Ischemic Heart Disease in Women: An Appropriate Time to Discriminate

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Although cardiovascular mortality for men has been declining, the number of women dying from cardiovascular disease has slightly increased. Differences between women and men have been identified throughout the entire spectrum of ischemic heart disease, from risk factors to presentation and from diagnosis to treatment and outcomes. In the setting of an acute coronary syndrome or acute myocardial infarction, women are significantly more likely than men to report multiple non–chest pain symptoms, including dyspnea, nausea/vomiting, abdominal pain, back pain, neck pain, and jaw pain. Investigations into the pathophysiology of ischemic heart disease in women have broken away from the traditional thinking that coronary artery disease simply equals epicardial stenosis. In women, the new paradigm of coronary artery disease also focuses on diffuse atherosclerosis, endothelial dysfunction, and microvascular disease. Further research focusing on sex differences in cardiovascular disease is needed, but enough is currently known to offer a sex-based approach, which may ultimately lead to improved outcomes.

[Rev Cardiovasc Med. *2007;8(2):61-68*]

Key words: Cardiovascular disease • Women • Diabetes • Diffuse atherosclerosis • Endothelial dysfunction • Percutaneous coronary intervention

Providing care for a woman with cardiac risk factors or coronary artery disease (CAD) in 2007 requires a shift from the traditional paradigm of care that developed in the latter half of the 20th century. The traditional paradigm was born in the early 1950s, when there was a surge of interest in understanding the high prevalence of CAD afflicting previously healthy, working, middle-aged men. From this interest grew an enormous body of scientific data and clinical experience that ultimately shaped and solidified our current thinking and teaching of ischemic heart disease (IHD). The paradigm was based on

men and it served them well—the number of men who died from cardiovascular disease (CVD) decreased steadily over the ensuing years. It was assumed that this paradigm could be applied to women, but that assumption has been challenged. Although cardiovascular mortality for men has been declining, the number of women dying from CVD has slightly increased. This difference has resulted in a widening sex gap, with more women than men dying from CVD each year since 1984.[1]

Efforts to raise awareness and calls for studies have resulted in a solid foundation of scientific literature on women. Differences between women and men have been identified throughout the entire spectrum of IHD, from risk factors to presentation and from diagnosis to treatment and outcomes. As the literature continues to grow and evolve, so emerges a new paradigm.

The Woman at Risk

Although women and men are both adversely affected by the traditional cardiac risk factors, the prevalence and relative importance of these risk factors in determining outcome is often different between the sexes. Diabetes in women is particularly distinct because it significantly narrows the gap in cardiovascular morbidity between women and men.[2] The relative risk of coronary heart disease (CHD) due to diabetes is much greater in women (3-fold to 7-fold) than in men (2-fold to 3-fold),[3] as is the risk of CHD death (3.50, 95% confidence interval [CI], 2.70-4.53 in women vs 2.06, 95% CI, 1.81-2.34; $P < .0001$).[4] Adjustment results in a larger attenuation of the relative risk of fatal coronary heart disease among women than men, suggesting that women with diabetes have an overall more unfavorable cardiovascular risk profile than men or that the cardiac risk factors associated with diabetes have a bigger impact on women than men. In both sexes, diabetes is considered a CHD risk equivalent.

Insulin resistance and the metabolic syndrome also predict future cardiovascular risk in women. The Women's Ischemia Syndrome Evaluation (WISE) study, a prospective 4-center project of over 900 women (mean age 59 ± 12 years) sponsored by the National Heart, Lung, and Blood Institute (NHLBI), was designed to evaluate diagnostic techniques and pathophysiologic mechanisms in women presenting with suspected myocardial ischemia and referred for elective coronary angiography. When women from the WISE study were divided into 3 categories of metabolic status (normal, metabolic syndrome, and diabetes), investigators found an approximately 2-fold increase in the adjusted risk of death (hazard ratio [HR] 2.01, 95% CI, 1.26-3.20; $P = .003$) and major adverse coronary events (HR 1.88, 95% CI, 1.38-2.57; $P < .0001$) for each unit increase in metabolic status.[5] The metabolic syndrome also conferred a significantly lower 4-year survival and event-free survival in women found to have angiographically significant CAD at study entry compared to women without angiographically significant CAD.[6] The WISE study was notably a sex-specific study so differences between women and men with insulin resistance and the metabolic syndrome could not be evaluated.

