CME Review Article

This article has been designated the CME Review Article for the January/February 2001 issue of *Menopause Management*. (Please refer to the CME Test on page 31.) This CME activity was planned and produced in accordance with the ACCME Essentials.

CME Learning Objectives

- Better understand the scope of the CHD problem in women
- Know the clinical outcomes of CHD and MI in women, compared to men
- Understand the clinical outcomes of PTCA and CABG surgery in women, compared to men
- Know the differential application of CHD and MI therapies by gender

CHD in Women: Clinical Characteristics, Gender Differences and Outcome Improvement

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Coronary heart disease (CHD) is the leading cause of mortality in adult women in the United States, accounting for approximately 250,000 deaths per year. Initial coronary events occur approximately 10 years later in women than in men, with myocardial infarction (MI) occurring as many as 20 years later. One in eight or nine 45- to 64-year-old women in the United States is likely to have clinical manifestations of CHD; the prevalence increases to one in three after age 65.[1] Furthermore, white postmenopausal women in the United States are 10 times more likely to die from CHD than from breast cancer; the lifetime mortality risk from CHD is 31%, versus 2.8% each for hip fracture and breast cancer.[2] Despite these facts, a 1995 Gallup poll revealed that four of five women in the United States, and one of three of their primary care providers, were not aware that heart disease was the leading cause of death among women. Examination of the trends in coronary deaths from the 1970s through the 1990s shows a prominent decline in coronary death among men, but a far less pronounced decline among women.[1]

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Coronary Risk Reduction

Coronary risk factors are highly prevalent in women of all racial and ethnic groups, but tend to predominate and cluster in women with lower incomes and levels of education, features that commonly coexist. Among the alarming risk factor trends in women are the following: Smoking rates have decreased less for women than for men; the prevalence of obesity is increasing; approximately 25% of women in the United States report engaging in no regular physical activity; 52% of women over age 45 have hypertension; and 40% of those over age 55 have hypercholesterolemia.

Observational data from the Nurses' Health Study[3] clearly demonstrate the benefits of coronary risk reduction. Between 1980 and 1994 there was a 31% decrease in the age-adjusted incidence of CHD in the study population. A 41% decrease in smoking accounted for 30% of this decline; substantial improvement in diet accounted for 16%; a 175% increase in the use of postmenopausal hormone therapy accounted for 9% of the decline, while a 38% increase in obesity explained 8% of the increase in CHD. At the same time, data collected by the Centers for Disease Control and Prevention

show that physicians in office practice are less likely to counsel women than men regarding nutrition, physical activity, weight control and smoking cessation. Particular attention to risk reduction should be directed to women at high risk, such as those with more than two coronary risk factors and women with diabetes.

Angina Pectoris

The need for evaluation, risk stratification and appropriate intervention in women with chest pain cannot be overstated. Angina pectoris is the predominant initial and subsequent presentation of CHD in women,[4] while MI and sudden death are the major presenting manifestations in men. Thus, there is considerable opportunity to evaluate women during the phase of stable angina, to perform risk stratification procedures and to identify women for whom myocardial revascularization procedures might prevent an initial coronary event. Women presenting with angina are older than their male counterparts and are more likely to have hypertension, diabetes and heart failure; they are less likely to have had a prior MI or myocardial revascularization procedure.

Myocardial Infarction

Up-to-date information relative to gender issues in acute MI is available from the U.S. National Registry of Myocardial Infarction. Data from 1990-1994, based on 354,435 patients in 1,234 U.S. hospitals, show that 36% of all myocardial infarctions occurred in women.[5] Women were older than men at presentation, (70 versus 63 years), and the duration between symptom onset and presentation to a hospital was longer for women than for men. Women with and without coronary thrombolysis had a higher mortality rate from acute MI than did men, even when matched for age. Among patients undergoing coronary thrombolysis, the mortality rate for women was 9.3%, compared to 4.5% for men; for those who did not receive thrombolysis the mortality rate was 16% for women and 10.9% for men.

Although women in the Registry were less likely to receive thrombolysis, they were more likely to experience major bleeding when this intervention was administered. Women were also more likely than men to have stroke, major bleeding and recurrent infarction, both with and without coronary thrombolysis. Importantly, women were less likely to receive heparin, beta blockers and aspirin, although there was greater use of these therapies in MI survivors (women and men) than in nonsurvivors. Women also were less likely to undergo coronary angiography, coronary angioplasty and coronary artery bypass graft (CABG) surgery. Women were more likely to die of cardiac rupture but less likely to die of arrhythmia than were their male counterparts.

Demonstrating that gender differences in mortality from acute MI are not unique to the United States, the RESCATE investigators from Catalonia, Spain, examined gender differences in first MI mortality among consecutive patients younger than 80 years between 1992 and 1994.[6] Women in this database were older than men and were more likely to have diabetes, hypertension and prior angina. Women had more pulmonary edema and cardiogenic shock (24.8%) than did men (10.5%). Women experienced longer delays, not only in arriving at the emergency department but also in being transferred from the emergency room to the coronary care unit. Men were more likely than women to receive thrombolytic therapy (41.3% versus 23.9%). Although the coronary angioplasty and CABG rates were similar by gender at 6 months, men were more likely to have had early coronary angiography, coronary angioplasty and CABG surgery.

