REVIEW

ANTONIO BELLASI, MD
Division of Cardiology, Department of Medicine, Emory University, Atlanta, GA; and Ospedale S. Paolo, Università degli Studi di Milano, Milano, Italy

PAOLO RAGGI, MD
Professor of Medicine, Division of Cardiology, Department of Medicine, Emory University, Atlanta, GA

C. NOEL BAIREY MERZ, MD*
Division of Cardiology, Department of Medicine, Cedars-Sinai Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA; Professor of Medicine, University of California, Los Angeles

LESLEE J. SHAW, PhD
Professor of Medicine, Division of Cardiology, Department of Medicine, Emory University, Atlanta, GA

New insights into ischemic heart disease in women

ABSTRACT

Coronary artery disease is different in women than in men in its pathogenesis, symptoms, and prognosis. Needed is a strategy for detecting and assessing coronary disease specifically in women. This review highlights recent evidence on sex differences in coronary artery disease.

KEY POINTS

Coronary artery disease is the leading cause of death in women, and more women than men die of it.

The prognosis after an acute myocardial infarction is worse in women than in men, possibly because women receive less aggressive treatment owing to atypical presentations.

Different risk factors and mechanisms of disease may be at work in women. When women with acute coronary syndromes undergo angiography, about half do not have any flow-limiting stenosis visible. Endothelial dysfunction and microvascular disease may account for ischemia in this situation.

Exercise stress electrocardiography does not appear to be as accurate in women as in men, but stress echocardiography and single-photon-emission computed tomography (SPECT) may be.

Research is needed to clarify how best to identify women at risk of coronary events and to assess those with suspected disease. Possible strategies involve measuring serum estrogen and testosterone concentrations, coronary calcium and atherosclerotic burden, vascular reactivity, and functional capacity.

ISCHEMIC HEART DISEASE appears to be substantially different in women than in men, and it is time to devise sex-specific strategies for detecting and assessing it. Compared with men, women have:

- As great a prevalence of coronary disease, at least in their older years
- A higher death rate from coronary disease
- Worse outcomes after acute coronary events
- Different pathophysiologic mechanisms of coronary disease
- Different presentations and risk factors.

Herein we summarize the current understanding of ischemic heart disease in women and challenges in detecting it.

THE LEADING CAUSE OF DEATH IN WOMEN

Coronary artery disease is the leading cause of death and disability in women in Western countries, responsible for nearly 250,000 deaths in women annually in the United States.[1] The US Centers for Disease Control and Prevention attributes 38% of deaths in women to coronary artery disease, compared with only 22% to cancer.[2]

The onset of disease is about 10 years later in women than in men. However, the preva-

*Dr. Bairey Merz has indicated serving as a consultant for the American College of Cardiology Foundation, AusAm, Bayer, CardioVasc Clin Trials, Dunn Group, Kieris Solutions, Ideon-Fujisawa, Pfizer, Merck, KOS, LABiomed, National Institutes of Health (NIH Study Section), CV Therapeutics, Rodale Press, Sanofi-Aventis, University of Pittsburgh, and VHA; lecturing for the American Heart Association, Charlotte Carolinas Healthcare System, Mayo Clinic, Institute for Medical Education of the American College of Cardiology, Rush University, Merck, National Youth Leadership Forum, Gacheon Medical School (Korea), Spanish Cardiac Society, Nuclear Cardiology, and Wake Forest University; and owning stock in Boston Scientific, Eli Lilly, Johnson and Johnson, and Medtronic corporations.

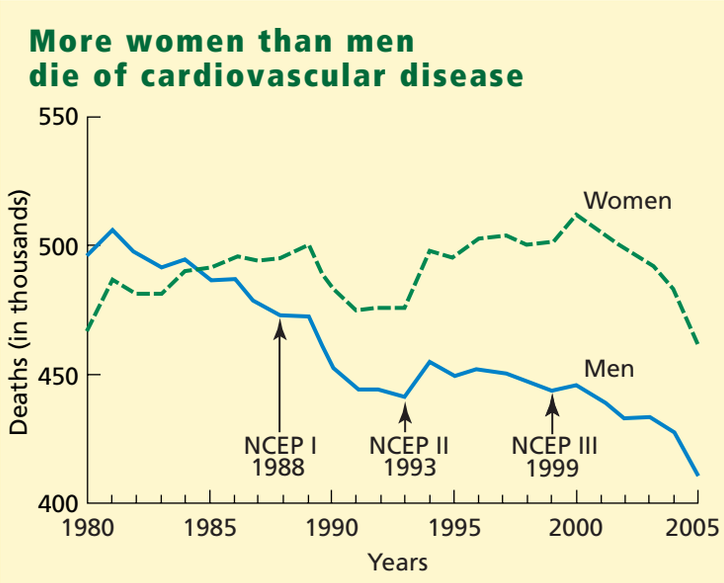


FIGURE 1. Cardiovascular disease deaths in the United States from 1979 through 2005 in women and men, highlighted by the introduction of new guidelines for cholesterol lowering from the National Cholesterol Education Panel (NCEP) I, II, and III.