Two major contributors to diabetes and insulin resistance are obesity and physical inactivity. Likewise, more adult women than men in the United States are obese[7] and sedentary.[8] The association of body mass index and physical activity with cardiovascular morbidity and mortality was examined at 20 years (or more) follow-up in a large cohort of women from the Nurses' Health Study who were initially free of CVD. Both a high body mass index and a low level of physical activity were significant and independent predictors of developing CHD and cardiovascular mortality.[9] In addition, even a modest weight gain (4 kg to 10 kg) during adulthood was associated with a 27% increased risk of CHD compared with women with a stable weight, after adjusting for physical activity and other cardiovascular risk factors.[10] Whether obesity and physical inactivity confer a greater overall risk in women than men remains to be determined, as does the relative impact of body fat distribution (central vs peripheral) between the sexes.

The lipid profile seen with insulin resistance and diabetes, specifically high triglyceride and low high-density lipoprotein (HDL) levels, has been shown to predict cardiovascular death in women, whereas low-density lipoprotein (LDL) and total cholesterol levels, stronger predictors in men, are poorer predictors in women. In a study of 1400 relatively healthy middle-aged women with an average of 14 years follow-up, the highest death rates occurred in those women with low HDL, high triglycerides, and normal LDL. In women with a high HDL (> 50 mg/dL), the increased risk associated with a high total cholesterol or LDL was essentially negated.[11] This effect may contribute to the lack of a cardiovascular benefit seen in lipid-lowering, primarily through statin drugs, in women without CVD.[12]

With differences in risk factor prevalence and relative impact on women compared with men, our current methods of risk stratifying and treating asymptomatic individuals by the Framingham risk score or the National Cholesterol Education Program Adult Treatment Panel III

(NCEP ATP III) criteria may be inadequate. There is growing evidence that these scores do a poor job of appreciating risk and predicting myocardial ischemia in women. In one study, 98% of the women fell into the low-risk category by Framingham, but nearly a third of them had evidence of significant subclinical atherosclerosis (as indicated by a coronary calcium score determined with multidetector computed tomography).[13] A retrospective analysis of young (age ≤ 65) women hospitalized for an acute myocardial infarction (AMI) showed similar findings. Although women had a higher mean number of major risk factors than men (2.9 vs 1.5; $P < .001$), when characterized according to the Framingham risk predictor, no woman in the study qualified as high risk, only 5% were considered intermediate risk, and the remaining 95% had a 10-year CHD risk of less than 10%.[14] The most recent guidelines for cardiovascular disease prevention in women have highlighted and attempted to address this problem.[15]

A Different Pathophysiology?

Women presenting with chest pain suggestive of angina are significantly less likely than men to have angiographic evidence of obstructive CAD.[16,17] Investigations into the pathophysiology of IHD in women have broken away from the traditional thinking that CAD simply equals epicardial stenosis. In women, the new paradigm of CAD also focuses on diffuse atherosclerosis, endothelial dysfunction, and microvascular disease. Our understanding of these pathophysiologic abnormalities comes predominately from the WISE study, which as mentioned, evaluated only women. Whether or not these abnormalities are unique to women or if they are equally applicable to all patients presenting with symptomatic non-obstructive CAD remains to be determined.

It is well known that women have smaller coronary arteries than men, even after adjusting for body surface area.[18] In addition, intravascular ultrasound studies have demonstrated that women with cardiac risk factors tend to have diffuse atherosclerosis in their coronary arteries associated with positive remodeling.[19,20] Such epicardial vessels may look acceptable on angiography, but they do not necessarily represent a benign pathology. It has been demonstrated by using a coronary pressure wire and calculating fractional flow reserve during a slow pullback that diffusely diseased epicardial vessels without angiographic evidence of a focal stenosis often have a graded, continuous loss in pressure along the arterial length, and that the presence and/or severity of this coronary pressure gradient cannot be predicted from the angiogram alone. This resistance to flow in diffusely atherosclerotic epicardial arteries likely contributes to myocardial ischemia that is noted in the absence of obstructive coronary disease.[21]

Endothelial vasomotor dysfunction, defined as a significantly blunted epicardial vasodilatory response (by quantitative coronary angiography) to an endothelial-dependent vasodilator, such as acetylcholine, was found in more than half of the women tested in the WISE study, 75% of whom had no or only mild epicardial CAD. Furthermore, the presence of endothelial dysfunction was an independent predictor of long-term cardiovascular events, including myocardial infarction, congestive heart failure, and death ($P = .001$).[22]

