Coronary heart disease (CHD) remains the leading cause of death in the United States, accounting for 26.6% of all deaths in 2005, with an age-adjusted male to female mortality ratio of 1.5. Although the CHD mortality rate has steadily declined since its peak in the 1960s, morbidity from CHD has shown opposite trends, with increasing rates of revascularization and an increasing prevalence of angina pectoris, now estimated at 9.1 million (4.6 million women [3.9%]; 4.4 million men [4.4%]). In stark contrast to CHD mortality rates, age-adjusted prevalence rates for angina in the United States are higher among women than men. Anginal symptoms tend to persist despite medical therapy and revascularization, lead to substantial functional disability, and be associated with high healthcare costs even in the absence of obstructive coronary artery disease (CAD).

The study by Hemingway et al in this issue was thus undertaken to determine whether differences in angina rates by gender are similarly constant in countries that greatly differ in the prevalence of CHD risk factors and prevalence of CHD. The authors conducted a meta-analysis of cross-sectional and prospective cohort studies of 74 populations within 31 countries encompassing around 40,000 individuals (nearly 50% women). All studies ascertained angina by Rose questionnaire. Countries were categorized by their male:female myocardial infarction mortality ratio, their geographical region, and their level of economic development. Angina prevalence varied approximately 20-fold between countries, ranging from 0.73% to 14.4% in women and 0.76% to 15.1% in men. Female and male angina prevalence was highly correlated across studies, and angina prevalence also significantly correlated with the respective myocardial infarction mortality rates. With few exceptions, the prevalence of angina was higher among women than among men, with a pooled summary sex ratio of 1.2 (95% confidence interval [CI], 1.14 to 1.28). Interestingly, the female excess was evident in premenopausal as well as postmenopausal age groups, suggesting a limited role for changes in the hormonal environment at the time of menopause.

Hemingway et al should be congratulated on a very well-done, methodologically transparent meta-analysis. The major strengths of their work are the global scope of the population-based investigations, the inclusion of unpublished data and of papers in languages other than English that, when omitted, often lead to substantial bias, and the careful correlation with corresponding myocardial infarction mortality rates. Use of the Rose questionnaire is simultaneously a strength and weakness. It is a standardized instrument validated in both genders, has been translated and validated in languages other than English, and is thus an excellent tool for cross-country comparisons of angina prevalence. As described in 1962, the Rose questionnaire ascertained typical exertional angina, but included an optional section that asked about other precipitants of discomfort and discomfort other than pain, pressure, or heaviness. The study by Hemingway et al only included the questions relating to typical exertional angina, which is the anginal pattern most closely linked with obstructive epicardial CAD. Angina with emotional upset, with mental stress, or at rest and angina that is atypical in nature were thus not captured. Clinical studies suggest that atypical anginal discomfort and angina precipitated by stimuli other than exertion are more common among women than men. Whether this is true in unbiased populations is unknown, but one wonders whether the sex ratio determined in this meta-analysis is not an underestimate of the female excess in angina pectoris.

Why do we know so little about the pathophysiology and determinants of angina pectoris in an era in which great strides have been made in the understanding, diagnosis, and treatment of acute coronary syndrome and myocardial infarction? Angina pectoris is a constellation of symptoms with heterogeneous origin. Although we generally equate angina pectoris with underlying obstructive CAD, anginal chest discomfort can also occur in the setting of epicardial coronary spasm, epicardial coronary endothelial dysfunction, and microvascular disease, as well as in settings with demand/supply mismatch in the absence of obstructive CAD. Multiple mechanisms may be operative in a given patient at different times or simultaneously. In addition, many causes of noncardiac chest pain can mimic the discomfort associated with myocardial ischemia. No questionnaire exists that reliably distinguishes between causes of chest pain. To differentiate noncardiac from cardiac discomfort in the clinical setting, we assess symptom characteristics and determine the probability...
of CAD on the basis of demographic and clinical characteristics, but we ultimately rely on a variety of diagnostic methods, some anatomic (eg, coronary calcium scoring, computed tomographic angiography, traditional coronary angiography, magnetic resonance angiography, intravascular ultrasound) and some physiological (eg, exercise or pharmacological stress testing with echocardiography, nuclear perfusion imaging, or magnetic resonance imaging, magnetic resonance spectroscopy, invasive hemodynamic assessment) without an agreed on gold standard. Patients may thus be classified as having ischemia by one testing modality and as having noncardiac chest pain by another. Furthermore, testing is most likely to be done in individuals in whom there is at least a moderate likelihood of obstructive CAD. Patients with more atypical symptom constellations are less likely to be investigated, are less likely to receive a diagnosis of angina, even if their symptoms represent myocardial ischemia, and are less likely to receive antianginal medications. Studies that rely on diagnostic codes or prescription of antianginal agents are thus inherently biased, as are studies conducted in highly selected settings such as emergency rooms, inpatient wards, or angiology laboratories or in tertiary care referral centers, which tend to attract patients with a high rate of comorbidities and complex symptom presentations. The method and setting of symptom ascertainment can also significantly influence results: Checklists tend to elicit different responses than do spontaneous descriptions of symptoms, recall bias likely accounts for differences in symptoms assessed before compared with after a diagnostic procedure/event, and symptom assessment, if not done with a standardized instrument, is greatly influenced by the perceptions of the interviewer.

