ABSTRACT

The epidemiology of coronary artery disease (CAD) is evolving. However, chronic angina affects millions of Americans and the sequelae are long term. Stress testing is typically the first-line diagnostic method for suspected coronary disease, whereas coronary angiography remains the gold standard for obstructive coronary disease. However, both stress testing and coronary angiography may miss extraluminal plaque resulting from coronary remodeling. In the presence of silent plaque formation, cardiologists must now change our patient paradigm from “you are at risk for CAD” to “you have CAD.” Treatment of chronic angina includes reducing the risk of mortality and morbidity events and reducing symptoms. However, despite the current pool of treatment options, including bypass surgery or angioplasty, there remains a pool of patients who experience angina and who are considered to be inoperable or high risk. Angina symptoms (thus functional capacity) are important to measure because they are associated with mortality rates. Clinical studies, including the Women’s Ischemia Syndrome Evaluation study, have taught us several important lessons regarding gender differences of CAD. Based on the data available at this time, we can say that heart disease in women is fundamentally different than in men, in presentation, progression, and response to treatment, at least until age 65 years, when event rates and treatment benefits in women become similar to those in men. Microvascular dysfunction in women is not necessarily always related to atherosclerosis, thus prognosis for CAD may be somewhat different between women and men. Therefore, identification of the highest risk groups and secondary prevention will play an even greater role in our management of CAD in both sexes.

THE CHANGING EPIDEMIOLOGY OF CORONARY ARTERY DISEASE

The epidemiology of coronary artery disease (CAD)—and its determinants—is evolving. The rapid surge in overweight and obesity rates in the United States over the past several decades is now well documented, as is the decline in smoking rates during the same period of time. Interestingly, those 2 measures have virtually exchanged prevalence rates between 1970 and 2002, as shown in Figure 1, and the trends are continuing.1

Chronic angina affects millions of Americans and the sequelae are long term. As of 2003, chronic angina affected at least 6.5 million Americans or 4% of the population. Each year an estimated 400 000 new cases...
are diagnosed. Each week there are more than 13 million episodes of angina in the United States; more than 1000 episodes occur every minute. The prevalence of chronic angina is increasing in part because our population is aging.\(^2\) Most of the current treatments have no proven effect on mortality, and results from the Bypass Angioplasty Revascularization Investigation study indicate that 30% of patients following coronary revascularization never return to work and 15% to 20% of patients following revascularization rate their health fair to poor.\(^3\) More recently, McCullough et al found that of those seeking external counterpulsation therapy for chronic stable angina (CSA), 41% were obese, and the mean ages were in the 60s and 70s.\(^4\) Most of these patients were taking several other antianginal treatments (eg, beta-blockers, up to 83.5%; angiotensin-converting enzyme inhibitors, up to 52%; nitrates, up to 81%). Approximately 80% had multivessel disease and approximately 70% had a prior myocardial infarction (MI) and prior coronary artery bypass grafting (CABG). This study also revealed that a pool of patients, comprising 10% to 20% of the study participants, continued to have severe angina after treatment.\(^6\) Therefore, CSA can be a persistent problem for some patients, despite best treatment efforts.

**THE NATURAL HISTORY OF CARDIOVASCULAR DISEASE**

Cardiovascular disease results in endothelial dysfunction, decreased hemodynamic flow and atherosclerosis, and, often, coronary events (Figure 2). The extent of endothelial dysfunction is determined by numerous factors; the most reliably predictive factor is age. (Importantly, although age may be a nonmodifiable determinant, exercise appears to consistently attenuate the vascular stiffening associated with aging.)\(^5\) Endothelial dysfunction and subclinical atherosclerosis may in fact be a continuum, thus the challenge to cardiologists is to determine which patients have increased cardiovascular risk in a setting of increasing endothelial dysfunction.

Central adiposity poses a greater cardiometabolic risk, but the reasons are not yet clear and the risk varies. For example, the INTERHEART study showed...
that Asian Indians are more prone to cardiovascular disease with only small increases in waist-to-hip ratio compared to other ethnic groups. Conversely, on an individual level, some patients with significant abdominal adiposity remain “metabolically clean,” with no hyperglycemia, hypertension, or dyslipidemia. Nonetheless, the overall increased cardiovascular risk with central adiposity is now well established, and some have termed this relationship “coronary metabolic syndrome,” to differentiate it from the metabolic syndrome defined in relation to diabetes risk.