FROM ROSAMOND W, FLEGAL K, FRIDAY G, ET AL. HEART DISEASE AND STROKE STATISTICS—2007 UPDATE. A REPORT FROM THE AMERICAN HEART ASSOCIATION STATISTICS COMMITTEE AND STROKE STATISTICS SUBCOMMITTEE. CIRCULATION 2007; 115:E69–E171

lence in women increases rapidly after menopause and approaches that of men in the seventh decade of life.[3–5]

WOMEN HAVE A WORSE PROGNOSIS

Advances in the diagnosis and treatment of coronary artery disease have reduced the cardiovascular death rate by 35% to 50% over the past decades, but the reduction among women has not matched that among men (FIGURE 1).[6,7] Furthermore, although women have a lower incidence of acute coronary syndromes, they have a worse prognosis after an acute myocardial infarction than do men,[8–10] with a mortality rate about twice as high (hazard ratio = 2.1; 95% confidence interval [CI] 1.1–3.9).[10]

WOMEN ARE TREATED DIFFERENTLY

One possible explanation for the poor cardiovascular prognosis among women is gender bias in the use of medical and interventional therapies.

Daly et al[10] recently reported that women with stable angina were less likely than men to undergo exercise electrocardiography (odds ratio = 0.81; 95% CI 0.69–0.95) or coronary angiography (odds ratio = 0.59; 95% CI 0.48–0.72). Similarly, medical therapy (antiplatelet agents and statins) and revascularization procedures were used significantly less in women than in men, both at the time of the initial visit and 1 year later. Thus, only the most severely affected women underwent aggressive diagnostic testing and were treated.

CORONARY DISEASE IS DIFFERENT IN WOMEN

Compared with men, more women with coronary artery disease have atypical manifestations, and fewer of them have flow-limiting coronary stenosis at angiography.[11–13]

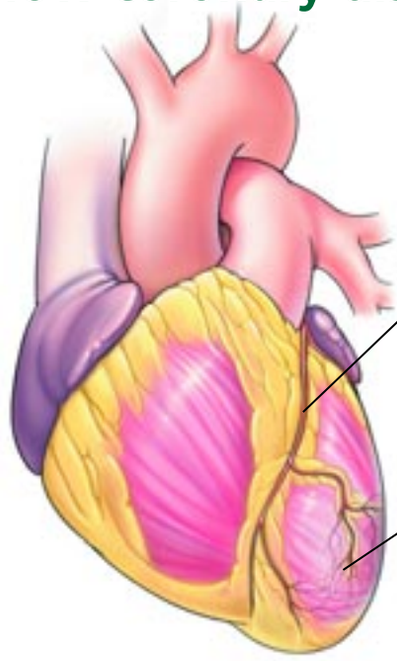
Less flow-limiting stenosis

Although donor hearts for cardiac transplantation show a similar prevalence of atherosclerotic lesions no matter if they come from male or female donors,[14] numerous angiographic studies have shown less obstructive epicardial coronary artery disease in women than in their male counterparts.[11–13] These differences were first reported several decades ago in the Coronary Artery Surgery Study registry and have persisted in current angiographic series.[15,16]

In the Women's Ischemia Syndrome Evaluation (WISE) study,[17] nearly 60% of women who underwent angiography to evaluate chest pain or an abnormal stress test result did not have a flow-limiting stenosis (defined as 50% or greater stenosis in more than one major epicardial coronary artery).[13] Nevertheless, even without luminal narrowing, their symptoms persisted or worsened, and they suffered a worse outcome during the ensuing 4 to 5 years when compared with expected event rates in similarly aged women in the general population.[13] Most of them also had stress test abnormalities, suggesting that their myocardial ischemia might be the result of microvascular disease or endothelial dysfunction, or both.[18]

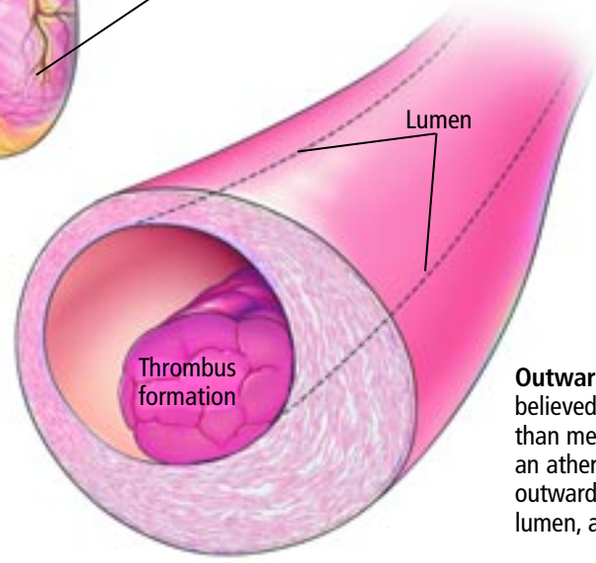
Of 375,886 patients (45% women) who underwent coronary angiography in the American College of Cardiology's National Cardiovascular Registry, 12% to 35% of women

