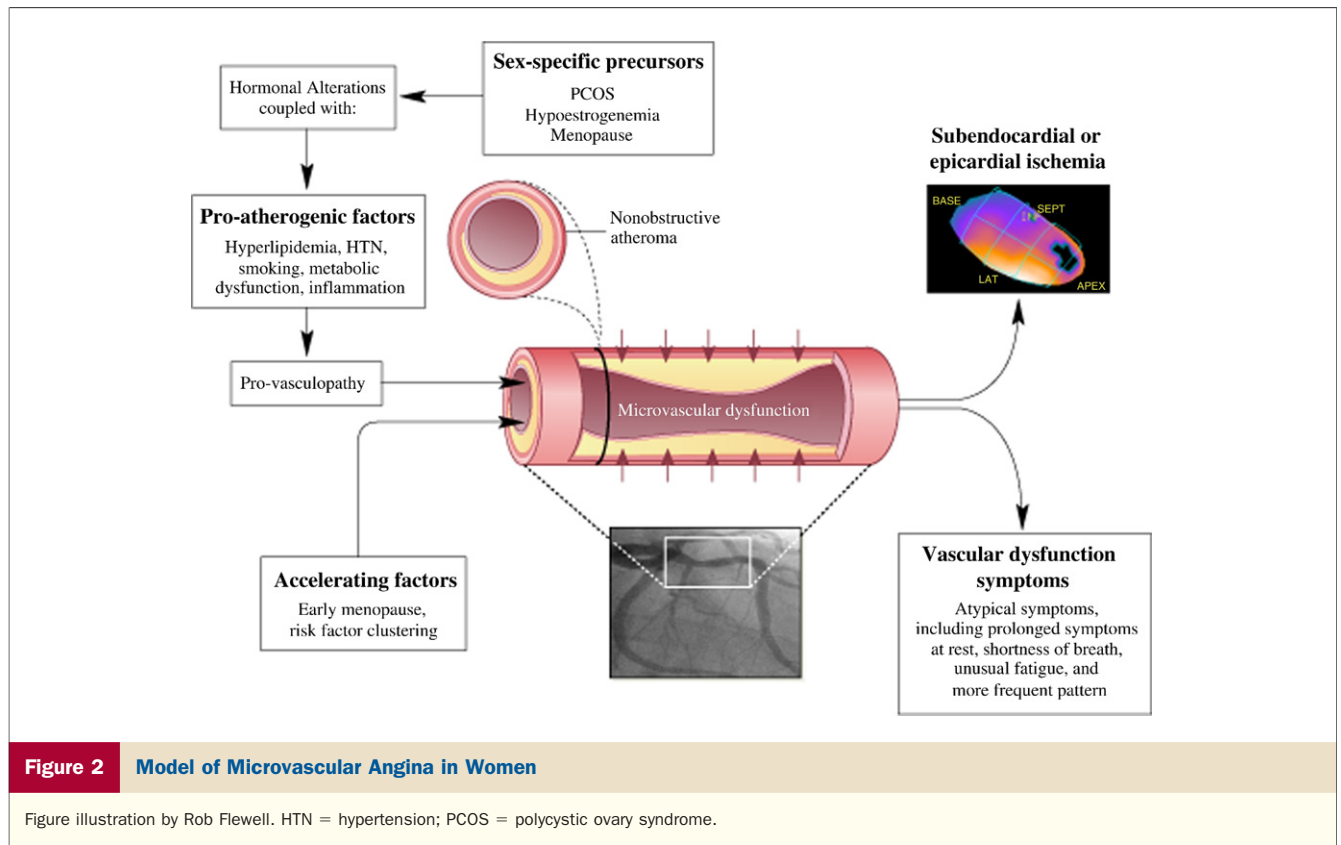
Prognosis in Women With IHD

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 mor-

tality 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-



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

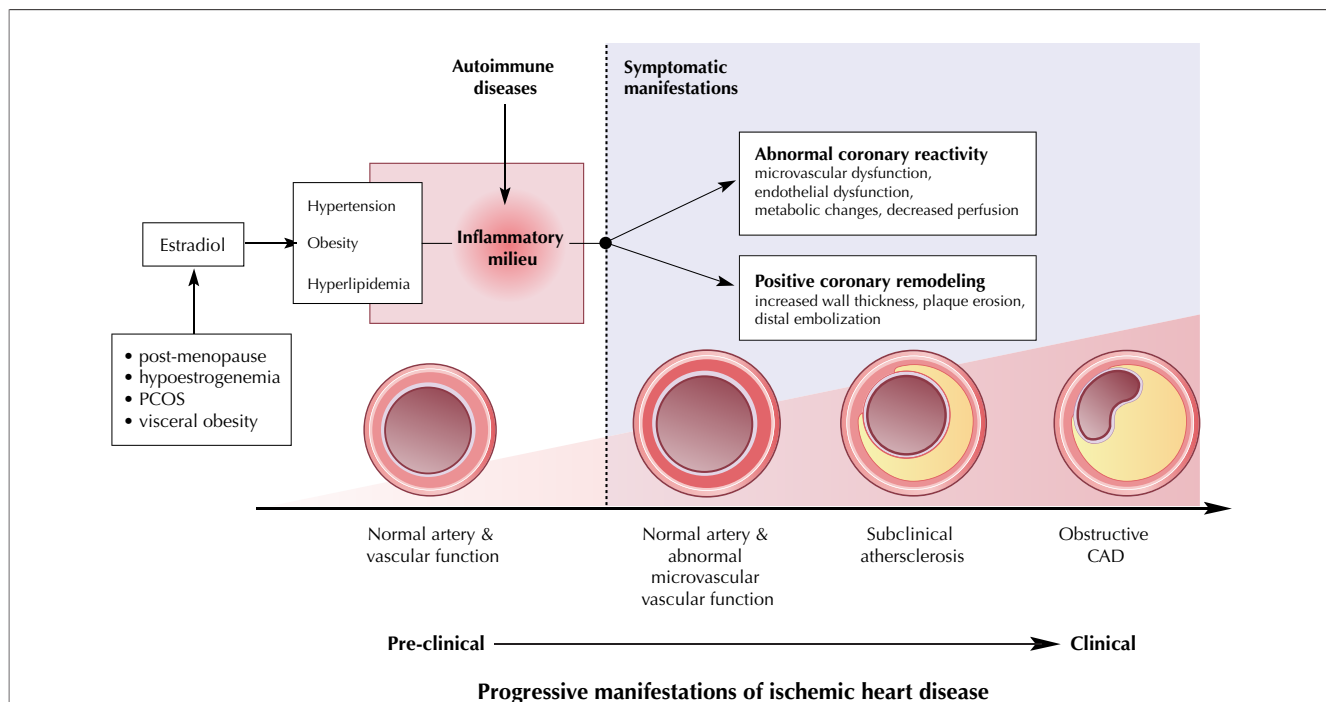


Figure 3 Overarching Working Model of Ischemic Heart Disease Pathophysiology in Women