The components of cardiometabolic risk are the same as those for metabolic syndrome (ie, impaired glucose tolerance, low high-density lipoprotein-cholesterol, hypertriglyceridemia, waist-to-hip ratio, body mass index, and hypertension); the debate centers around which components of this cluster are the “biological tipping point” for cardiovascular disease. Central adiposity is clearly a prerequisite, especially as its physiology creates an environment for vascular disease (ie, increased inflammation, a separate blood supply, and neurohormonal regulation). However, once the liver becomes insulin resistant, this may be the point of no return for cardiovascular disease.

Clinically, angina is classified as typical or atypical, depending on the presenting symptoms, and assigned a severity level (Class I–IV) based on the disability. The classification scheme follows the functional classification by the American Heart Association (AHA) for dyspnea. However, it is important to note that these classifications are physician assigned, thus they are often based not only on patient-reported symptoms and disability but also other information to which the physician may be privy (eg, angiography results and history of revascularization). Patients may insert their own bias into this measure by denying symptoms or incorporating dyspnea, which may not be part of the definition of angina. Thus, discordance may arise between physician and patient perception of angina severity.

Stress testing is typically the first-line diagnostic method for suspected coronary disease, whereas coronary angiography remains the gold standard for obstructive coronary disease. However, both stress testing and coronary angiography may miss extraluminal plaque resulting from coronary remodeling. As shown in Figure 3, plaque progression typically proceeds external to the lumen, thus noninvasive testing results remain normal. It is only when the plaque encroaches into the lumen that symptoms may appear—if the patient is lucky. Some patients may experience infarct or sudden death with no signs of coronary atherosclerosis by our current testing methods. With the increasing availability of 64- and 128-slice computed tomography angiography, we will most likely be initiating secondary prevention in patients who have not yet had an event but who have been determined to have the anatomic presence of coronary atherosclerosis.

This will be an important challenge for cardiologists as many patients do not understand the risk of atherosclerosis in the absence of symptoms, nor do they understand that the results measuring coronary atherosclerosis indicate diffuse atherosclerosis. For example, patients who receive a stent may feel they have “dodged a bullet,” not realizing that 90% blockage in their coronary arteries indicates that they have blockages elsewhere. Cardiologists need to start thinking about heart disease the way we have traditionally thought about diabetes—a patient does not have “a little bit” of diabetes. In the presence of silent plaque formation, we must now change our patient paradigm from “you are at risk for CAD” to “you have CAD.”
The Treatment Gap for Chronic Coronary Syndrome

Treatment of chronic angina includes reducing the risk of mortality and morbidity events and reducing symptoms. Patients not only experience discomforting symptoms but also limited activity and associated anxiety due to symptoms and uncertainty about diagnosis. There is no universally accepted definition of treatment success because of the variety of symptoms and patient perceptions, expectations, and preferences for treatment. However, the American College of Cardiology/AHA guideline for CSA states that “the goal of treatment should be complete, or nearly complete, elimination of anginal chest pain and return to normal activities and a functional capacity of Canadian Cardiovascular Society (CCS) class I angina…with minimal side effects of therapy.” According to the guideline, first-line treatments include medication and lifestyle changes, followed by bypass surgery or angioplasty. However, despite the current pool of treatment options, including bypass surgery or angioplasty, there remains a pool of patients who experience angina and who are considered to be inoperable or high risk. Several studies bear this out.

For example, Pepine et al, in one of the only studies characterizing contemporary, nonhospitalized patients with chronic angina, showed that 50% of angina patients have attacks at least weekly and approximately 25% have attacks every day or every other day, despite medication (Figure 4). Of the 5125 study participants, 13% had a previous revascularization procedure. Their cardiovascular medications included calcium channel blockers (46%), beta-blockers (25%), and nitrates (61%). In another study, roughly 25% of patients who underwent enhanced external counterpulsation (a novel treatment alternative for angina patients ineligible for revascularization with percutaneous coronary intervention) experienced Class III or Class IV angina up to 24 months after treatment. A recent study evaluated the medical therapy of 100 outpatients with CSA. Approximately 88%, 84%, and 61% of patients reported taking calcium channel blockers, nitrates, and beta-blockers, respectively, to control their angina symptoms. Mean scores from the Seattle Angina Questionnaire (SAQ; a disease-specific health status questionnaire for patients with coronary artery disease) for physical limitation, anginal stability, anginal frequency, and quality of life were 48.9, 50.5 (indicating very little change in angina symptoms), 56.7, and 48.7, respectively.

