

## Diagnostic, Prognostic, and Cost Assessment of Coronary Artery Disease in Women

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Women with obstructive coronary disease appear to be more challenging diagnostically and suffer a more adverse prognosis than men. More than one half of women with symptoms of ischemic heart disease have no obstructive coronary artery disease at coronary angiography, yet these women frequently have persistent symptom-related disability and consume large amounts of healthcare resources. Prior evidence has been limited regarding effective diagnostic strategies for the assessment of symptomatic women. The current report synthesizes existing evidence on diagnostic testing in women, including research from the ongoing National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. In addition to recent published evidence (drawn from much larger cohorts of women) that stress echocardiography and nuclear imaging are similar in their ability to risk-stratify women, the WISE study is exploring new pathophysiological mechanisms of microvascular dysfunction in women. An unfolding body of evidence suggests that as tests become more diagnostically and prognostically accurate, the process will become more cost efficient. The results from a growing number of large observational series and National Institutes of Health-sponsored studies are expected to be the foundation for cost-effective diagnostic and prognostic strategies for the approximately 5 million women who undergo evaluation for coronary disease annually.

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**W**omen with symptoms suggestive of obstructive coronary disease appear to be more challenging diagnostically and suffer a more adverse prognosis than men.<sup>1</sup> More than one half of women with chest pain symptoms have no obstructive coronary disease at coronary angiography despite frequent evidence of provocative ischemia.<sup>1</sup> The majority of women with chest pain and discomfort have persistent symptom-related disability and continue to consume large amounts of healthcare resources, in part because

the pathophysiology of ischemic heart disease in women is poorly understood and because accurate diagnostic and effective treatment strategies are underdeveloped.

### Diagnosis of Obstructive Coronary Disease in Women: Symptom Assessment

The common perception is that chest pain related to exertion or occurring in the postprandial state is "typical" of ischemic heart disease. Patients who present with typical chest pain symptoms generally are evaluated with 1 of an array of provocative stress tests in cardiology today. This definition of traditional angina was derived from predominantly male populations and is less reliable in female cohorts.<sup>2</sup>

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Women more often present with “atypical” chest pain symptoms that are nonexertional and have various components to their history, including shortness of breath, dizziness, fainting, or arm/shoulder pain. These are perhaps more non-specific indicators that lead to less precise and aggressive evaluation of at-risk women.

Comparative results between traditional anginal pain assessment developed primarily in men<sup>3</sup> and the newly developed Women’s Ischemia Syndrome Evaluation (WISE) female angina assessment for identification of obstructive coronary disease reveal important differences in symptom quality (Johnson BD, Bairey Merz CN, Kelsey SF, et al, submitted for publication) (Table). The female angina model is 1.8- to 2.3-fold more likely to estimate the probability of at least 50% coronary stenosis in 1 or more epicardial coronary arteries than the traditional angina model, after controlling for other qualitative pain descriptors. These results suggest that traditional predictive models developed from studies of predominantly male populations may not be optimal in women.

**Prognosis in Ischemic Heart Disease in Women: Coronary Angiography and Symptoms**

Contrary to popular beliefs, our understanding of the prognosis for women presenting with symptoms or signs of myocardial ischemia is incomplete. A review of published reports on 7132 patients (54%

women) who underwent cardiac catheterization without stress testing revealed consistent results for the estimation of prognosis.<sup>4-13</sup> Survival was better (97%) in patients with nonobstructive coronary disease than in those with obstructive coronary disease (90%). Because the average 3-year follow-up in these studies is too short to account for the known delay in clinical presentation of women with atherosclerosis compared with men, and because of the longevity experienced by women, studies with longer follow-up times and with women as reference control subjects are needed. In 1 recent study of 164 patients (55% women) with a median follow-up of 12 years, there was no relationship between angina-like chest pain and subsequent coronary events.<sup>14</sup>

These observations suggest that although coronary angiography is an important predictor of cardiac events, prognosis varies widely and is poorly quantified by the anatomical angiographic disease. The functional significance of the stenoses is unknown in these prior angiographic studies, because stress testing was not used. Further studies suggest that coronary angiography, the reference standard, fails to assess the physiologic significance of coronary stenosis and therefore may be a suboptimal prognostic test. Reports have demonstrated the inadequacy of visually interpreted angiograms to determine the physiologic significance of many coronary stenoses.<sup>15</sup> Although patients with coronary stenosis of more than 75% have clear-cut reductions in coronary reserve, there is marked variation in flow reserve values with lesions of 50% to 70%. Studies performed predominantly in men suggest that noninvasive imaging can identify those lesions that are physiologically significant and help predict those patients at risk for subsequent cardiac events. Also of concern is the finding, again from predominantly male populations, that minimal stenoses (<50%) account for the majority of acute cardiac events. Although these issues have not yet been studied specifically in women, they may be particularly relevant for women because biologic reproductive hormone variations may contribute to this.