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-

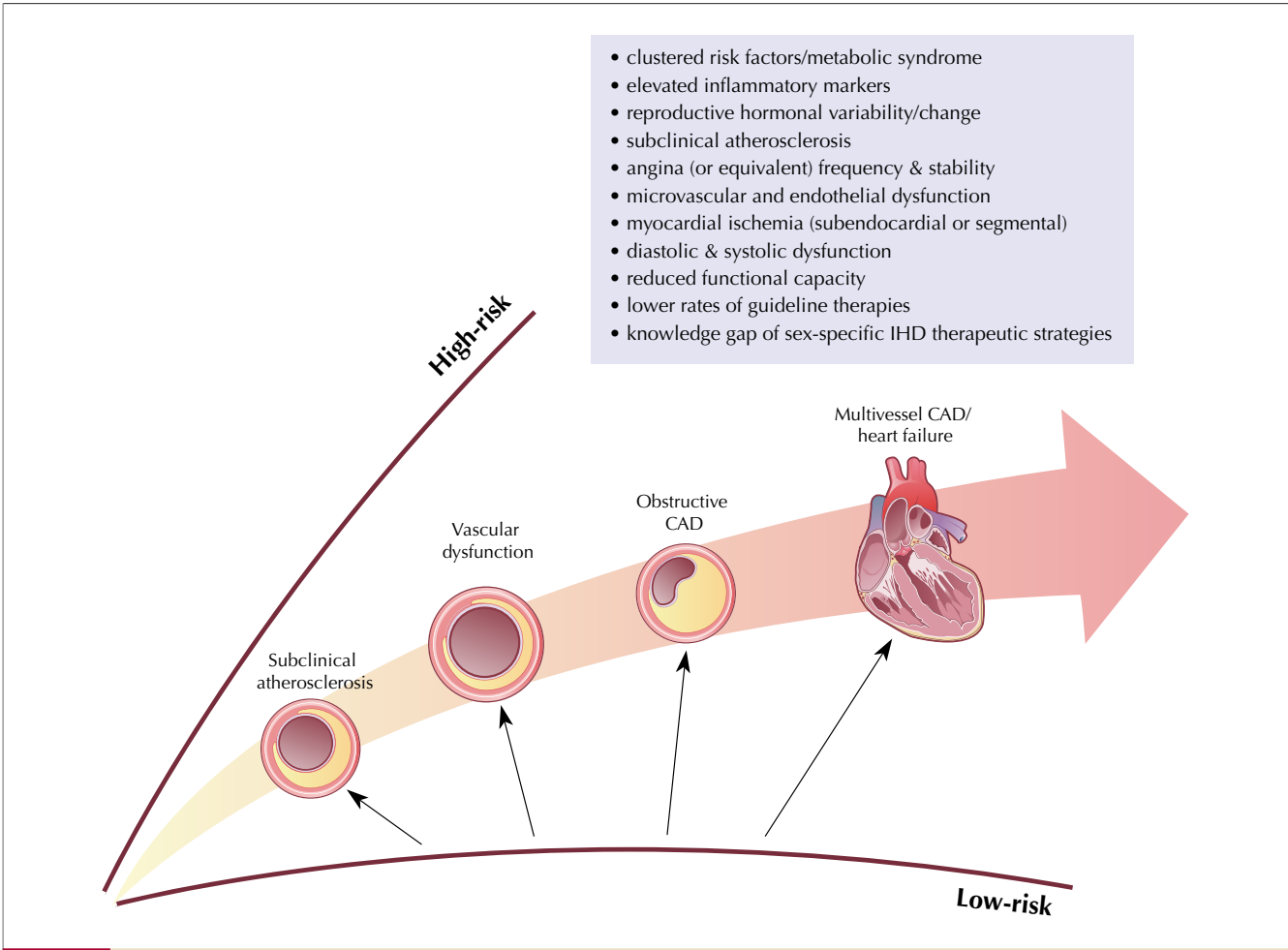


Figure 4 Factors That Have an Impact on the Risk of IHD Events in Women

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-

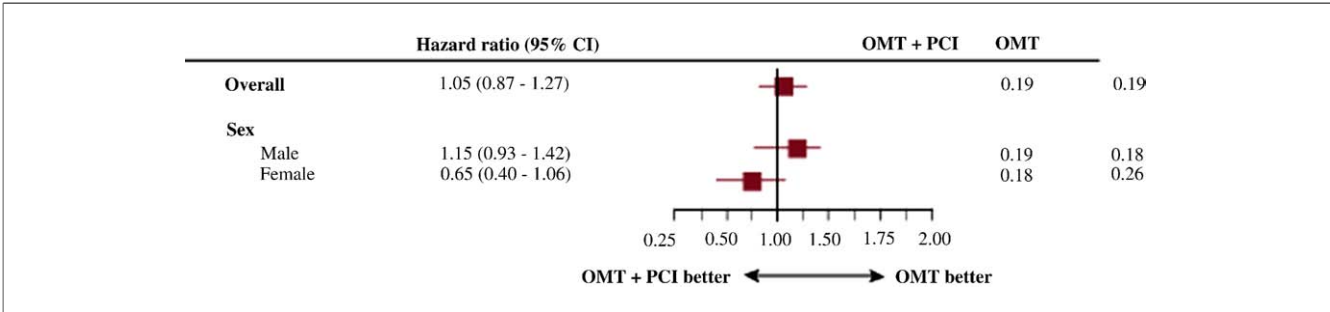


Figure 5 Relative Hazard (95% CIs) for Death or MI for Women and Men Enrolled in the COURAGE Trial

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 identifica-

tion 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.

REFERENCES

- Centers for Disease Control and Prevention. State-Specific Mortality from Sudden Cardiac Death—United States, 1999. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5106a3.htm>. Accessed August 25, 2008.
- Heron MP, Hoyert DL, Xu J, Scott C, Tejada-Vera B. Deaths: preliminary data for 2006. *Natl Vital Stat Rep* 2008;56:1–52.
- Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol* 2007;50:2128–32.
- Rosamond W, Flegal K, Furie K, et al., for the Writing Group Members. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117:e25–146.
- Bairey Merz CN, Shaw LJ, Reis SE. Ischemic heart disease in women: insights from the NHLBI-sponsored Women’s Ischemia Syndrome Evaluation (WISE) Study. Part II: Gender differences in presentation, diagnosis, and outcome with regard to sex-based pathophysiology of atherosclerosis, macro- and micro-vascular CAD. *J Am Coll Cardiol* 2006;47 Suppl:21s–9s.
- Mosca L, Banka CL, Benjamin EJ, et al., for the Expert Panel/ Writing Group. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *J Am Coll Cardiol* 2007;49:1230–50.
- Benjamin EJ, Smith SC Jr., Cooper RS, Hill MN, Luepker RV. Task force #1—magnitude of the prevention problem: opportunities and challenges. 33rd Bethesda Conference. *J Am Coll Cardiol* 2002;40:588–603.
- Roger VL, Jacobsen SJ, Weston SA, et al. Trends in the incidence and survival of patients with hospitalized myocardial infarction, Olmsted County, Minnesota, 1979 to 1994. *Ann Intern Med* 2002;136:341–8.