How coronary disease is different in women



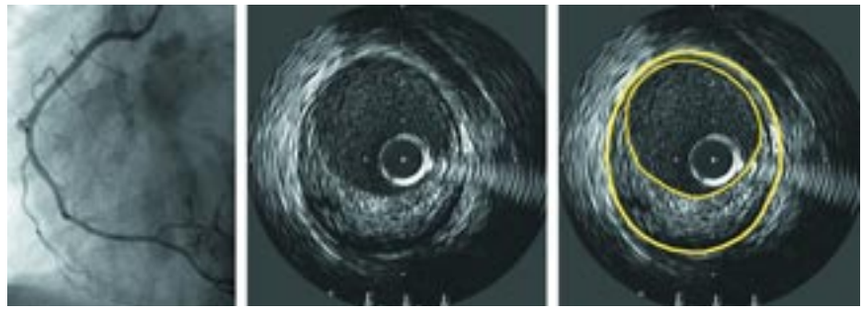
Smaller coronary arteries
Women have smaller coronary arteries than men, even after correcting for body surface area. Thus, they might be more seriously affected than men by anything that further reduces the diameter of the artery, be it stenosis or endothelial dysfunction.

Endothelial dysfunction of smaller arteries and arterioles can partly explain atypical symptoms in women. The endothelial dysfunction in these smaller blood vessels might be responsible for myocardial ischemia even in the absence of flow-limiting stenosis in epicardial coronary arteries.



Plaque erosion with subsequent thrombus formation is twice as likely to be the precipitating event in women than in men. (More men have plaque rupture.)

Outward (positive) remodeling is believed to be more common in women than men. Outward remodeling refers to an atherosclerotic lesion that protrudes outward rather than impinging on the lumen, as in "negative" remodeling.



Although many women with chest pain seem to have no obstructive stenosis on coronary angiography (left), intravascular ultrasonography reveals that lesions are indeed present but do not impinge on the lumen (middle and right images).

CCF
Medical Illustrator: Joseph Pangrace ©2007

FIGURE 2

TABLE 1

Effect of menopause on risk factors for cardiovascular disease

Lipid levels worsen
- Total cholesterol levels increase
- High-density lipoprotein cholesterol levels decrease

Prevalence increases
- Hypertension
- Metabolic syndrome

Outcome risk increases
- Triglycerides
- Diabetes mellitus
- Obesity (body mass index ≥ 30)
- Abdominal obesity (waist circumference > 35 inches)

ADAPTED FROM SHAW LJ, BAIREY MERZ CN, PEPINE CJ, ET AL. INSIGHTS FROM THE NHLBI-SPONSORED WOMEN'S ISCHEMIA SYNDROME EVALUATION (WISE) STUDY: PART I: GENDER DIFFERENCES IN TRADITIONAL AND NOVEL RISK FACTORS, SYMPTOM EVALUATION, AND GENDER-OPTIMIZED DIAGNOSTIC STRATEGIES. J AM COLL CARDIOL 2006; 47:S4–S20

and 32% to 65% of men ages 50 to 80 years presented with a flow-limiting stenosis ($P < .0001$). Similarly, flow-limiting stenoses are found in only about half of women undergoing cardiac catheterization for acute coronary artery syndromes.[13]

In contrast, rates of obstructive disease are similar for elderly women and men.[19]

A reason for the poor prognosis in women may be gender bias in treatment

Smaller coronary arteries

Women have smaller coronary arteries than men, even after correcting for body surface area.[20,21] Thus, they might be more seriously affected than men by anything that further reduces the diameter of the artery, be it stenosis or endothelial dysfunction.

More outward remodeling

Although men and women have a similar amount of coronary plaque and calcification,[22] pathology studies and intravascular ultrasonography reveal that outward ("positive") remodeling is more common in women than in men.[23] (Outward remodeling refers to atherosclerotic lesions that protrude outward (FIGURE 2) rather than impinging on the lumen, as in "negative" remodeling.)

Plaque erosion as the precipitating event

Another important sex difference is the mechanism of plaque disruption as the inciting event in acute coronary syndromes. Arbustini et al[24] found that the precipitating event in women was twice as likely as in men to be plaque erosion with subsequent thrombus formation (37% for women vs 18% for men). In contrast, more men presented with plaque rupture (82% for men vs 63% for women).[24]

More endothelial dysfunction

The atypical symptoms and worse prognosis for women with symptoms might be partly explained by endothelial dysfunction—inability of the arteries and arterioles to dilate, due to inability of the endothelium to produce nitric oxide, a relaxant of vascular smooth muscle. Dysfunctional endothelium within smaller arteries and arterioles might be responsible for myocardial ischemia even in the absence of flow-limiting stenosis in an epicardial coronary artery.[25–28] The WISE group has recently reviewed this topic in detail.[18]

Several studies demonstrated that impaired endothelium-dependent vasomotor function of the coronary and brachial arteries is associated with long-term risk of cardiovascular events in women.[25–28]

These preliminary findings require substantial validation as well as models to define a causal pathway between vascular dysfunction and cardiac symptom provocation.