Therefore, despite taking several antianginal medications, patients with CSA continue to report low levels of functional status, which signals an important and marked treatment gap. Angina also continues in many patients despite revascularization. In a randomized clinical trial, 1205 patients with stable angina, unstable angina, or silent ischemia were randomly assigned to undergo stent implantation or bypass surgery for relief of ischemia symptoms. Twelve months after revascularization, approximately 21% of patients who received stents and 11% of patients who received surgery continued to have angina; 79% and 59%, respectively, were still taking antianginal medications. A total of 81% and
62%, respectively, of patients continued having angina and/or taking antianginal medication.17

Angina symptoms (and functional capacity) are also important to measure because they are associated with mortality rates. Spertus et al followed 5558 patients from 6 Veterans’ Affairs internal medicine clinics for up to 2 years (although the primary outcome measure was 1-year all-cause mortality).18 After 1 year of follow-up, mortality rates were strongly associated with each of the 4 SAQ domains, with physical limitation most strongly associated (Figure 5).18 This association with also seen with the angina stability scale, which measures symptom changes in the preceding month: 1-year mortality rates of 11% versus 4% in those who did not have recent symptom changes. These trends continued out through 24 months of follow-up and for hospitalization for acute coronary syndrome (the secondary outcome). Multivariate analysis also revealed that prior hospitalization for acute coronary syndrome was a strong predictor of future hospitalization (odds ratio, 11.7; 95% confidence interval [CI], 7.4–18.1; \(P<.001\)).18 Therefore, medicines that reduce anginal frequency could reduce hospitalization or perhaps mortality from acute coronary syndrome.

**Diagnostic Testing and Clinical Monitoring: Men Versus Women**

Although the US population has enjoyed an overall decline in coronary events over the past 15 years, heart disease is, in fact, the number one cause of death in women.19 Clinical studies of gender-specific aspects of coronary heart disease (CHD) have taught us several important lessons. First, treatment disparities between the sexes exist, in part because of gender-specific responses to therapy. Second, the presentation of CHD is different in women compared to men, thus it may be somewhat more difficult to diagnose CHD in women. Finally, the consequences of MI are more severe in women versus men. Therefore, clinical research is now focused on identifying women most at risk of heart disease.

The traditional methods for cardiac testing—cardiac perfusion imaging, echocardiogram, electrocardiogram, exercise electrocardiogram/echocardiogram, and cardiac catheterization—have been studied extensively in men and angiography remains the gold standard for diagnosing CAD. However, in women, these

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**Figure 5. Angina Is an Independent Predictor of Mortality**

- **SAQ Physical Limitation Scores**
  - Severe (n = 681)
  - Moderate (n = 1728)
  - Mild (n = 1239)
  - Minimal (n = 856)

- **SAQ Angina Frequency Score**
  - Severe (n = 240)
  - Moderate (n = 539)
  - Mild (n = 1268)
  - Minimal (n = 2437)

- **SAQ Quality of Life Scores**
  - Poor (n = 319)
  - Fair (n = 916)
  - Good (n = 1461)
  - Excellent (n = 1781)

Models controlling for demographic and clinical characteristics indicated significant independent mortality risk with lower Seattle Angina Questionnaire (SAQ) physical limitation scores.

<table>
<thead>
<tr>
<th>Odds Ratios</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>(P)</th>
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<tbody>
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<td>Physical limitation</td>
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<td>2.0</td>
<td>4.0</td>
<td>&lt;.001</td>
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<tr>
<td>Angina frequency</td>
<td>0.8</td>
<td>1.2</td>
<td>1.6</td>
<td>.078</td>
</tr>
<tr>
<td>ACS admission</td>
<td>1.4</td>
<td>2.0</td>
<td>2.2</td>
<td>.016</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome.

methods of cardiac testing offer lower sensitivity and specificity. This is an important consideration because the results of angiography determine all future testing and treatment decisions. The major goal of angiography is detection of epicardial coronary atherosclerosis, but arteries that appear angiographically normal may respond to vasomotor influences with a detrimental amount of vasoconstriction. Because many women have angina with undetected CAD, should angiography remain the gold standard for cardiac testing in women? And, does absence of significant angiographic epicardial stenosis rule out ischemia?