9. Moriel M, Rozanski A, Klein J, Berman DS, Bairey Merz CN. Women, prognosis and coronary artery disease: the limited efficacy of exercise radionuclide ventriculography. *Am J Cardiol* 1995; 76:1030-5.
10. Shaw LJ, Bairey Merz CN, Reis SE, et al., for the WISE Investigators. Ischemic heart disease in women: insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Part I: sex differences in traditional and novel risk factors, symptom evaluation and gender-optimized diagnostic strategies. *J Am Coll Cardiol* 2006;47:S4-20.
11. Shaw LJ, Shaw RE, Bairey Merz CN, et al. Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Circulation* 2008;117:1787-801.
12. Von Mering GO, Arant CB, Wessel TR, et al., for the National Heart, Lung, and Blood Institute. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004;109: 722-5.
13. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. *JAMA* 2002;287:1153-9.
14. Burke AP, Farb A, Malcolm GT, Liang Y, Smialek J, Virmani R. Effects of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. *Circulation* 1998;97:2110-16.
15. Burke AP, Virmani R, Galis Z, Haudenschild CC, Muller JE. 34th Bethesda Conference: Task force #2—what is the pathologic basis for new atherosclerosis imaging techniques? *J Am Coll Cardiol* 2003; 41:1874-86.
16. Centers for Disease Control and Prevention. Racial/Ethnic Disparities in Prevalence, Treatment, and Control of Hypertension—United States, 1999–2002. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5401a3.htm>. Accessed August 25, 2008.
17. Murphy SL. Death: final data for 1998. *Natl Vital Stat Rep* 2000;48: 1-105.
18. Ni H, Coady S, Rosamond W, et al. Trends from 1987 to 2004 in sudden death due to coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2009;157:46-52.
19. Olson MB, Kelsey SF, Matthews K, et al. Symptoms, myocardial ischaemia and quality of life in women: results from the NHLBI-sponsored WISE Study. *Eur Heart J* 2003;24:1506-14.
20. Johnson BD, Bairey Merz CN, Kelsey SF, et al. Persistent chest pain predicts cardiovascular events in women with and without obstructive coronary artery disease: results from the NHLBI-sponsored WISE study. *Eur Heart J* 2006;27:1408-15.
21. Raine R, Hutchings A, Black N. Is publicly funded health care really distributed according to need? *Health Policy* 2004;67:227-35.
22. Agency for Healthcare Research and Quality. Available at: <http://www.ahrq.gov/hcup/factbk3/factbk3.htm#men>. Accessed October 14, 2008.
23. Hemingway H, Crook AM, Feder G, et al. Underuse of coronary revascularization procedures in patients considered appropriate candidates for revascularization. *N Engl J Med* 2001;344:645-54.
24. Shaw LJ, Sharaf BL, Johnson BD, et al. The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2006;114:894-904.
25. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; 289:76-9.
26. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J* 1986;111:383-90.
27. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006;295:549-55.
28. McTigue K, Larson JC, Valoski A, et al. Mortality and cardiac and vascular outcomes in extremely obese women. *JAMA* 2006; 296:79-86.
29. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk* 1996;3:213-9.
30. Kanaya AM, Grady D, Barrett-Connor E. Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med* 2002;162: 1737-45.
31. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 1991;265:627-31.
32. Spencer EA, Pirie KL, Stevens RJ, et al., for the Million Women Study Collaborators. Diabetes and modifiable risk factors for cardiovascular disease: the prospective Million Women Study. *Eur J Epidemiol* 2008;23:793-9.
33. Gregg EW, Gu Q, Cheng YJ, Narayan KM, Cowie CC. Mortality trends in men and women with diabetes. *Ann Intern Med* 2007;147: 149-55.
34. Daviglus ML, Stamler J, Pirzada A, et al. Favorable cardiovascular risk profile in young women and long-term risk of cardiovascular and all-cause mortality. *JAMA* 2004;292:1588-92.
35. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683-9.
36. Lakka H-M, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular mortality in middle aged men. *JAMA* 2002;288:2709-16.
37. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults—findings from the Third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356-9.
38. Ramos RG, Olden K. The prevalence of metabolic syndrome among US women of childbearing age. *Am J Public Health* 2008;98:1122-7.
39. Pilote L, Dasgupta K, Guru V, et al. A comprehensive view of sex-specific issues related to cardiovascular disease. *CMAJ* 2007;176: S1-44.
40. Hecht HS, Superko HR. Electron beam tomography and National Cholesterol Education Program guidelines in asymptomatic women. *J Am Coll Cardiol* 2001;37:1506-11.
41. Pasternak RC, Abrams J, Greenland P, Smaha LA, Wilson PW, Houston-Miller N. 34th Bethesda Conference: task force #1—identification of coronary heart disease risk: is there a detection gap? *J Am Coll Cardiol* 2003;41:1863-74.
42. Shaw LJ, Lewis JF, Hlatky MA, et al. Women's Ischemic Syndrome Evaluation: current status and future research directions, report of the National Heart Lung Blood Institute (NHLBI) Workshop, October 2-4, 2002: section 5: gender-related risk factors for ischemic heart disease. *Circulation* 2004a;109:56e-8e.
43. Michos ED, Nasir K, Braunstein JB, et al. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. *Atherosclerosis* 2006;184:201-6.
44. Lakoski SG, Greenland P, Wong ND, Schreiner PJ, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med* 2007; 167:2437-42.
45. Nasir K, Michos ED, Blumenthal RS, Raggi P. Detection of high-risk young adults and women by coronary calcium and National Cholesterol Education Program Panel III guidelines. *J Am Coll Cardiol* 2005;46:1931-6.
46. Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol* 2002;86:1007-13.
47. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 2003;107:391-7.
48. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Ann Intern Med* 2006;145:21-9.
49. Raggi P, Shaw LJ, Berman DS, Callister TQ. Gender-based differences in the prognostic value of coronary calcium. *J Women Health* 2004;13:273-88.
50. Wong ND, Pio J, Valencia R, Thakal G. Distribution of C-reactive protein and its relation to risk factors and coronary heart disease risk