CORONARY DISEASE IS DIFFICULT TO EVALUATE IN WOMEN

Evaluation of coronary artery disease in women is complicated by a greater burden of symptoms in stable chest pain syndromes, more functional disability,[2,19] and a more frequent atypical presentation than in men.[19] Furthermore, traditional tests for obstructive coronary artery disease are less sensitive and specific in female patients.[12,29,30]

Women may have atypical or no prodromal symptoms

Although typical anginal symptoms appear to be equally accurate in identifying underlying coronary artery disease in men and women with acute coronary syndromes, prodromal symptoms in women are often atypical and

nonspecific and include fatigue, sleep disturbance, and dyspnea.[31]

Women with more frequent chest pain symptoms, including those associated with stressful circumstances and those occurring during activities of daily living or household tasks, should receive more intensive evaluation. Symptoms occurring at rest are also classified as more unstable. Additionally, women may accommodate their physical activity level to avert symptom provocation. Thus, clinicians should inquire about changes in activities of daily living when discussing a woman's symptom burden.

A recent National Heart, Lung, and Blood Institute consensus conference reported that 65% of women with coronary artery disease did not have typical angina.[13] Additionally, up to 50% of the women presenting with an acute myocardial infarction report no prior chest pain.[32] Similarly, more women than men with sudden cardiac death had no symptoms beforehand.[1]

Symptoms at presentation are more similar for older women and men.[33]

Traditional risk factors differ

Multivariable predictive models have revealed that traditional risk factors account for up to 70% of the variance in estimating cardiovascular events,[34] but this explanatory variation is less in women than in men.[35] In fact, substantial sex differences exist in the prevalence of traditional cardiovascular risk factors and in the clinical outcomes associated with them. For example:

- Smoking and hypertension are more prevalent among men.[1] When present, these factors generally pose the same degree of risk in women and men.
- Elevated triglyceride levels and low levels of high-density lipoprotein (HDL) cholesterol are more prominent and more potent independent risk factors for ischemic heart disease in women.[5,36] (Elevated levels of total cholesterol and low-density lipoprotein cholesterol pose a similar relative risk in women and men.[2,5])
- Cardiovascular mortality rates are nearly three times higher in diabetic women than in diabetic men.[37–39]

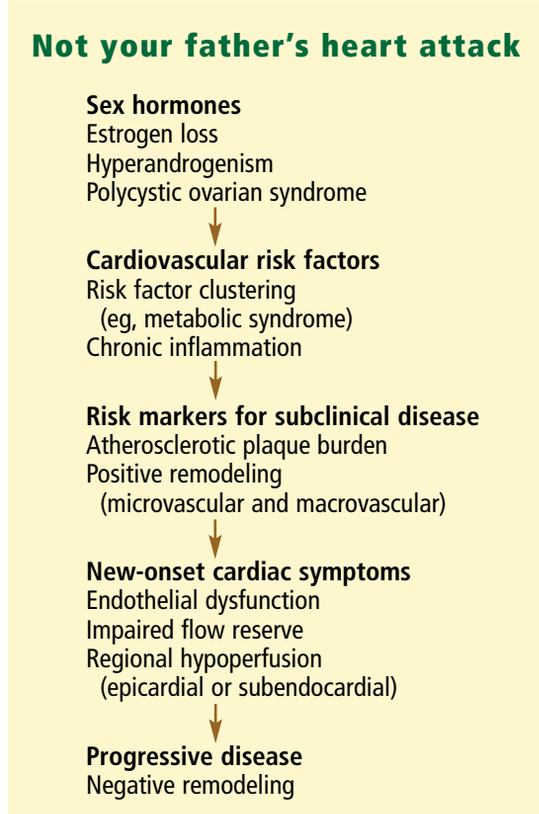


FIGURE 3. Theoretical model of risk factors, subclinical disease risk markers, symptoms, and progressive disease states in women.

Novel risk factors

Several novel and evolving cardiovascular risk factors suggest that more women are at risk than are currently identified by routine clinical practice.

Abdominal obesity. Women with an androidal shape (ie, waist circumference than hip circumference, as opposed to the common "pear" shape of women) have an increased risk of coronary artery disease. In women, metabolically active abdominal fat[40] leads more frequently to insulin resistance[40,41] and to higher levels of C-reactive protein, a generalized measure of inflammation[2,11,42] than in nonobese women.

Metabolic syndrome. A growing body of evidence reveals that metabolic dysfunction plays a key role in placing a woman at risk for coronary artery disease and cardiac events.

Cardiovascular mortality rates are nearly 3 times higher in diabetic women than in diabetic men

The WISE study revealed that women with the metabolic syndrome had a higher risk of death and major cardiovascular events than those without metabolic syndrome or with normal metabolic status, and that this risk was independent of body mass index.[43]

Low estrogen levels would logically seem to be a risk factor in women, in view of the greater prevalence of heart disease in women after menopause.[2,3] Furthermore, certain traditional risk factors worsen or become prognostically more important after menopause (TABLE 1). However, estrogen replacement therapy does not seem to reduce cardiovascular risk in postmenopausal women with[44,45] or without[46] existing coronary artery disease.