Investigation of gender differences in anginal symptoms is even more complicated, as women tend to develop CHD at a more advanced age than do men, making it difficult to distinguish differences in symptoms due to gender from differences in symptoms due to advanced age and/or its associated comorbidities. Furthermore, it is unclear whether differences observed between genders are variations in symptoms within the same disease process or whether women indeed have a unique vasculopathy, as suggested by both structural and functional differences in the coronary circulation between genders. Awareness of disease risk and knowledge of common heart disease symptoms are important determinants of symptom attribution and subsequent healthcare-seeking behavior. Serial surveys among women between 1997 and 2006 have shown a marked increase in awareness of the fact that heart disease is the most common cause of death among women. Major knowledge gaps remain, however. In the latest iteration of the survey, only 68% of white women, 31% of black women, and 29% of Hispanic women correctly named heart disease as the leading cause of death among women. Although approximately 60% identified pain in the chest, neck, or arms as a symptom of a heart attack, only 15% were aware that chest tightness could signify a myocardial infarction. Similar data for US men are not available.

At this time, it is unclear whether the prognosis of angina differs between men and women. This fact is not surprising, as different studies are likely to capture different subsets of causes of chest discomfort and populations that differ in absolute event risk independent of their symptoms. In the study by Hemingway et al, the ecological correlation between angina pectoris prevalence and myocardial infarction mortality was somewhat greater in men than in women ($r=0.42$, 95% CI, 0.20 to 0.60, $P=0.0005$ versus $r=0.27$, 95% CI, 0.03 to 0.48, $P=0.03$). In the Framingham study, men who developed angina were at greater risk of myocardial infarction (hazard ratio, 2.2; 95% CI, 1.45 to 3.34) and coronary death (hazard ratio, 2.11; 95% CI, 1.32 to 3.36) than were their female counterparts after adjustment for age and CHD risk factors. More recently, Hemingway et al reported data from Finland in which angina was ascertained by use of nitrates and by a history of positive diagnostic testing. When compared with the general population, both categories of angina were associated with greater mortality risk in men and women after a median follow-up of 4 years, and the magnitude of risk increase was generally similar in both genders. Among patients with nitrate angina, there was a strong dose–response relationship between the extent of nitrate use and subsequent outcome in men and women. In fully adjusted models, the male:female sex ratio for coronary events was 1.07 (95% CI, 0.81 to 1.41). In the Women’s Ischemia Syndrome Evaluation (WISE), which investigated a group of highly selected women presenting for diagnostic angiography because of suspected ischemia, women with obstructive CAD had higher event rates than did women without obstructive disease. Persistent chest pain in the absence of obstructive CAD was associated with a doubling of subsequent cardiovascular events (composite end point of nonfatal myocardial infarction, stroke, heart failure, and cardiovascular death, $P=0.03$) however, whereas persistent chest pain in the setting of obstructive CAD did not confer an excess in risk. Whether these relationships would hold in a similarly recruited cohort of men is unknown.

The study by Hemingway et al puts investigation of angina among women on a firm epidemiological foundation and will be a classic paper referenced throughout studies on women’s health. There is a clear need for additional epidemiologic work with broader definitions of anginal symptoms and careful prognostic evaluations in both genders, not just in terms of hard coronary outcomes and mortality, but also in terms of functional disability, quality of life, and healthcare costs. Future clinical research in women and men would clearly benefit from refined tools to assess symptoms as well as from more uniform and standardized definitions of clinical syndromes, underlying pathophysiology, diagnostic labels, and methodologies to investigate coronary pathophysiology. While awaiting the results of such research studies, what should clinicians do? Revascularization remains the tool of choice in high-risk subsets of patients (eg, unprotected left main disease or 3-vessel disease with left ventricular dysfunction). The recent Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study has shown us in a cohort of men and women with chronic angina and moderate risk that optimal medical therapy with selective use of revascularization can control symptoms in up to 72% of patients and can limit the annual mortality rate to 1.7%.15
Implementation of optimal medical therapy should thus be uniform in all CAD patients. There is no randomized controlled trial to guide therapy for individuals with angina in the absence of obstructive CAD. Available data, however, tell us that these individuals are not low risk and should be followed closely. Given their high burden of cardiovascular risk factors, implementation of optimal medical therapy seems reasonable even in the absence of conclusive proof of benefit.

Disclosures
Dr Bittner has received research grants from NIH-Abbot, Pfizer, Atherogenics, Merck, and CV Therapeutics and has served as a consultant to CV Therapeutics, Pfizer, Reliant, and Novartis.

References

Key Words: Editorials ■ angina ■ coronary disease ■ prognosis ■ women