Endothelial dysfunction is not only thought to be an early marker of atherosclerotic CAD, but it may also contribute to myocardial ischemia at the level of the microcirculation. Dysfunction of the endothelial-lined resistance vessels has important implications because these vessels are the primary regulators of myocardial perfusion, particularly in the absence of significant epicardial disease. Disorder of the coronary microcirculation leading to myocardial ischemia has long been postulated as a prominent cause of angina-like chest pain in patients without angiographic evidence of obstructive CAD.[23] Advances in noninvasive and invasive techniques have improved testing of this microscopic vascular bed.

Seventy-four women from the WISE cohort without angiographic evidence of CAD underwent phosphorus-31 nuclear magnetic resonance spectroscopy (MRS). During low-level isometric handgrip exercises, 19% of them were found to have an abnormal ratio of myocardial high-energy phosphates, phosphocreatine to adenosine triphosphate, indicating myocardial ischemia. These women were then compared with women having no CAD and a normal MRS, as well as with women having CAD (≥ 50% stenosis in ≥ 1 coronary artery). The cumulative 3-year rate of freedom from events, including death, myocardial infarction, congestive heart failure, stroke, other vascular events, or hospitalization for unstable angina, was highest in women with no CAD and a normal MRS (87%). This rate was significantly better than the rate in women with no CAD but an abnormal MRS (57%; $P = .009$) and in women with CAD (52%; $P < .0001$).[24]

In addition, WISE researchers found that 60% of the women tested had evidence of microcirculatory dysfunction by coronary flow reserve (CFR) using an intracoronary Doppler-tipped guidewire (mean CFR = 1.84). Women with evidence of microcirculatory dysfunction also tended to

have a blunted epicardial dilation to intracoronary adenosine compared with women who had normal microvascular reserve function (−1.7% vs +17.2% change in epicardial cross-sectional area by quantitative coronary angiography), suggesting the presence of endothelial dysfunction.[25]

Although methods of evaluating the coronary microcirculation have improved, they are still limited. Both CFR and P-31 nuclear MRS likely underestimate the presence of microvascular dysfunction because they evaluate a limited portion of the myocardium. CFR is generally performed in a single vessel and P-31 nuclear MRS spectroscopy evaluates metabolism in only a small area of myocardium in the anterior wall of the left ventricle. When microvascular function is evaluated by ^{13}N-NH_3 positron emission tomography, there is substantial discordance of classification of microvascular function among coronary artery distributions in women with chest pain and no CAD, suggesting that microvascular dysfunction is distributed heterogeneously in the myocardium.[26]

Platelet function and plaque vulnerability appear to differ between the sexes. Among young survivors of myocardial ischemia, women have more platelet aggregability to adenosine diphosphate and less platelet inhibition to prostacyclin than men.[27] Thrombi found at autopsy in women who died of sudden cardiac death are more often associated with erosion of a proteoglycan and smooth muscle cell–rich plaque rather than rupture of a thin fibrous cap exposing a lipid-rich, often calcified plaque.[28] In addition, when compared with women who die from plaque rupture, women who die from plaque erosion tend to be younger and more likely to smoke, and they have relatively little coronary narrowing associated with their plaque.[29] Women who die from plaque rupture tend to be older and more hypercholesterolemic, and to have a relatively severe coronary stenosis associated with their plaque.

Symptomatic and Clinical Presentation

The contemporary paradigm suggests that clinicians who evaluate women for possible ischemic coronary disease should listen for a broader range of symptomatic complaints than are typically heard from men. In the setting of an acute coronary syndrome (ACS) or AMI, the most common symptom reported by both women and men is chest pain, and they are equally likely to report it. However, women are significantly more likely to report multiple non–chest pain symptoms including dyspnea, nausea/vomiting, abdominal pain, back pain, neck pain, and jaw pain. Women report a mean of 3.4 ± 1.8 symptoms, whereas men report a mean of 2.5 ± 1.4 symptoms ($P = .0002$).[30-32] In addition, although men and women are equally likely to have exertional angina, women are more likely to experience pain at rest, during sleep, or with mental stress.[33] This difference may reflect the pathophysiology of endothelial and microcirculatory dysfunction. Although such symptoms have been traditionally called "atypical," the term is a misnomer in the current era. They may be atypical for a man, but they are typical for a woman, and failure to recognize this distinction may contribute to delays in diagnosis and treatment.