Elevated testosterone levels and polycystic ovary syndrome (PCOS). There is a strong link between PCOS and diabetes and the metabolic syndrome; however, the link between altered metabolism and increased coronary artery disease is less well defined.

Elevated C-reactive protein. As women have higher levels of inflammatory markers (eg, C-reactive protein) than men after the approximate age of 12 years, this milieu combined with a clustering of risk factors appears to be more atherogenic and may result in greater deposition of atherosclerotic plaque.[47]

Half of women with acute MI have no prior chest pain symptoms

Recently, a global risk score was devised that includes the C-reactive protein level.[48] This risk score is similar to the Framingham Risk Score but adds C-reactive protein to the equation to estimate 10-year risk of cardiac death or myocardial infarction. This score, called the Reynolds Risk Score, resulted in substantial improvements in detecting risk in women, far better than the Framingham Risk Score alone.

Toward a new model of heart disease in women

Taken together, these findings emphasize the need for a better understanding of the sex-specific pathophysiology of coronary artery disease. We would like to propose a model of heart disease in women (FIGURE 3), emphasizing that it is a hypothesis that requires validation and that must be viewed within the limited scope and depth of current evidence. In our view, altered levels of sex hormones exacerbate or lead to other cardiovascular risk factors in women. Atherosclerosis develops, but often with a pattern of outward remodeling. Acute coronary events may be due to endothelial dysfunction or to erosion and thrombosis of atherosclerotic plaques.

NEEDED: A BETTER WAY TO DETECT SUBCLINICAL DISEASE

Newer tests for atherosclerosis (eg, coronary artery calcium screening) and testing of endothelial function have some advantages over traditional risk assessment algorithms in women.

Coronary calcium screening. In 4,191 women and 6,186 men without symptoms who underwent electron beam computed tomography, coronary calcification was associated with a higher risk of death in women than in men at each level of calcification. At 5 ± 3.5 years of follow-up, 98.4% of women without coronary artery calcification were still alive, compared with 80% of women with extensive coronary calcification (ie, a score > 1,000, $P < .001$). Of note, calcium screening added incremental prognostic information over and above traditional risk factors for death from any cause in both women and men.[49]

Endothelial function is assessed invasively or noninvasively.

Invasive assessment of endothelial function is determined by injecting acetylcholine into the coronary or brachial arteries. This testing has a demonstrated value in coronary artery disease assessment. An impaired response to an acetylcholine challenge has been shown to add independently to the prediction of death even after adjustment for confounders in women with and without epicardial coronary artery disease.

Noninvasive detection of endothelial dysfunction is measured using brachial artery reactivity testing.

Impaired coronary or brachial endothelial function is associated with reduced cardiovascular event-free survival.[25–28] Bairey Merz et al[19] summarized 15 studies of coronary and peripheral testing for endothelial dysfunction. The risk of cardiovascular events was 10 times higher (95% CI 7.8–12.8) if the test results were abnormal.

Furthermore, restoration of endothelial function is associated with improved outcomes. In a study of 400 hypertensive postmenopausal women, those who had an improvement in brachial flow-mediated vasodilatation of more than 10% in response to antihypertensive treatment had a rate of cardiovascular events that was one seventh that of women who had no response to treatment.[27]

These findings are important, given that few therapies are available for women with vascular dysfunction. Additional research is needed to devise targeted treatment strategies for women.

ASSESSING ISCHEMIC DISEASE: WHAT WORKS, WHAT DOESN'T?

Stress electrocardiography may be less useful in women

Several studies found that exercise stress electrocardiography is of limited value in assessing inducible ischemia and risk in women.[12,29,30] The reason often cited is that women cannot exercise as long as men and are therefore more likely to have an inconclusive study. However, guidelines still support its use as a diagnostic test for women with a normal resting 12-lead electrocardiogram who can perform maximal exercise.[50]

A randomized trial is currently comparing exercise electrocardiography and exercise single-photon emission computed tomography (SPECT) for risk prediction.

Decreased functional capacity may predict bad outcomes

Recent evidence suggests that postmenopausal women have a greater decline in their ability to perform physical activity than men do,[51] leading to a greater functional severity of ischemic heart disease in women upon presentation. Reduced functional capacity may predict bad outcomes.