**Prognosis in Ischemic Heart Disease in Women: Noninvasive Testing**

Figure 1 details the clinical workup of coronary disease, including optimal patient selection for noninvasive testing. Over the

**Table.** Newly Developed Women’s Ischemia Syndrome Evaluation: Female Angina Assessment for the Identification of Obstructive Coronary Disease\*

Characteristic	Percent		P
	No Coronary Disease (n = 337)	Obstructive Coronary Disease (n = 98)	
Presence of neck pain	55	41	.01
Weakness or fatigue	63	47	.004
Palpitations	62	46	.006
Sharp, knifelike pain	28	18	.04
Sweating	44	33	.04
Strong emotion is a trigger	60	48	.004
Pain is relieved by nitroglycerin	25	38	.01

\*Sponsored by the National Heart, Lung, and Blood Institute.

past several years, a number of reports have documented the prognostic accuracy of noninvasive testing in women. In recent years, the average sample size of studies has increased dramatically (range = 976-7024 patients), enabling greater understanding of the relationship between test results and prognosis.<sup>16-20</sup> Overall, these results reveal that a variety of noninvasive stress tests, including exercise stress testing,<sup>16</sup> stress echocardiography,<sup>17</sup> and stress nuclear imaging,<sup>18</sup> can be used to differentiate prognostic risk in women.

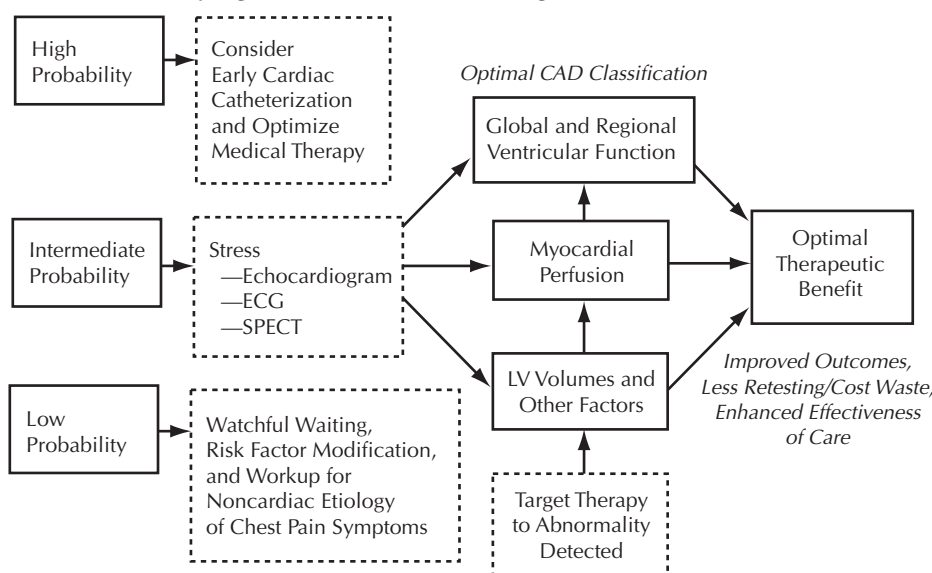
A recent evaluation of symptomatic women demonstrated that dobutamine echo-cardiography is able to identify high-risk women with severe multivessel obstructive coronary disease.<sup>21</sup> Prior data suggested that identification of inducible myocardial ischemia offers independent and perhaps greater prognostic information than coronary angiography.<sup>16</sup> Indeed, a recent report indicated that functional measurement of myocardial ischemia using stress radionuclide perfusion testing with Tc-99m sestamibi provided improved estimation of prognostic risk in women compared with men.<sup>19</sup> **Figure 2** and **Figure 3** detail cardiac survival curves for exercise echocardiography (n = 508 women) and stress nuclear imaging (n = 3402 women). Both tests apparently can differentiate between low-risk (normal test results) and high-risk (markedly abnormal) subsets of women.