The Women’s Ischemia Syndrome Evaluation (WISE) study was designed to answer some of these questions. Specifically, it was designed to “optimize symptom evaluation and diagnostic testing for ischemic heart disease”; “explore mechanisms for symptoms and MI in the absence of epicardial coronary artery stenosis”; and “evaluate the influence of reproductive hormones on symptoms and diagnostic test response” in women. The WISE study began as a pilot study in 1996 and continued into a prospective study of 936 adult women with chest pain and a clinical indication for angiography. Women were excluded from the study if they (among other criteria) had severe cardiac disease, such as chronic heart failure, severe valvular disease, recent MI, recent percutaneous transluminal coronary angioplasty/CABG, or congenital heart disease. Based on these exclusion criteria, one could argue that results from the WISE study represent a “best-case scenario” (ie, finding women with hitherto undetected CAD).

The WISE study was based on the premise that small vessel coronary artery disease is sometimes present in women with negative angiography. Therefore, small vessel disease was measured using coronary flow velocity reserve testing, which assesses the ability of coronary arteries to dilate when injected with a vasodilator (eg, adenosine and acetylcholine). Abnormal coronary flow velocity reserve can be measured as a change in flow velocity using intracoronary Doppler. The ratio of maximum flow velocity with a vasodilating agent over baseline flow velocity is called the reserve and is typically 3 to 4. In the WISE study, the cutoff for women was 2.5. The investigators also used a more crude measure of flow reserve (ie, the ability of an epicardial coronary artery to dilate at least 90% in response to a vasodilator). CAD group categorization was based on the following definition: normal/minimal disease, less than 20% stenosis; mild disease, 20% to 49% stenosis; significant disease, 50% or greater stenosis in any one major epicardial coronary artery.

A pilot study in 92 women who underwent dobutamine-stress echocardiography showed that the overall sensitivity of noninvasive testing was only 50%, but increased to 82% in those with multivessel epicardial CAD. The specificity was 81%. Thus, standard dobutamine echocardiography may be missing a large number of women with “silent CAD.” A pilot study of 159 women with normal angiography in the presence of chest pain showed that 47% had coronary flow velocity reserve less than 2.5, suggestive of microvascular dysfunction.

The main WISE study focused on hard cardiovascular outcomes: 4-year rates of death or MI. The
results showed that the extent of stenosis was inversely proportional to the event-free survival rate over 4 years (Figure 6). Importantly, in women with less than 20% stenosis, the event rate was 2.5% over 4 years; and in those with less than 40% stenosis, the event rate increased to 9%. Therefore, in a group of women not traditionally defined as being high risk, the event rate was approaching 10%, suggesting that women at high risk of CAD cannot be reliably identified with noninvasive testing or angiography.24

Similarly, in another substudy of WISE, 163 study participants were referred for coronary angiography for investigation of suspected MI. When the study patients were stratified according to dilation, those who showed more than 90% dilation with acetylcholine had significantly fewer events than those who were not able to dilate to this extent (P < 0.0037). Multivariate regression analysis showed that the degree of CAD and percent dilation in response to acetylcholine were the only variables that predicted adverse cardiovascular events (P < 0.05). The investigators also observed that when the outcome was restricted to death, MI, congestive heart failure, or stroke, response to Ach [acetylcholine] remained a significant (P = .006) predictor of outcomes.25 These results suggest a greater role of the microvasculature in CHD in women than has previously been realized. Women have smaller arterial size and potentially more prominent endothelial remodeling, and perhaps greater danger from endothelial dysfunction. For practicing cardiologists, the traditional diagnostic tests that focus on identifying obstructive disease may not be as effective in women compared to men. The persistent signs and symptoms of chest pain in the setting of nonobstructive coronary disease is a significant health problem for women. Therefore, a greater understanding of these gender-specific pathophysiologic processes in women is needed.