The WISE investigators used a simple 12-item questionnaire called the Duke Activity Status Index (DASI) to estimate functional capacity.[52] Women whose responses indicated they could not achieve 4.7 metabolic equivalents (METs) of work in activities of daily living had a risk of death or nonfatal myocardial infarction 3.7 times higher than that of women reporting a better functional capacity.[52] Almost two thirds of the cardiovascular events in the WISE cohort occurred in women who had an estimated capacity of less than 4.7 METs, and for every 1-MET increase in the DASI, the risk of major cardiovascular events decreased by 8% (hazard ratio = 0.92; 95% CI 0.85–0.99; P = .02). Low DASI scores correlated with impaired coronary flow reserve, perhaps due to a sedentary lifestyle in these women.[53]

Stress echocardiography and SPECT may be good options in women

Large studies, including some that included more than 1,000 patients, indicate that stress echocardiography and SPECT imaging are as

Subendocardial perfusion is diminished in metabolic syndrome

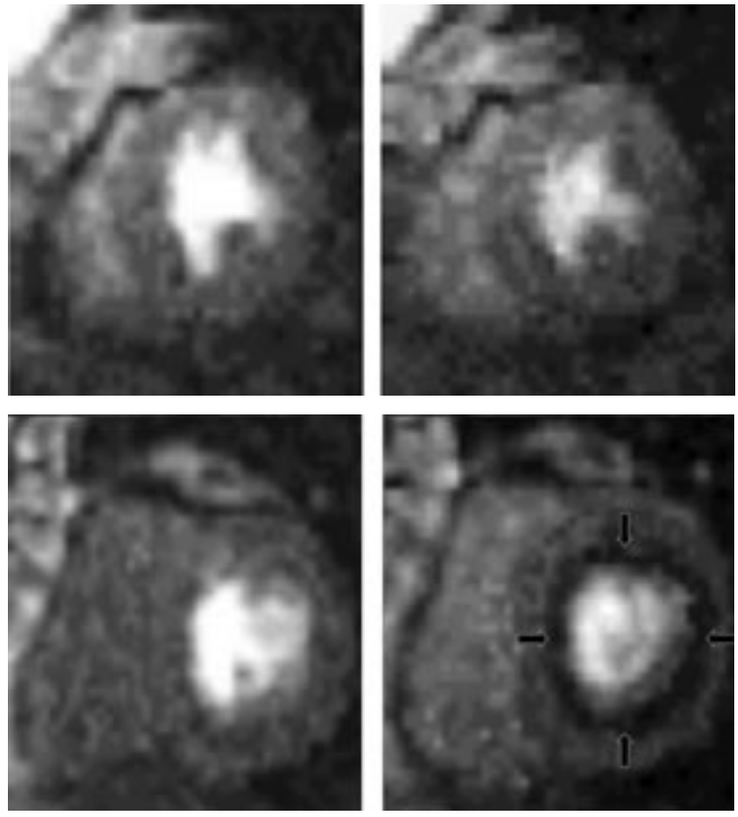


FIGURE 4. Top, cardiovascular magnetic resonance imaging in a control subject at rest (left) and during stress (right). **Bottom,** images in a patient with syndrome X at rest (left) and during stress (right)

FROM 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; 346:1948–1953.

accurate in women as in men,[49,54–56] and a recent statement from the American Heart Association includes recommendations for cardiac imaging in women.[50]

Shaw et al[54] performed a meta-analysis and estimated that women who had high-risk results on stress echocardiography or SPECT had a nearly 10-fold higher risk of cardiovascular death or myocardial infarction compared with women who had a low-risk or negative scan.

Metz et al[55] compared the rates of cardiac death or myocardial infarction in women and men with negative test results. Among patients with no inducible wall-motion abnormalities on exercise echocardiography, annual rates of cardiac events were 0.8% in women and 1.2% in men. Among patients with normal perfusion scans on exercise SPECT imaging, annual rates of cardiac events were 0.3% in women and 0.8% in men.

Therefore, both echocardiography and SPECT are highly accurate in predicting risk, with rates of cardiovascular events of less than 1% in patients with normal studies, increasing by as much as 10 times with a markedly abnormal study. Given this high rate of events, most clinical guidelines recommend referring patients for coronary angiography if they have a markedly abnormal scan. However, physicians should carefully exclude technical artifacts, especially in obese women, in whom the image quality may be impaired in both echocardiography and SPECT.

Outward remodeling could hide extensive atherosclerosis in coronary arteries

Which women should get an imaging test?

Previous guidelines recommended exercise electrocardiography in women with suspected ischemic heart disease, to be followed by selective cardiac imaging if the results are indeterminate or abnormal. Now, the American Heart Association[50] has revised these recommendations to identify women at risk who would benefit from initial testing with a cardiac imaging test. It now recommends the use of echocardiography or SPECT as an initial test for evaluation of suspected ischemic heart disease in women with symptoms and any of the following:

- Diabetes
- Functional impairment (ie, who cannot achieve at least 5 METs of exercise on a treadmill or stationary bicycle)
- Abnormal resting electrocardiogram.

Other women to receive an imaging test include those who present for evaluation of chest pain symptoms or their equivalents and who are at intermediate risk of coronary disease. This latter group would largely consist of women older than 55 years and those with multiple cardiac risk factors.

Intravascular ultrasonography, coronary reactivity, magnetic resonance imaging

If a woman experiences ischemic symptoms but has no flow-limiting stenoses on standard angiography, intravascular ultrasonography may document atherosclerosis within the arterial wall (FIGURE 2).

Additionally, with significant positive remodeling, impaired coronary flow reserve or endothelial dysfunction may occur more frequently and be the cause of a woman's symptoms. Testing for endothelial function in women without obstructive coronary artery disease at angiography is not routine.