Furthermore, when stress nuclear-inducible ischemia is used as a gatekeeper to the cardiac catheterization laboratory (**Figure 4**), diagnosis of coronary artery disease is enhanced. Thus, if a noninvasive stress test is required for patients with stable chest pain before referral to coronary angiography, then more multivessel coronary disease will be discerned; ie, if subsequent catheterization is limited to patients with moderate to severe ischemia.

### Pathophysiology and Significance of Myocardial Ischemia in the Absence of Obstructive Coronary Disease

Previous work suggestive of microvascular dysfunction as a pathophysiological mechanism has included evidence of myocardial ischemia by exercise electrocardiography, myocardial perfusion imaging, radionuclide angiography, echocardiographic imaging, or positron emission tomography in approximately one third of subjects without obstructive coronary disease at angiography.<sup>22-35</sup> Subsequent investigation into the underlying pathophysiology of endothelial dysfunction has centered on the small arteries of the coronary endothelial bed.<sup>36</sup> Impaired coronary flow reserve has been proposed as an etiology for abnormal noninvasive stress test results,<sup>37</sup> although no study has definitively linked abnormal flow reserve with evidence of myocardial ischemia. The above-mentioned reports were based on much smaller patient samples (average of 47 patients) than those in the ongoing WISE study, which includes 936 women evaluated with a variety of tests, standardized prospective testing protocols, and blinded core laboratories. In the WISE study, the prevalence of microvascular dysfunction was high (47%) in the selected cohort of women with nonobstructive coronary disease.<sup>38</sup>

**Figure 1.** Risk Factor-Based Approach to Evaluation of Suspected Coronary Artery Disease: Developing Precatheterization Strategies



ECG = electrocardiogram; CAD = coronary artery disease; LV = left ventricular; SPECT = single photon emission computed tomography.

Results of long-term follow-up of women with nonobstructive coronary disease, symptoms, and exertional ischemia are not currently available. However, women with chest pain but nonobstructive coronary angiography appear to have a relatively good survival rate through an average of 3 years of follow-up.<sup>5-7,9-13,27,35,39-41</sup> It is also unknown how many of these subjects had noncardiac etiologies for chest pain, because markers of ischemia were not mea-

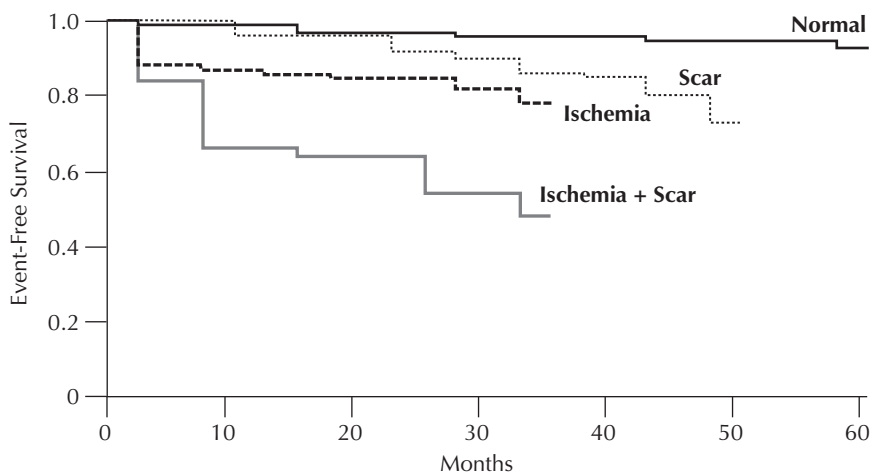
sured. Several small series have correlated signs and symptoms suggestive of ischemia with a worsening long-term cardiac outcome in subjects with no evidence of obstructive coronary disease.<sup>5,14,38-41</sup> Over 5 years of follow-up, deterioration in ventricular function was reported in 15 (25%) of 61 patients.<sup>41</sup>

Recently, Radice and colleagues<sup>14</sup> reported hospitalization for unstable angina in 13.3% of 30 patients with microvascular angina and initially abnormal