- estimation in the National Health and Nutrition Examination Survey (NHANES) III. *Prev Cardiol* 2001;4:109-14.
51. Bessant R, Hingorani A, Patel L, MacGregor A, Isenberg DA, Rahman A. Risk of coronary heart disease and stroke in a large British cohort of patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2004;43:924-9.
52. Johnson BD, Kip KE, Marroquin OC, et al, National Heart, Lung, and Blood Institute. Serum amyloid A as a predictor of coronary artery disease and cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004;109:726-32.
53. Marroquin OC, Kip KE, Kelley D, et al. The metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from WISE. *Circulation* 2004;109:714-21.
54. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347:1557-65.
55. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998;98:731-33.
56. Kuller LH, Tracy RP. The role of inflammation in cardiovascular disease. *Arterioscler Thromb Vasc Biol* 2000;20:901-6.
57. Tracy RP. Inflammation in cardiovascular disease: cart, horse or both—revisited. *Arterioscler Thromb Vasc Biol* 2002;22:1514-5.
58. Kip KE, Marroquin OC, Kelley DE, et al. Clinical importance of obesity versus the metabolic syndrome on cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004;109:706-13.
59. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med* 2008;358:2107-16.
60. Arant CB, Wessel TR, Ridker PM, et al. Multimarker approach predicts adverse cardiovascular events in women evaluated for suspected ischemia: a report from the NHLBI-sponsored WISE study. *Clin Cardiol* 2009;32:244-50.
61. Bairey Merz CN, Johnson BD, Sharaf BL, et al. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. *J Am Coll Cardiol* 2003;41:413-9.
62. Tannenbaum C, Barrett-Connor E, Laughlin GA, Platt RW. A longitudinal study of dehydroepiandrosterone sulphate (DHEAS) change in older men and women: the Rancho Bernardo Study. *Eur J Endocrinol* 2004;151:717-25.
63. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones & risk of type 2 diabetes. *JAMA* 2006;295:1288-99.
64. Shaw LJ, Bairey Merz CN, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health-National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. *J Clin Endocrinol Metab* 2008;93:1276-84.
65. Zamboni S, Zanoni S, Romanato G, et al. Metabolic syndrome and all-cause and cardiovascular mortality in an Italian elderly population: the Progetto Veneto Anziani (Pro.V.A.) study. *Diabetes Care* 2009;32:153-9.
66. The National Heart, Lung, and Blood Institute. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>. Accessed December 8, 2008.
67. The National Heart, Lung, and Blood Institute. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). Available at: <http://www.nhlbi.nih.gov/guidelines/hypertension/index.htm>. Accessed December 8, 2008.
68. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;297:611-9.
69. Ingelsson E, Sullivan LM, Fox CS, et al. Burden and prognostic importance of subclinical cardiovascular disease in overweight and obese individuals. *Circulation* 2007;116:375-84.
70. Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med* 2007;32:328-33.
71. Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham risk score to predict cardiovascular events and mortality. *JAMA* 2008;300:197-208.
72. Touboul P-J, Hennerici MG, Meairs S, et al. Mannheim Carotid Intima-Media Thickness Consensus (2004-2006): an update on behalf of the advisory board of the 3rd and 4th Watching the Risk Symposium 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis* 2007;23:75-80.
73. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima media thickness: a systematic review and meta-analysis. *Circulation* 2007;115:459-67.
74. Devine J, Carlson DW, Taylor AJ. Clinical value of carotid-intima media thickness. *J Nucl Cardiol* 2006;13:710-8.
75. Simon A, Chironi G, Levinson J. Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals. *Eur Heart J* 2007;28:2967-71.
76. Stein JH, Korcarz CE, Hurst RT, et al, American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008;21:93-111.
77. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *J Am Coll Cardiol* 2007;49:378-402.
78. Redberg RF, Rifai N, Gee L, Ridker PM. Lack of association of C-reactive protein and coronary calcium by electron beam computed tomography in postmenopausal women: implications for coronary artery disease screening. *J Am Coll Cardiol* 2000;36:39-43.
79. Nasir K, Raggi P, Rumberger JA, et al. Coronary artery calcium volume scores on electron beam tomography in 12,936 asymptomatic adults. *Am J Cardiol* 2004;93:1146-9.
80. Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. *Am J Cardiol* 2001;87:1335-9.
81. Nasir K, Budoff MJ, Shaw LJ, Blumenthal RS. Value of multislice computed tomography coronary angiography in suspected coronary artery disease. *J Am Coll Cardiol* 2007;49:2070-1.
82. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;358:1336-45.
83. Bellasi A, Lacey C, Taylor AJ, et al. Comparison of prognostic usefulness of coronary artery calcium in men versus women (results from a meta- and pooled analysis estimating all-cause mortality and coronary heart disease death or myocardial infarction). *Am J Cardiol* 2007;100:409-14.
84. Raggi P, Gongora MC, Gopal A, Callister TQ, Budoff M, Shaw LJ. Coronary artery calcium to predict all-cause mortality in elderly men and women. *J Am Coll Cardiol* 2008;52:17-23.
85. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. *N Engl J Med* 1996;334:1311-5.
86. Hendrix KH, Mayhan S, Lackland DT, Egan BM. Prevalence, treatment, and control of chest pain syndromes and associated risk factors in hypertensive patients. *Am J Hypertens* 2005;18:1026-32.
87. Alexander KP, Shaw LJ, Shaw LK, DeLong ER, Mark DB, Peterson ED. Value of exercise treadmill testing in women. *J Am Coll Cardiol* 1998;32:1657-64.