Recently, in a small series, Panting et al[57] noted that women with symptoms and no obstructive coronary artery disease may be manifesting subendocardial ischemia (the initial manifestation of ischemia) as detected by cardiovascular magnetic resonance imaging (FIGURE 4). Thus, clinicians should verify that "true" ischemia may be occurring in women presenting with symptoms, even for those without obstructive coronary disease. True ischemia or symptoms may be the result of increased demand and impaired coronary flow reserve resulting in subendocardial ischemia.

We hope that additional clinical research will be undertaken to more clearly define the role of intravascular ultrasonography, magnetic resonance imaging, and testing of vascular function in risk detection in women and as a preamble to devising sex-specific targeted therapeutic strategies.

WHAT SHOULD DOCTORS DO NOW?

As strategies evolve over the next few years, physicians should consider the symptom burden in women as well as their functional abilities and quality of life as markers of the global burden of risk in females. Strategies aimed at diagnosing and treating a woman's athero-

sclerotic disease burden, with or without obstructive coronary artery disease, will be the aim of future diagnostic and therapeutic strategies aimed at risk reduction for women.

While we await this evidence, physicians should treat all women to optimal goals for risk factors and should not ignore cardiac symptoms, given credible evidence of ischemia, vascular dysfunction, or some other marker of atherosclerosis. Although treatment strategies are ill-defined for these women, at a minimum, focused risk-factor modification should be a short-term goal for women with nonobstructive coronary artery disease. ■

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. **Shaw LJ, Bairey Merz CN, Pepine CJ, et al.** Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol 2006; 47:S4–S20.
3. **Bairey Merz N, Bonow RO, Sopko G, et al.** Women's Ischemic Syndrome Evaluation: current status and future research directions: report of the National Heart, Lung and Blood Institute workshop: October 2–4, 2002: executive summary. Circulation 2004; 109:805–807.
4. **Mosca L, Appel LJ, Benjamin EJ, et al.** Evidence-based guidelines for cardiovascular disease prevention in women. Circulation 2004; 109:672–693.
5. **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; 111:383–390.
6. **Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V.** AHA/ACC scientific statement: assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. J Am Coll Cardiol 1999; 34:1348–1359.
7. **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. J Am Coll Cardiol 1999; 33:1751–1755.
8. **Vaccarino V.** Angina and cardiac care: are there gender differences, and if so, why? Circulation 2006; 113:467–469.
9. **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.
10. **Daly C, Clemens F, Lopez Sendon JL, et al.** Gender differences in the management and clinical outcome of stable angina. Circulation 2006; 113:490–498.
11. **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 and Blood Institute workshop: October 2–4, 2002: Section 5: gender-related risk factors for ischemic heart disease. Circulation 2004; 109:e56–58.
12. **Merz NB, Johnson BD, Kelsey PSF, et al.** Diagnostic, prognostic, and cost assessment of coronary artery disease in women. Am J Manag Care 2001; 7:959–965.
13. **Pepine CJ, Balaban RS, Bonow RO, et al.** Women's Ischemic Syndrome Evaluation: current status and future research directions: report of the National Heart, Lung and Blood Institute workshop: October 2–4, 2002: section 1: diagnosis of stable ischemia and ischemic heart disease. Circulation 2004; 109:e44–e46.
14. **Tuzcu EM, Berkalp B, De Franco AC, et al.** The dilemma of diagnosing coronary calcification: angiography versus intravascular ultrasound. J Am Coll Cardiol 1996; 27:832–838.
15. **Chaitman BR, Bourassa MG, Davis K, et al.** Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). Circulation 1981; 64:360–367.
16. **Enriquez-Sarano M, Klodas E, Garratt KN, Bailey KR, Tajik AJ, Holmes DR Jr.** Secular trends in coronary atherosclerosis—analysis in patients with valvular regurgitation. N Engl J Med 1996; 335:316–322.
17. **Merz CN, Kelsey SF, Pepine CJ, et al.** The Women's Ischemia Syndrome Evaluation (WISE) Study: protocol design, methodology and feasibility report. J Am Coll Cardiol 1999; 33:1453–1461.
18. **Quyyumi AA.** Women and ischemic heart disease: pathophysiologic implications from the Women's Ischemia Syndrome Evaluation (WISE) study and future research steps. J Am Coll Cardiol 2006; 47:S66–S71.
19. **Bairey Merz CN, Shaw LJ, Reis SE, et al.** Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol 2006; 47:S21–S29.
20. **Dodge JT Jr, Brown BG, Bolson EL, Dodge HT.** Lumen diameter of normal human coronary arteries. Influence of age, sex, anatomic variation, and left ventricular hypertrophy or dilation. Circulation 1992; 86:232–246.
21. **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.
22. **Kornowski R, Lansky AJ, Mintz GS, et al.** Comparison of men versus women in cross-sectional area luminal narrowing, quantity of plaque, presence of calcium in plaque, and lumen location in coronary arteries by intravascular ultrasound in patients with stable angina pectoris. Am J Cardiol 1997; 79:1601–1605.
23. **Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R.** Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation 1998; 97:2110–2116.
24. **Arbustini E, Dal Bello B, Morbini P, et al.** Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart 1999; 82:269–272.
25. **Bonetti PO, Lerman LO, Lerman A.** Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003; 23:168–175.
26. **Verma S, Buchanan MR, Anderson TJ.** Endothelial function testing as a biomarker of vascular disease. Circulation 2003; 108:2054–2059.
27. **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; 40:505–510.
28. **Halcox JP, Schenke WH, Zalos G, et al.** Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002; 106:653–658.
29. **Detrano R, Froelicher VF.** Exercise testing: uses and limitations considering recent studies. Prog Cardiovasc Dis 1988; 31:173–204.
30. **Lewis JF, McGorray SP, Pepine CJ.** Assessment of women with suspected myocardial ischemia: review of findings of the Women's Ischemia Syndrome Evaluation (WISE) Study. Curr Womens Health Rep 2002; 2:110–114.
31. **Milner KA, Funk M, Arnold A, Vaccarino V.** Typical symptoms are predictive of acute coronary syndromes in women. Am Heart J 2002; 143:283–288.