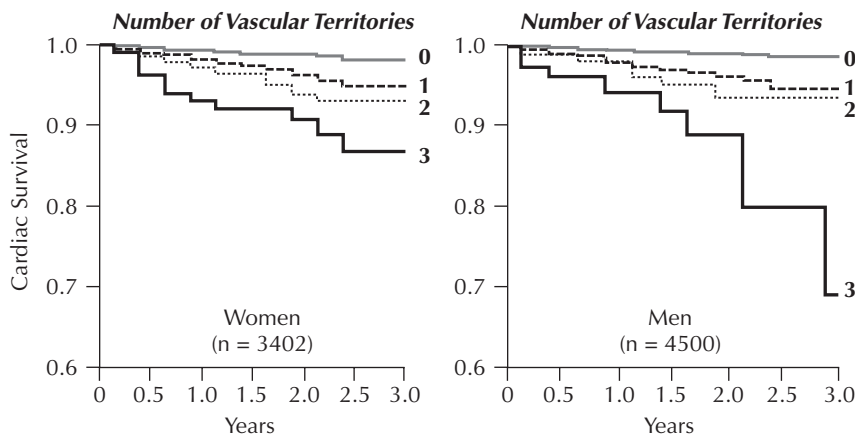
exercise treadmill tests, with 1 noncardiovascular death. Preliminary data from another group suggested that evidence of provocative ischemia in women was associated with a high rate of myocardial infarction despite an excellent survival rate.<sup>41</sup> Data appear controversial in that 3-year survival without myocardial infarction or revascularization was 97% in a series of 82 patients with at least 1 reversible segment by tomographic thallium-201 imaging and no significant coronary disease.<sup>39</sup> Similarly, none of the 31 patients with a positive exercise test experienced a cardiac event during 12 years of follow-up.<sup>40</sup> However, with fewer than 500 patient-years of follow-up, current evidence is insufficient to confirm or exclude an adverse prognosis for the subset of women with nonobstructive coronary disease and evidence of myocardial ischemia.

Findings from the National Heart, Lung, and Blood Institute-sponsored WISE study document for the first time that a significant subset of these women have metabolic evidence of myocardial ischemia, as indicated by magnetic resonance spectroscopy, which appears to be related to microvascular flow abnor-

**Figure 2.** Event-Free (Death, Myocardial Infarction, or Late Revascularization) Survival With Exercise Echo in 508 Women



**Figure 3.** Stress Nuclear Imaging Predicts Cardiac Mortality in Women Based on the Extent of Ischemia in Vascular Territories



Source: The Economics of Noninvasive Diagnosis Multicenter Registry.



malities.<sup>42</sup> We also have reported that coronary endothelial dysfunction in response to acetylcholine challenge is an independent predictor of adverse cardiac events in these women.<sup>43</sup> Furthermore, preliminary WISE work demonstrates a significant association between coronary endothelial dysfunction and a genetic polymorphism at the 573 position of the AT-1 receptor gene, indicative of a hereditary pathogenesis for this coronary dysfunction in these women.<sup>44</sup> If confirmed, these findings will aid our understanding of the pathophysiology of nonobstructive ischemia, as well as potential therapeutic interventions, including a new hormone replacement regimen (continuous combined ethinyl estradiol and norethindrone acetate) and an angiotensin-converting enzyme inhibitor (quinapril), for both diagnosis and treatment of this vexing problem.

**Costs of Evaluating Chest Pain in Women: Comparative Costs of Various Diagnostic Modalities**

Because of the paucity of data on the diagnosis of symptoms and exertional ischemia in women, substantial evidence suggests that management strategies for women are less cost efficient than those for men.<sup>1,20,26,45-48</sup> High rates of cost waste have been reported in female cohorts evaluated in the diagnostic cardiology setting from 1980 to 1995.<sup>1,2,49</sup> Cardiac catheterization is currently the most frequently performed procedure for women over age 65 years.<sup>46</sup> Estimates from prior research have noted the diagnostic cost of evaluating chest pain in women approaches \$800 million annually. When the cost of noninvasive tests is added, the total diagnostic cost may exceed \$1 billion (or 1% of US healthcare expenditures).<sup>50</sup>