Asking premenopausal women with symptoms where they are in their menstrual cycle can be informative. Estrogen increases nitric oxide synthase activity in the vascular endothelium and directly relaxes vascular smooth muscle by antagonizing calcium channels.[34] It has been demonstrated in both healthy women and women with evidence of endothelial dysfunction that flow-mediated dilation of the brachial artery is significantly lower during the menstrual phase, when estrogen levels are lowest.[35] In women with evidence of endothelial dysfunction, ischemic episodes defined by ST-segment changes on 24-hour ambulatory electrocardiographic monitoring are most common during the menstrual phase and least common during the follicular phase, when estrogen levels are highest (3.9 ± 0.6 episodes per day vs 0.3 ± 0.1 episodes per day; $P < .001$).[36]

Multiple studies show that compared with men, women who present with ACS or AMI are older at presentation (by about 3 to 8 years) and are more likely to have a history of hypertension, diabetes, hyperlipidemia, prior angina, and prior congestive heart failure. Women are less likely than men to have a history of myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). In addition, women tend to present later, are more likely to present with unstable angina than a myocardial infarction, and have a higher Killip class upon presentation (despite a more preserved left ventricular function). These differences in baseline characteristics persist even after adjustment for other baseline characteristics, including age.[17,37] Finally, women presenting with ACS are less likely than men to have elevated creatinine kinase-myocardial band and troponin T (TnT) or troponin I (TnI) levels, but are more likely to have elevated high-sensitivity C-reactive protein (hs-CRP) and brain natriuretic peptide (BNP).[38] Elevated biomarkers, particularly TnT and TnI, predict adverse outcomes—including death or myocardial infarction—in both sexes. These findings have implications for optimal

treatment strategies, as will be discussed.

Noninvasive Diagnostic Testing

When it comes to diagnosing CAD, noninvasive tests appear to be less accurate in women than in men. The least accurate is exercise electrocardiography.[39] Reasons for the lower accuracy in women include a lower CAD prevalence, digoxin-like estrogen effects, differences in chest wall anatomy, the inability of many women to reach maximum aerobic capacity, and the fact that the methods and thresholds for exercise electrocardiography were developed using men almost exclusively. Imaging, with either echocardiography or radionuclide scans, improves diagnostic accuracy, particularly in terms of specificity. In general, exercise echocardiography has the highest sensitivity and specificity for women, with rates that are equivalent to those for men.[40] The slightly lower accuracy of nuclear imaging in women has been attributed to breast attenuation, the higher prevalence of single-vessel disease, and a smaller left ventricular chamber size.[41] Modernization of nuclear perfusion imaging, however, has improved its accuracy so that now it is on par with stress echocardiography. In women, the use of Tc-99m sestamibi radioisotopes instead of thallium-201 in electrocardiogram-gated single-photon emission computed tomography (SPECT) improves the specificity for detecting stenoses of 70% or greater from 58.8% to 82.4% ($P = .01$).[42]

As the pathophysiology of IHD in women becomes clearer, diagnostic testing will likely incorporate modalities capable of interrogating endothelial function and the microcirculation, such as flow-mediated dilation, positron emission tomography, and cardiac magnetic resonance. Given the prognostic implications of endothelial and microcirculatory dysfunction in women, there is a need for practical methods of identifying these derangements.

Management and Prognosis of ACS/AMI

Women, particularly older women, who present with ACS or AMI are less likely to receive coronary angiography than are men.[17] The reason for this difference remains unclear, although women's "atypical" presentations, lower incidence of traditionally elevated cardiac biomarkers or significant electrocardiography changes, and higher rates of comorbidities may all contribute. The effect of this referral difference on clinical outcomes appears to be small, but not null.