88. Shaw LJ, Heller GV, Travin MI, et al. Cost analysis of diagnostic testing for coronary artery disease in women with stable chest pain. *J Nucl Cardiol* 1999;6:559-69.
89. O'Keefe-McCarthy S. Women's experiences of cardiac pain: a review of the literature. *Can J Cardiovasc Nurs* 2008;18:18-25.
90. Ghali JK, Anand IS, Abraham WT, et al. Study of Anemia in Heart Failure Trial (STAMINA-HeFT) Group. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. Available at: <http://www.ahrq.gov/data/hcup/factbk3/factbk3.htm>. Accessed September 9, 2009.
91. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;300:1350-8.
92. Johnson BD, Kelsey SF, Bairey Merz CN. Clinical risk assessment in women: chest discomfort. Report from the WISE study. In: Shaw LJ, Redberg RF, editors. *CAD in Women: Evidence-Based Diagnosis and Treatment*. Totowa, NJ: Humana Press, 2003:129-42.
93. Sharaf BL, Pepine CJ, Kerensky RA, et al. Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation [WISE] Study Angiographic Core Laboratory). *Am J Cardiol* 2001;87:937-41.
94. Merz NB, Johnson BD, Kelsey PSF, et al. Diagnostic, prognostic, and cost assessment of coronary artery disease in women. *Am J Manag Care* 2001;7:959-65.
95. Robinson JG, Wallace R, Limacher M, et al. Cardiovascular risk in women with non-specific chest pain (from the Women's Health Initiative Hormone Trials). *Am J Cardiol* 2008;102:693-9.
96. Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from The National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE) study and the St James Women Take Heart (WTH) project. *Arch Intern Med* 2009;169:843-50.
97. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. *JAMA* 2005;293:477-84.
98. Hochman JS, Tamis JE, Thompson TD, et al., for the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *N Engl J Med* 1999;341:226-32.
99. Hochman JS, McCabe CH, Stone PH, et al. Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB. *J Am Coll Cardiol* 1997;30:141-8.
100. Anderson RD, Pepine CJ. Gender differences in the treatment for acute myocardial infarction: bias or biology? *Circulation* 2007;115:823-6.
101. Panza JA. Myocardial ischemia and the pains of the heart. *N Engl J Med* 2002;346:1934-5.
102. Humphries KH, Pu A, Gao M, Carere RG, Pilote M. Angina with "normal" coronary arteries: sex differences in outcomes. *Am Heart J* 2008;155:375-81.
103. Reynolds HR, Farkouh ME, Lincoff AM, et al., for the GUSTO V Investigators. Impact of female sex on death and bleeding after fibrinolytic treatment of myocardial infarction in GUSTO V. *Arch Intern Med* 2007;167:2054-60.
104. Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in diagnosis & treatment of non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2005;45:832-37.
105. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. *N Engl J Med* 1999;341:217-25.
106. Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P, Keskimäki I. Incidence and prognostic implications of stable angina pectoris among women and men. *JAMA* 2006;295:1404-11.
107. Kwok YS, Kim C, Grady D, et al. Meta-analysis of exercise testing to detect coronary artery disease in women. *Am J Cardiol* 1999;83:660-6.
108. Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women. *JAMA* 2003;290:1600-7.
109. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women. *Circulation* 2003;108:1554-9.
110. Mieres JH, Shaw LJ, Arai A, et al., for the Cardiovascular Imaging Committee. American Heart Association-Cardiac Imaging Committee Consensus Statement: the role of cardiac imaging in the clinical evaluation of women with known or suspected coronary artery disease. *Circulation* 2005;111:682-96.
111. Gulati M, Arnsdorf MF, Shaw LJ, et al. Prognostic value of the duke treadmill score in asymptomatic women. *Am J Cardiol* 2005;96:369-75.
112. Alexander KP, Shaw LJ, Shaw LK, DeLong ER, Mark DB, Peterson ED. Diagnostic and prognostic value of the Duke treadmill score in women. *J Am Coll Cardiol* 1998;32:1657-64.
113. Shaw LJ, Olson MB, Kip K, et al. The value of estimated functional capacity in estimating outcome: results from the NHLBI-sponsored women's ischemia syndrome evaluation. *J Am Coll Cardiol* 2006;47:S36-43.
114. Kavanagh T, Mertens DJ, Hamm LF, et al. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol* 2003;42:2139-43.
115. Wessel TR, Arant CB, Olson MB, et al. Relationship of physical fitness vs BMI with CAD & CV events in women. *JAMA* 2004;292:1179-87.
116. Gulati M, Black HR, Shaw LJ, et al. The prognostic value of a nomogram for exercise capacity in women. *N Engl J Med* 2005;353:18-25.
117. Shaw LJ, Vasey C, Sawada S, Rimmerman C, Marwick TH. Impact of gender on risk stratification by exercise and dobutamine stress echocardiography: long-term mortality in 4,234 women and 6,898 men. *Eur Heart J* 2005;26:447-56.
118. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol* 2007;49:227-37.
119. Shaw LJ, Iskandrian AE. Prognostic value of stress gated SPECT in patients with known or suspected coronary artery disease. *J Nucl Cardiol* 2004;11:171-85.
120. Marwick TH, Shaw LJ, Lauer MS, et al., for the Economics of Noninvasive Diagnosis (END) Study Group. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. *Am J Med* 1999;106:172-8.
121. Berman DS, Kang X, Hayes SW, et al. Adenosine myocardial perfusion SPECT in women compared with men: impact of diabetes mellitus on incremental prognostic value and effect on patient management. *J Am Coll Cardiol* 2003;41:1125-33.
122. Yoshinaga K, Chow BJ, Williams K, et al. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 2006;48:1029-39.
123. Lertsburapa K, Ahlberg AW, Bateman TM, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. *J Nucl Cardiol* 2008;15:745-53.
124. Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. *Circulation* 2007;116:1290-305.
125. Panting JR, Gatehouse PD, Yang GZ, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002;346:1948-53.
126. Pilz G, Klos M, Ali E, Hoefling B, Scheck R, Bernhardt P. Angiographic correlations of patients with small vessel disease diagnosed by adenosine-stress cardiac magnetic resonance imaging. *J Cardiovasc Magn Reson* 2008;10:8.
127. Vermeltfoort IA, Bondarenko O, Rajmakers PG, et al. Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study. *Eur Heart J* 2007;28:1554-8.
128. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;359:2324-36.
129. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multi-