Nonetheless, several gender-related questions remain unanswered. For example, how does atherosclerosis differ between the sexes? Strokes are more prevalent in women, and women account for approximately 60% of stroke deaths.19 One model to explain this suggests that women disseminate fat throughout their vessels and develop more generalized disease of the smaller blood vessels than men. Men tend to accumulate plaque in the lining of the large coronary arteries and to be prone to plaque disruption leading to a heart attack.26

Women are also at greater risk for mortality and stroke in the presence of diabetes or the metabolic syndrome. Data from the First National Health and Nutrition Examination Survey showed declines in age-adjusted heart disease mortality in nondiabetic and diabetic men (36% and 13%, respectively), and a 27% decline in nondiabetic women; however, this rate increased by 23% in diabetic women—patterns that were mirrored in all-cause mortality and ischemic heart disease mortality.27 Similarly, in the Northern Manhattan Study, the risk of stroke increased more than 2-fold in women with metabolic syndrome compared to men with metabolic syndrome.28,29 Also of note are data from 35 years of the Framingham Heart Study, which show an increased relative risk of cardiovascular disease in women compared to men as triglyceride levels increase.30

Another obvious question of the gender differences in heart disease is the role of reproductive hormones. Early results from the Heart and Estrogen/Progestin Replacement Study (HERS) suggested a higher risk of CHD events during the first year, and a decreased risk during years 3 to 5, in postmenopausal women with CHD receiving hormone replacement therapy. With 6.8 years of follow-up in 2321 women, HERS II showed “no significant decreases in rates of primary CHD events or secondary cardiovascular events among women assigned to the hormone group compared to the placebo group in HERS, HERS II, or overall.”31,32 Even the WISE study found no difference in reproductive hormone levels between women with normal or abnormal microvascular function (as measured by coronary flow reserve).33

Data from the overall cohort of the Multiple Outcomes of Raloxifene Evaluation trial—a randomized, double-blind, placebo-controlled trial of 7705 osteoporotic postmenopausal women—showed no significant differences between treatment groups in the number of combined coronary and cerebrovascular events. However, analysis of a cohort subset (1035 women with increased cardiovascular disease risk at baseline) revealed an apparently lower risk of cardiovascular events compared to placebo (relative risk, 0.60; 95% CI, 0.38–0.95 for both raloxifene groups), with no increased risk of breast cancer.34 However, the investigators noted that “before raloxifene is used for prevention of cardiovascular events, these findings require confirmation in trials with evaluation of cardiovascular outcomes as the primary objective.” The
recently published Raloxifene Use for the Heart trial showed no beneficial cardiovascular effect.

Finally, are these differences in CAD between women and men going to translate into differences in pharmacotherapy for CAD? The Women’s Health Study received an enormous amount of attention in the lay media when it was first published. This randomized, double-blind, placebo-controlled study assessed the benefits and risks of low-dose aspirin (100 mg every other day) and vitamin E (600 IU natural source, every other day) for primary prevention of cardiovascular disease and cancer among 36 876 female health professionals age 45 years or older. The study showed significant reductions in total stroke and ischemic stroke in women taking aspirin compared to placebo, but no differences in MI or hemorrhagic stroke.

Thus, the potential benefits of aspirin use are unclear because the findings with the primary endpoint (first major cardiovascular event [ie, nonfatal MI, nonfatal stroke, or death from cardiovascular causes]) were not significant and counterbalanced by an increase in gastrointestinal bleeds. Therefore, the benefits and risks of aspirin use are uncertain with the primary endpoint (first major cardiovascular event [ie, nonfatal MI, nonfatal stroke, or death from cardiovascular causes]) were not significant and counterbalanced by an increase in gastrointestinal bleeds.

Based on the data available at this time, we can say that heart disease in women is somewhat different than in men, in presentation, progression, and response to treatment, at least until age 65 years, when event rates and treatment benefits in women become similar to those in men. Microvascular dysfunction in women is not necessarily always related to atherosclerosis, thus prognosis for CAD may be different between women and men. Identification of the highest risk groups and secondary prevention will play an even greater role in our management of CAD in both sexes.

**Conclusions**

The epidemiology of CAD is not stable; the evolving trends may be due to multiple factors, including a declining smoking rate, a rapidly increasing prevalence of obesity, and our better understanding of the gender differences of CAD pathophysiology, presentation, progression, and response to treatment. Symptoms of chronic coronary syndrome are common, despite studies now showing that although treating symptoms may not affect mortality, functional limitations predict mortality and angina frequency predicts hospitalization. As we begin to appreciate the full spectrum of chronic coronary syndrome, our treatment approaches must therefore broaden.

**References**