A post-hoc analysis of data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial evaluated sex differences in the management and prognosis of ACS.[16] Significantly fewer women than men received coronary angiography during their initial hospitalization (39.4% vs 45.5%, $P = .0001$). The lower rate of angiography in women initially seems reasonable given that among those who had angiography, women were more likely than men to have normal coronary vessels (26.7% vs 13.2%; $P = .0001$) and less likely to have significant CAD (34.9% vs 44.7%; $P = .00001$). However, the rate of angiography was lower for women regardless of their Thrombolysis In Myocardial Infarction (TIMI) risk score. High-risk women went to angiography less often than similarly high-risk men (38.1% vs 45.5%; $P < .001$), but, unlike low- and moderate-risk women, the high-risk women were found to have an incidence of significant CAD similar to their male counterparts (60.8% vs 59.4%; $P = .68$). This finding raises the concern that CAD in high-risk women is underidentified and treated. Overall, there was no difference in cardiovascular death, myocardial infarction, or stroke between women and men, although the incidence of refractory angina and rehospitalization for chest pain during follow-up was significantly higher among women, particularly high-risk women (23.9% vs 15.3%; $P = .0001$). Endothelial and microcirculatory dysfunction may contribute to a higher incidence of refractory angina by limiting collateral function in the territory of a diseased vessel or causing ischemia in territories other than those supplied by the diseased vessel.

The Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18 (TACTICS-TIMI 18) study was a randomized trial in 2220 patients (34% women) with ACS comparing early conservative therapy versus early invasive therapy. Women in this trial were similarly less likely than men to have significant CAD on angiography. In addition, regardless of the TIMI risk score, the adjusted likelihood of death, nonfatal myocardial infarction, or rehospitalization was not different between women receiving the early invasive therapy compared with the conservative approach, except in those women who had an elevated troponin T.[43] Further investigation found that any elevated cardiac biomarker (including TnT, TnI, CRP, and BNP) was associated with a benefit from the invasive strategy in both sexes. However, women with no positive biomarker had an increased risk of death, myocardial infarction, or rehospitalization with the invasive strategy (odds ratio [OR] 3.1, 95% CI, 1.17-8.31), whereas men with no positive biomarker had no significant difference

in outcome by treatment strategy.[38] This consistent finding of no significant benefit, and possibly harm, with angiography in lower risk women likely reflects the fact that these women are less likely to have obstructive coronary disease but more likely to have moderate or severe bleeding than men.[17,44] In essence, they incur all of the risk of catheterization without any of the potential benefit. Still, accurately identifying these higher risk women remains difficult.

In addition, simply performing an analysis by sex may not reveal the whole story. There is a body of evidence that further sex differences in in-hospital mortality rates for myocardial ischemia appear if one also stratifies by age. The National Registry of Myocardial Infarction 2 (NRMI 2) was initiated in 1994 to gather data on consecutive patients admitted with AMI to 1658 hospitals within the United States. An analysis of 248,878 patients (155,565 women) from this registry revealed that for every 5-year decrease in age, the adjusted odds of death during hospitalization for women relative to men increased by 7% (95% CI, 5.9-8.1).[37] In women younger than 50 years of age, the mortality rate during hospitalization was more than twice as high as for similar-aged men (6.1% vs 2.9%). Younger women were more likely than younger men to have diabetes and a history of congestive heart failure; to present with more severe clinical findings, such as a higher Killip class and lower systolic blood pressure; and to have complications such as hypotension, heart failure, cardiogenic shock, and major bleeding. Younger women ($\leq$ 55 years) also have a greater than 2 times higher rate of coronary vascular injury (intimal tear, dissection, acute occlusion, or side branch injury) compared with women over the age of 55 and with men of all ages.[45] However, these sex-based differences are not apparent between older women and older men. Several explanations for these sex and age–based differences have been postulated, including delays in recognition by both the patient and physician, variation in the pathophysiology of IHD (with premature disease in young women being a particularly aggressive type), or sex-based differences in the mortality rate before hospitalization. This interaction between sex and age persists for long-term outcomes. Younger women have a lower 5-year adjusted survival rate than younger men, whereas older women have a higher 5-year survival rate than older men, so that for every 10 years of increasing age, the relative hazard change of death in women as compared with men decreases by 14.2% (95% CI, 10.1-17.5; $P < .001$).[46]