- center ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;52:1724-32.
130. Pundziute G, Schuijff JD, Jukema JW, et al. Gender influence on the diagnostic accuracy of 64-slice multislice computed tomography coronary angiography for detection of obstructive coronary artery disease. *Heart* 2008;94:48-52.
131. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359:2324-36.
132. Sekhri N, Timmis A, Chen R, et al. Inequity of access to investigation and effect on clinical outcomes: prognostic study of coronary angiography for suspected stable angina pectoris. *BMJ* 2008;336:1058-61.
133. Anderson RD, Pepine CJ. Gender differences in the treatment of acute myocardial infarction: bias or biology? *Circulation* 2007;115:823-6.
134. Harding MB, Leithe ME, Mark DB, et al. Ergonovine maleate testing during cardiac catheterization: a 10-year perspective in 3,447 patients without significant coronary artery disease or Prinzmetal's variant angina. *J Am Coll Cardiol* 1992;20:107-11.
135. Sun H, Mohr M, Shimokawa H, Usai M, Hrakami L, Takeshita A. Coronary microvascular spasm causes myocardial ischemia in patients with vasospastic angina. *J Am Coll Cardiol* 2002;39:847-51.
136. Hibino H, Kurachi Y. A new insight into the pathogenesis of coronary vasospasm. *Circ Res* 2006;98:579-81.
137. Kakkar R, Ye B, Stoller DA, et al. Spontaneous coronary vasospasm in KATP mutant mice arises from a smooth muscle-extrinsic process. *Circ Res* 2006;98:682-9.
138. Burke AP, Kolodgie FD, Farb A, Weber D, Virmani R. Morphological predictors of arterial remodeling in coronary atherosclerosis. *Circulation* 2002;105:297-303.
139. Burke AP, Farb A, Malcom G, Virmani R. Effect of menopause on plaque morphologic characteristics in coronary atherosclerosis. *Am Heart J* 2001;141:S58-62.
140. Burke AP, Kolodgie F, Farb A, Virmani R. Gender differences in coronary plaque morphology in sudden coronary death. *Circulation* 2003;108:IV165.
141. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol* 2006;47 Suppl 8:C13-8.
142. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities (ARIC) study. *Ophthalmology* 1999;106:2269-80.
143. Reis SE, Holubkov R, Conrad Smith AJ, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. *Am Heart J* 2001;141:735-41.
144. Han SH, Bac JH, Holmes DR, et al. Sex differences in atheroma burden and endothelial function in patients with early coronary atherosclerosis. *Eur Heart J* 2008;29:1359-69.
145. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E, for the American Society of Echocardiography; Society for Vascular Medicine and Biology. American society of echocardiography report. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society for Vascular Medicine and Biology. *Vasc Med* 2006;11:201-11.
146. Colacurci N, Manzella D, Fornaro F, Carbonella M, Paolisso G. Endothelial function and menopause: effects of raloxifene administration. *J Clin Endocrinol Metab* 2003;2135-2140.
147. Rossi R, Nuzzo A, Origiani G, Modena MG. Prognostic role of flow-mediated dilation and cardiac risk factors in post-menopausal women. *JACC* 2008;51:997-1002.
148. Elesber AA, Redfield MM, Rihal CS, et al. Coronary endothelial dysfunction and hyperlipidemia are independently associated with diastolic dysfunction in humans. *Am Heart J* 2007;153:1081-7.
149. Rossi R, Chiurlia E, Nuzzo A, Cioni E, Origiani G, Modena MG. Flow-mediated vasodilation and the risk of developing hypertension in healthy postmenopausal women. *J Am Coll Cardiol* 2004;44:1636-40.
150. Schachinger V, Britten M, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long term outcome of CHD. *Circulation* 2000;101:1899-906.
151. Lerman A, Zeiher AM. Endothelial function: cardiac events. *Circulation* 2005;111:363-8.
152. Jaffe R, Charron T, Puley G, Dick A, Strauss BH. Microvascular obstruction and the no-reflow phenomenon after percutaneous coronary intervention. *Circulation* 2008;117:3152-6.
153. Ong P, Athanasiadis A, Hill S, Volgelsberg H, Voehringer M, Sechtem U. Coronary artery spasm as a frequent cause of acute coronary syndrome: the CASPAR (Coronary Artery Spasm in Patients with Acute Coronary Syndrome) study. *J Am Coll Cardiol* 2008;52:523-7.
154. Modena MG, Bonetti L, Coppi F, Bursi F, Rossi R. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. *J Am Coll Cardiol* 2002;40:505-10.
155. MacIntyre K, Stewart S, Capewell S, et al. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. *J Am Coll Cardiol* 2001;38:729-35.
156. Chang WC, Kaul P, Westerhout CM, Graham MM, Fu Y, Chowdhury T, Armstrong PW. Impact of sex on long-term mortality from acute myocardial infarction vs. unstable angina. *Arch Intern Med* 2003;163:2476-84.
157. Lee KL, Woodlief LH, Topol EJ, et al., for the GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. *Circulation* 1995;91:1659-68.
158. Woodfield SL, Lundergan CF, Reiner JS, et al. Gender and acute myocardial infarction: is there a different response to thrombolysis? *J Am Coll Cardiol* 1997;29:35-42.
159. Becker RC, Burns M, Every N, et al. Early clinical outcomes and routine management of patients with non-ST-segment elevation myocardial infarction: a nationwide perspective. *Arch Intern Med* 2001;161:601-7.
160. Grines C, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1999;341:1949-56.
161. Antman EM, Morrow DA, McCabe CH, et al., for the ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006;354:1477-88.
162. Becker RC, Burns M, Every N, et al. Early clinical outcomes and routine management of patients with non-ST-segment elevation myocardial infarction: a nationwide perspective. *Arch Intern Med* 2001;161:601-7.
163. Koek HL, de Bruin A, Gast F, et al. Short- and long-term prognosis after acute myocardial infarction in men versus women. *Am J Cardiol* 2006;98:993-9.
164. Bonarjee VVS, Rosengren A, Snapinn SM, James MS, Dickstein K. Sex-based short- and long-term survival in patients following complicated myocardial infarction. *Eur Heart J* 2006;27:2177-83.
165. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. *J Am Coll Cardiol* 1986;7:479-83.
166. Lichtlen PR, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. *J Am Coll Cardiol* 1995;25:1013-8.
167. Kaski JC, Rosano GM, Collins P, et al. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. *J Am Coll Cardiol* 1995;25:807-14.
168. Diver DJ, Bier JD, Ferreira PE, et al. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIa trial). *Am J Cardiol* 1994;74:531-7.
169. Bugiardini R, Manfredini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease. A study on women with chest pain and normal angiograms. *Circulation* 2004;109:2518-23.
170. Bugiardini R, Manfredini O, De Ferrari GM. Unanswered questions for management of acute coronary syndrome: risk stratification of patients with minimal disease or normal findings on coronary angiography. *Arch Intern Med* 2006;166:1391-5.
171. Lansky AJ, Hochman JS, Ward PA, et al. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. *Circulation* 2005;111:940-53.

172. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2008;300:71-80.
173. Lansky AJ. Outcomes of percutaneous and surgical revascularization in women. *Prog Cardiovasc Dis* 2004;46:305-19.
174. Solinas E, Dangas G, Kirtane AJ, et al. Angiographic patterns of drug-eluting stent restenosis and one-year outcomes after treatment with repeated percutaneous coronary intervention. *Am J Cardiol* 2008;102:311-5.
175. Cho L, Topol EJ, Balog C, et al. Clinical benefit of glycoprotein IIb/IIIa blockade with Abciximab is independent of gender: pooled analysis from EPIC, EPICLOG and EPISTENT trials. Evaluation of 7E3 for the Prevention of Ischemic Complications. Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stent. *J Am Coll Cardiol* 2000;36:381-6.
176. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359:189-98.
177. Alexander KP, Chen AY, Newby LK, et al, for the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Investigators. Sex differences in major bleeding with glycoprotein IIb/IIIa Inhibitors: results from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) initiative. *Circulation* 2006;114:1380-7.
178. Novack V, Cutlip DE, Jotkowitz A, Lieberman N, Porath A. Reduction in sex-based mortality difference with implementation of new cardiology guidelines. *Am J Med* 2008;121:597-603.
179. Bowling A, Bond M, McKee D, et al. Equity in access to exercise tolerance testing, coronary angiography, and coronary artery bypass grafting by age, sex and clinical indications. *Heart* 2001;85:680-6.
180. Battelman DS, Callahan M. Gender differences in utilization of exercise treadmill testing: a claims-based analysis. *J Healthc Qual* 2001;23:38-41.
181. Stafford RS. Aspirin use is low among United States outpatients with coronary artery disease. *Circulation* 2000;101:1097-10.
182. Mosca L, Grundy SM, Judelson D, et al. AHA/ACC scientific statement consensus panel statement. Guide to preventive cardiology for women. American Heart Association/American College of Cardiology. *Circulation* 1999;99:2480-4.
183. Rathore SS, Chen J, Wang Y, Radford MJ, Vaccarino V, Krumholz HM. Sex differences in cardiac catheterization: the role of physician gender. *JAMA* 2001;286:2849-56.
184. Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of acute myocardial infarction and 30-day mortality among women and men. *N Engl J Med* 2000;343:8-15.
185. Daly C, Clemens F, Lopez Sendon JL, et al., for the Euro Heart Survey Investigators. Gender differences in the management and clinical outcome of stable angina. *Circulation* 2006;113:490-8.
186. Dey S, Flather MD, Devlin G, et al., for the Global Registry of Acute Coronary Events Investigators. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart* 2009;95:20-6.
187. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-16.
188. Bugiardini R, Navarro Estrada JL, Nikus K, Hall AS, Manfrini O. Gender bias in acute coronary syndromes. *Curr Vasc Pharmacol* 2010 Jan 1 [E-pub ahead of print].
189. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2008;51:210-47.
190. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction). *J Am Coll Cardiol* 2007;50:e1-157.
191. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 2003;41:159-68.
192. Sutsch G, Oechslin E, Mayer I, Hess OM. Effect of diltiazem on coronary flow reserve in patients with microvascular angina. *Int J Cardiol* 1995;52:135-43.
193. Lanza GA, Colonna G, Pasceri V, Maseri A. Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X. *Am J Cardiol* 1999;84:854-6.
194. Pizzi C, Manfrini O, Fontana F, Bugiardini R. Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac Syndrome X: role of superoxide dismutase activity. *Circulation* 2004;109:53-8.
195. Kayikcioglu M, Payzin S, Yavuzgil O, Kultursay H, Can LH, Soydan I. Benefits of statin treatment in cardiac syndrome-X1. *Eur Heart J* 2003;24:1999-2005.
196. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. *Am J Cardiol* 2002;90:974-82.
197. Manfrini O, Pizzi C, Morgagni GL, Fontana F, Bugiardini R. Effects of pravastatin on myocardial perfusion after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 2004;93:1391-3.
198. Eriksson BE, Tyni-Lenne R, Svedenham J, et al. Physical training in Syndrome X: physical training counteracts deconditioning and pain in Syndrome X. *J Am Coll Cardiol* 2000;36:1619-25.
199. Kelley BM, Porter JH. The role of muscarinic cholinergic receptors in the discriminative stimulus properties of clozapine in rats. *Pharmacol Biochem Behav* 1997;57:707-19.
200. Lerman A, Burnett JC Jr, Higano ST, McKinley LJ, Holmes DR Jr. Long-term L-arginine supplementation improves small-vessel coronary endothelial function in humans. *Circulation* 1998;97:2123-8.
201. Dzavik V, Cotter G, Reynolds HR, et al., for the SHould we inhibit nitric Oxide synthase in Cardiogenic shock 2 (SHOCK-2) Investigators. Effect of nitric oxide synthase inhibition on haemodynamics and outcome of patients with persistent cardiogenic shock complicating acute myocardial infarction: a phase II dose-ranging study. *Eur Heart J* 2007;28:1109-16.
202. Adamson DL, Webb CM, Collins P. Esterified estrogens combined with methyltestosterone improve emotional well-being in postmenopausal women with chest pain and normal coronary angiograms. *Menopause* 2001;8:233-8.
203. Berger JS, Bairey-Merz CN, Redberg RF, Douglas PS. Improving the quality of care for women with cardiovascular disease. Report of a DCRI Think Tank, March 8 to 9, 2007. *Am Heart J* 2008;156:816-25.

Key Words: ischemic heart disease ■ sex differences ■ women.