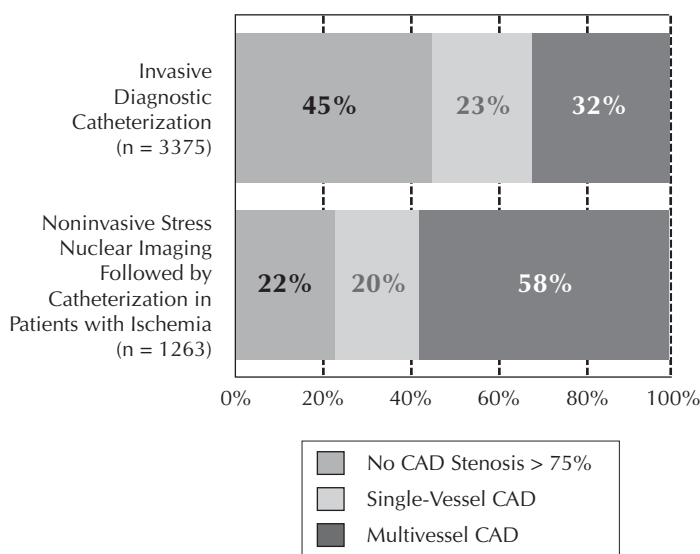
Improved management of women with suspected coronary disease could have far-reaching effects on the US healthcare system. Current evidence on the cost of diagnosis for women has been published by several investigators, including (1) the cost of catheterization, (2) the cost of nuclear imaging, (3) the cost of echocardiography; and (4) the cost of electron beam tomography.<sup>20,48,50,51</sup> The lowest test cost is for treadmill exercise testing. The highest cost of care ranges from \$800 to \$5200 for cardiac catheterization.

Overall, 65% of women found to have normal coronary arteries have persistent or worsening symptoms, test abnormalities,

and disability at 5 years after catheterization.<sup>52</sup> When patient diagnosis and management is ill defined, significant variability in resource use is expected. For women with normal coronary arteries, expected annual cost of care is low (\$384-\$520), with higher costs noted for women with minimally obstructed lesions (<\$3469).<sup>47</sup> These figures fail to consider medical therapy costs, which may add approximately \$1300 to \$5000 to cost of care annually.<sup>53</sup> A disproportionate share of healthcare costs in women is driven by symptoms and evidence of ischemia, despite the relatively low underlying obstructive coronary disease burden. Therefore, development of evidence in larger cohorts of women is essential to reduce the currently excessive cardiovascular mortality in women (~500,000 deaths annually) and to organize cost-effective care of at-risk women.

Several prior investigations have reported a highly interactive relationship between quality and cost effectiveness in the diagnosis of coronary disease.<sup>20,47</sup> That is, as diagnostic tests become more accurate (ie, more clinically effective), care becomes more cost efficient. In particular, a marked reduction in the need for cardiac hospitalizations has been noted for women with normal stress echocardiography and nuclear imaging results.<sup>17,47</sup> This concept of using a cardiac imaging test as a “gatekeeper” to

**Figure 4.** Comparison of 2 Diagnostic Testing Strategies: Invasive vs Noninvasive



CAD = coronary artery disease.

invasive cardiac catheterization has resulted in a reported 20% to 35% cost savings compared with referring women directly to receive coronary angiography.<sup>20,47</sup> Incrementally higher costs of care are then aggregated to those highest-risk women who benefit the most from aggressive intervention.

The link between clinical test effectiveness and cost-efficient care promotes a targeted approach to treatment that may result in improved outcomes for high-risk women. A risk-based evaluation can foster more precise posttest management of women and lead to greater reductions in cost inefficiency in the workup for suspected coronary disease. When both improvements in outcome and reductions in cost can be effected, cost-effective strategies are possible for women.

### Conclusions

Women have different presenting symptoms of coronary disease than men, leading to imprecise management, less effective outcome estimation, and cost-inefficient care. Although few historic data are available in women, results of recent larger observational series and National Institutes of Health-sponsored studies (eg, the WISE study) are becoming available. Evidence based on larger cohorts of women is revealing the new paradigm for the workup of women at risk for coronary artery disease, which is based on a varying symptom presentation and evidence of provocative ischemia as a guide to treatment. This workup includes sex-specific tools for the evaluation of symptoms and diagnostic tests known to aid in the risk stratification of women. The development of high-quality evidence regarding the diagnosis of coronary disease in women can enable substantial progress in lowering cardiovascular mortality in this country.

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