PCI

Once significant CAD is identified by angiography, there is no significant difference in the rate of revascularization, either percutaneous or surgical, between women and men (69.2% vs 72.7%; $P = 1.0$).[16] Women undergoing PCI are less likely to have multivessel disease, but more likely to have ostial disease.[45] Although attempted lesions in women have a smaller reference vessel diameter than in men (2.96 mm vs 3.06 mm; $P \leq .001$), overall angiographic characteristics tend to be similar.[44] There is a growing body of data on sex differences in the era of drug-eluting stents (DES). A single-center study evaluating consecutive patients undergoing PCI for de novo CAD during the first-year experience with DES in the United States found that women were just as likely as men to receive DES and to have a successful procedure. Women had a smaller stent diameter (2.90 mm vs 3.04 mm, $P < .0001$) and received fewer stents per case than men, although this difference may be attributed to the fact that they had fewer vessels with CAD. PCI complexity and the percentage of multivessel interventions did not differ between the sexes.[47]

Short- and long-term outcomes for women undergoing PCI have traditionally been worse than for men, but with refinements in management and techniques, outcomes now appear to be relatively similar between the sexes. The most recent update of the NHLBI Dynamic Registry, which included patients receiving DES, found no difference in in-hospital or 1 year death or myocardial infarction between women and men undergoing PCI, nor was there a sex difference in stent thrombosis rates. Still, even in the DES era, women are more likely to have recurrent angina prior to hospital discharge (15.8% vs 8.2%; $P = .0004$). Major vascular complications also remain significantly more likely in women (12.0% vs 4.2%; $P < .0001$), even after adjusting for age, body surface area, sheath size, heparin dose, glycoprotein (GP) IIb/IIIa use, and thrombolysis (OR = 3.375, 95% CI, 1.81-6.31; $P = .0001$).[47] Although women have higher rates of bleeding complications than men, they benefit similarly from GP IIb/IIIa use in terms of decreased rates of death, myocardial infarction, and urgent revascularization at 30 days.[48] Much of the excess bleeding rate in women secondary to GP IIb/IIIa use has been attributed to excessive dosing.[49] Studies comparing the long-term outcomes of women versus men in the DES era are underway.

CABG

The National Cardiovascular Network database contains data on 51,187 patients (30% women) who underwent CABG at 23 centers.[50] Consistent with other reports, as compared with the men, the women were older; had more comorbid

conditions such as diabetes, heart failure, and renal insufficiency; and had a more severe triage status and angina (as classified by the Canadian Cardiovascular Society). However, the women had less severe CAD and left ventricular dysfunction than the men. These sex differences became less marked in the older patients. The adjusted in-hospital mortality following CABG was significantly higher among women, particularly younger women (< 60 years), who were twice as likely to die as men in the same age category (age < 50, OR 2.23, 95% CI, 1.41-3.52 and age 50-59, OR 1.86, 95% CI, 1.32-2.61). Less than 30% of the mortality difference between the sexes could be explained by the higher rate of comorbid conditions in women. Women, especially younger women again, were also more likely to suffer early post-op myocardial infarction, neurologic complications, and renal failure.

Older studies found that women were less likely to receive arterial grafts,[51] although that trend appears to be improving.[52,53] Rates of complete revascularization also appear similar, with women and men receiving the same mean number of grafts. The 30-day mortality after CABG decreased significantly from 1991 to 2004, particularly in women.[53] A notable change over this time was that the rate of increase in the use of arterial grafts was greater in women than in men, although this study found that women remained consistently less likely across time to receive an arterial graft, independent of the number of diseased vessels. Long-term follow-up data show that once discharged, women have better or equivalent rates of death (HR 0.9, 95% CI, 0.83-0.98) and repeat revascularization (HR 1.0, 95% CI, 0.91-1.06), but they have higher rates of cardiac readmission (HR 1.3, 95% CI, 1.28-1.41), due to readmissions for unstable angina and congestive heart failure, but not AMI.[54]

Conclusions

The differences in IHD between women and men are broad-ranging and numerous, yet often subtle. Put together, they are creating a new paradigm by which women can be thought about and cared for as women, instead of as men. Elucidation of this paradigm will come with further research aimed specifically at investigating sex differences, as well as from studies performed on women independently of men. It is hoped that shifting paradigms and discriminating between the sexes will lead to improved outcomes for all. ■