32. **McSweeney JC, Cody M, O'Sullivan P, Elberson K, Moser DK, Garvin BJ.** Women's early warning symptoms of acute myocardial infarction. Circulation 2003; 108:2619–2623.
33. **Rosengren A, Wallentin L, Gitt KA, Behar S, Battler A, Hasdai D.** Sex, age, and clinical presentation of acute coronary syndromes. Eur Heart J 2004; 25:663–670.
34. **Greenland P, Knoll MD, Stamler J, et al.** Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA 2003; 290:891–897.
35. **Sharrett AR, Ballantyne CM, Coady SA, et al.** Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2001; 104:1108–1113.
36. **Hokanson JE, Austin MA.** Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996; 3:213–219.
37. **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; 162:1737–1745.
38. **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; 265:627–631.
39. **Raggi P, Shaw LJ, Berman DS, Callister TQ.** Prognostic value of coronary artery calcium screening in subjects with and without diabetes. J Am Coll Cardiol 2004; 43:1663–1669.
40. **Lamon-Fava S, Wilson PW, Schaefer EJ.** Impact of body mass index on coronary heart disease risk factors in men and women. The Framingham Offspring Study. Arterioscler Thromb Vasc Biol 1996; 16:1509–1515.
41. **Carey VJ, Walters EE, Colditz GA, et al.** Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. Am J Epidemiol 1997; 145:614–619.
42. **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; 98:731–733.
43. **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.
44. **Hulley S, Grady D, Bush T, et al.** Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280:605–613.
45. **Grady D, Herrington D, Bittner V, et al, for the HERS Research Group.** Cardiovascular outcomes during 6–8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002; 288:49–57.
46. **Writing Group for the Women's Health Initiative Investigators.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's health Initiative Randomized Controlled Trial. JAMA 2002; 288:321–333.
47. **Onat A, Avci GS, Barlan MM, Uyarel H, Uzunlar B, Sansoy V.** Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. Int J Obes Relat Metab Disord 2004; 28:1018–1025.
48. **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; 297:611–619.
49. **Raggi P, Shaw LJ, Berman DS, Callister TQ.** Gender-based differences in the prognostic value of coronary calcification. J Womens Health (Larchmt) 2004; 13:273–283.
50. **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; 111:682–696.
51. **Handberg E, Johnson BD, Arant CB, et al.** Impaired coronary vascular reactivity and functional capacity in women: results from the NHLBI Women's Ischemia Syndrome Evaluation (WISE) Study. J Am Coll Cardiol 2006; 47:S44–S49.
52. **Shaw LJ, Olson MB, Kip K, et al.** The value of estimated functional capacity in estimating outcome: results from the NHBLI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study. J Am Coll Cardiol 2006; 47:S36–S43.
53. **Gierach GL, Johnson BD, Bairey Merz CN, et al.** Hypertension, menopause, and coronary artery disease risk in the Women's Ischemia Syndrome Evaluation (WISE) Study. J Am Coll Cardiol 2006; 47:S50–S58.
54. **Shaw LJ, Vasey C, Sawada S, Rimmerman C, Marwick TH.** Impact of gender on risk stratification by exercise and dobutamine stress echocardiography: longterm mortality in 4,234 women and 6,898 men. Eur Heart J 2005; 26:447–456.
55. **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; 49:227–237.
56. **Mieres JH, Shaw LJ, Hendel RC, et al.** Consensus statement: American Society of Nuclear Cardiology: task force on women and coronary artery disease—the role of myocardial perfusion imaging in the clinical evaluation of coronary artery disease in women. J Nucl Cardiol 2003; 10:95–101.
57. **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; 346:1948–1953.

ADDRESS: *Leslee J. Shaw, PhD, Professor of Medicine, Emory University School of Medicine, 1256 Briarcliff Road NE, Atlanta, GA 30306; e-mail leslee.shaw@emory.edu.*