References

1. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113:e85-e151.
2. Barrett-Connor E, Giardina EG, Gitt AK, et al. Women and heart disease: the role of diabetes and hyperglycemia. *Arch Intern Med*. 2004; 164:934-942.
3. Mosca L, Grundy SM, Judelson D, et al. Guide to preventive cardiology for women. AHA/ACC Scientific Statement Consensus panel statement. *Circulation*. 1999;99:2480-2484.
4. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ*. 2006;332:73-76.
5. Kip KE, Marroquin OC, Kelley DE, et al. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Circulation*. 2004;109: 706-713.
6. Marroquin OC, Kip KE, Kelley DE, et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from the Women's Ischemia Syndrome Evaluation. *Circulation*. 2004;109:714-721.
7. CDC. National Center for Health Statistics. Available at: http://www.cdc.gov/nchs/pressroom/04facts/obesity.htm. Accessed June 19, 2007.
8. CDC. US Physical Activity Statistics: 2003 State Demographic Data Comparison. Available at: http://apps.nccd.cdc.gov/PASurveillance/DemoCompareResultV.asp?State=0&Cat=3&Year=2003&Go=GO. Accessed June 19, 2007.
9. Hu FB, Willett WC, Li T, et al. Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med*. 2004;351: 2694-2703.
10. Li TY, Rana JS, Manson JE, et al. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. *Circulation*. 2006;113:499-506.
11. Bass KM, Newschaffer CJ, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women. *Arch Intern Med*. 1993;153:2209-2216.
12. Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA*. 2004;291:2243-2252.
13. Michos ED, Vasamreddy CR, Becker DM, et al. Women with a low Framingham risk score and

Main Points

- Every year since 1984, more women than men have died from cardiovascular disease.
- The relative risk of coronary heart disease due to diabetes is much greater in women (3-fold to 7-fold) than in men (2-fold to 3-fold), as is the adjusted relative risk of coronary heart disease death.
- In the setting of an acute coronary syndrome or acute myocardial infarction, women are significantly more likely to report multiple non–chest pain symptoms including dyspnea, nausea/vomiting, abdominal pain, back pain, neck pain, and jaw pain. Women are more likely than men to experience angina at rest, during sleep, or with mental stress.
- There is growing evidence that the Framingham risk score and the National Cholesterol Education Program Adult Treatment Panel III criteria do a poor job of appreciating risk and predicting myocardial infarction in women.
- Noninvasive tests for diagnosing coronary artery disease appear to be less accurate in women than in men. The least accurate test is exercise electrocardiography.

a family history of premature coronary heart disease have a high prevalence of subclinical coronary atherosclerosis. *Am Heart J*. 2005;150: 1276-1281.
14. Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? *J Am Coll Cardiol*. 2003;41:1475-1479.
15. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation*. 2007;115:1481-1501.
16. Anand SS, Xie CC, Mehta S, et al. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. *J Am Coll Cardiol*. 2005;46:1845-1851.
17. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. *N Engl J Med*. 1999;341:226-232.
18. Sheifer SE, Canos MR, Weinfurt KP, et al. Sex differences in coronary artery size assessed by intravascular ultrasound. *Am Heart J*. 2000; 139:649-653.
19. Khuddas MA, Sizemore BC, Bairey Merz CN, et al. Coronary atherosclerosis by intravascular ultrasound in women with suspected myocardial ischemia, but no or minimal angiographic disease: a report from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation Study (WISE) study. *J Am Coll Cardiol*. 2006;47:329A.
20. Khuddas MA, Sizemore BC, Pepine CJ, et al. Positive coronary artery remodeling in women with no or minimal angiographic disease: intravascular findings from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol*. 2006;47:331A.
21. De Bruyne B, Hersbach F, Pijls NH, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. *Circulation*. 2001;104: 2401-2406.
22. von Mering GO, Arant CB, Wessel TR, et al. 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;109:722-725.
23. Cannon RO 3rd, Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol*. 1988;61:1338-1343.
24. Johnson BD, Shaw LJ, Buchthal SD, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation*. 2004;109:2993-2999.
25. Reis SE, Holubkov R, Lee JS, et al. Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease. Results from the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol*. 1999;33:1469-1475.
26. Marroquin OC, Holubkov R, Edmundowicz D, et al. Heterogeneity of microvascular dysfunction in women with chest pain not attributable to coronary artery disease: implications for clinical practice. *Am Heart J*. 2003;145:628-635.
27. Berglund U, Wallentin L, von Schenck H. Platelet function and plasma fibrinogen and their relations to gender, smoking habits, obesity and beta-blocker treatment in young survivors of myocardial infarction. *Thromb Haemost*. 1988;60:21-24.
28. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. *Circulation*. 1996;93: 1354-1363.
29. Burke AP, Farb A, Malcom GT, et al. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. *Circulation*. 1998;97:2110-2116.
30. Goldberg RJ, O'Donnell C, Yarzebski J, et al. Sex differences in symptom presentation associated with acute myocardial infarction: a population-based perspective. *Am Heart J*. 1998;136:189-195.
31. Milner KA, Funk M, Richards S, et al. Gender differences in symptom presentation associated with coronary heart disease. *Am J Cardiol*. 1999;84:396-399.
32. Arslanian-Engoren C, Patel A, Fang J, et al. Symptoms of men and women presenting with acute coronary syndromes. *Am J Cardiol*. 2006; 98:1177-1181.
33. Pepine CJ, Abrams J, Marks RG, et al. Characteristics of a contemporary population with angina pectoris. TIDES Investigators. *Am J Cardiol*. 1994;74:226-231.
34. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med*. 1999;340:1801-1811.
35. Hashimoto M, Akishita M, Eto M, et al. Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. *Circulation*. 1995;92:3431-3435.
36. Kawano H, Motoyama T, Ohgushi M, et al. Menstrual cyclic variation of myocardial ischemia in premenopausal women with variant angina. *Ann Intern Med*. 2001;135:977-981.
37. Vaccarino V, Parsons L, Every NR, et al. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. *N Engl J Med*. 1999;341:217-225.
38. Wiviott SD, Cannon CP, Morrow DA, et al. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST-elevation myocardial infarction: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18) substudy. *Circulation*. 2004;109:580-586.
39. Kwok Y, Kim C, Grady D, et al. Meta-analysis of exercise testing to detect coronary artery disease in women. *Am J Cardiol*. 1999;83:660-666.
40. Marwick TH, Anderson T, Williams MJ, et al. Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. *J Am Coll Cardiol*. 1995;26:335-341.
41. Hansen CL, Crabbe D, Rubin S. Lower diagnostic accuracy of thallium-201 SPECT myocardial perfusion imaging in women: an effect of smaller chamber size. *J Am Coll Cardiol*. 1996; 28:1214-1219.
42. Taillefer R, DePuey EG, Udelson JE, et al. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. *J Am Coll Cardiol*. 1997;29:69-77.
43. Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. *JAMA*. 2002;288:3124-3129.
44. Abbott JD, Vlachos HA, Selzer F, et al. Gender-based outcomes in percutaneous coronary intervention with drug-eluting stents (from the National Heart, Lung, and Blood Institute Dynamic Registry). *Am J Cardiol*. 2007;99:626-631.
45. Argulian E, Patel AD, Abramson JL, et al. Gender differences in short-term cardiovascular outcomes after percutaneous coronary interventions. *Am J Cardiol*. 2006;98:48-53.
46. Alter DA, Naylor CD, Austin PC, Tu JV. Biology or bias: practice patterns and long-term outcomes for men and women with acute myocardial infarction. *J Am Coll Cardiol*. 2002; 39:1909-1916.
47. Thompson CA, Kaplan AV, Friedman BJ, et al. Gender-based differences of percutaneous coronary intervention in the drug-eluting stent era. *Catheter Cardiovasc Interv*. 2006;67:25-31.
48. 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, EPILOG 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: 381-386.
49. Alexander KP, Chen AY, Newby LK, et al. 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: 1380-1387.
50. Vaccarino V, Abramson JL, Veledar E, Weintraub WS. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. *Circulation*. 2002;105:1176-1181.
51. Jacobs AK, Kelsey SF, Brooks MM, et al. Better outcome for women compared with men undergoing coronary revascularization: a report from the bypass angioplasty revascularization investigation (BARI). *Circulation*. 1998;98:1279-1285.
52. Zhang Z, Weintraub WS, Mahoney EM, et al. Relative benefit of coronary artery bypass grafting versus stent-assisted percutaneous coronary intervention for angina pectoris and multivessel coronary disease in women versus men (one-year results from the Stent or Surgery trial). *Am J Cardiol*. 2004;93:404-409.
53. Humphries KH, Gao M, Pu A, et al. Significant improvement in short-term mortality in women undergoing coronary artery bypass surgery (1991 to 2004). *J Am Coll Cardiol*. 2007; 49:1552-1558.
54. Guru V, Fremes SE, Austin PC, et al. Gender differences in outcomes after hospital discharge from coronary artery bypass grafting. *Circulation*. 2006;113:507-516.