In this same database women had an increased risk of 28-day and 6-month mortality, and of hospital readmission within the initial 6 months following MI (23.3% for women versus 12.2% for men). It is important to note that it was during the initial 6 months after MI—when women's hospital readmissions exceeded those of men—that coronary arteriography was performed in women with resulting coronary angioplasty and CABG surgery rates equivalent to those performed in men. In other words, it was only upon hospital readmission for a recurrent event that women received the PTCA or CABG surgery provided for men during the first admission. The investigators concluded that the excess mortality and morbidity rates resulted primarily from increased MI severity in the women; this was independent of age, comorbidity and use of thrombolytic therapy.

Coronary thrombolysis administered for acute MI confers a comparable survival benefit for women and for men but does not obviate the gender differences in mortality. This benefit persists despite the excess of bleeding complications, particularly intracerebral bleeding, encountered in women. Women are less eligible for coronary thrombolysis than their male counterparts, primarily because of their late arrival to hospitals. In addition, women's less frequent and, perhaps, atypical chest pain presentations and higher prevalence of non-Q-wave MI alter their eligibility for coronary thrombolysis.

Primary coronary angioplasty in the setting of acute MI improves survival for women more so than coronary thrombolysis; this is mainly because there is less intracranial bleeding with primary angioplasty. In the Primary Angioplasty and Myocardial Infarction (PAMI) trial[7] there was a comparable favorable in-hospital prognosis for women and for men treated with primary angioplasty.

Summary data from numerous randomized trials of MI therapies, including antiplatelet agents, beta blockers, calcium channel blockers, fibrinolytic drugs and ACE inhibitors, show comparable reductions in mortality rates for treated versus control male and female patients. Because of the similar rates of risk reduction in women and men so treated, there is no empirical evidence to support different medical treatments based on gender.

CABG Surgery

Numerous data on gender and CABG mortality rates are available from the So-

ciety of Thoracic Surgeons database of 344,913 CABG patients (28% women) undergoing surgery between 1994 and 1996.[8] Women in this database were older and more likely to have diabetes, hypertension and peripheral vascular disease, and to undergo nonelective procedures. Men were more likely to have ventricular dysfunction, to be smokers and to need reoperation. Nonetheless, the operative mortality for women was 4.5%, versus 2.6% for men.

For each risk factor examined univariately, including subgroups with and without internal mammary artery (IMA) grafting and including body surface area, women had increased operative mortality. In multivariate analysis, women had significantly increased mortality compared with equally matched men in the low- and medium-risk groups; only for the highest-risk patients (characterized as elderly individuals undergoing nonelective procedures or reoperation) was there no gender difference. The study investigators concluded that female gender independently predicted CABG operative mortality, except in the very high-risk category.

Does this mean that women should not undergo CABG surgery? Unquestionably not, since women who are CABG candidates who refuse surgery or are, for other reasons, treated medically have less favorable outcomes than those who undergo CABG surgery.

Percutaneous Transluminal Coronary Angioplasty (PTCA)

Because women were relatively underrepresented in their 1985-1986 Registry, the National Heart, Lung, and Blood Institute instituted a PTCA Registry for women only in 1993-1994. Comparison of the databases from both registries showed that the women in the more recent Registry[6] who underwent PTCA were older and more likely to have diabetes, heart failure and comorbidities, but had comparable left ventricular function and multivessel disease. Despite their higher risk profiles, however, the women in the more recent Registry had better clinical and angiographic success rates than did their earlier counterparts; there was a decrease in the major complication rate, and the mortality, MI and emergency CABG surgery rates were comparable. The combined endpoint of death, MI and the need for emergency CABG surgery was decreased. Thus, older and sicker women today do better with PTCA than the women of a decade ago. For example, the angiographic and clinical success rates were 85% and 79%, respectively, in the 1985-1986 Registry, compared with 90% and 89%, respectively, in the 1993-1994 Registry.[6] The combined endpoint of death, MI and emergency CABG was 9.7% in 1985-1986 and 4.4% in 1993-1994.

In the Bypass Angioplasty Revascularization Investigation (BARI),[7] 27% of the 1,829 patients randomized to CABG or PTCA were women. Unadjusted hospital and 5-year mortality rates with CABG were comparable in women and men; the hospital mortality rate was 1.3% in women and 1.4% in men, and the Q-wave MI rates were 4.7% and 4.6%, respectively. There was, however, an excess of heart failure and pulmonary edema in the women: 9.8% versus 1.8%. Five-year survival was comparable: 87% for women and 88% for men. For those randomized to PTCA, the hospital mortality rate was 0.8% for women versus 1.2% for men, and the Q-wave MI rates were 1.2% and 2.4%, respectively. Again, there was predominance of heart failure and pulmonary edema among the women: 4.8% versus 1.4%. Nonetheless, 5-year MI-free survival was 75% for women versus 77% for men.

Women in the BARI database were older and more likely to have heart failure, hypertension, diabetes, hypercholesterolemia and unstable angina, with left ventricular function and multivessel disease comparable to that of men. Women received fewer IMA grafts (72% versus 85%) but had more lesions successfully dilated at PTCA (76% versus 71%). After adjustment for their increased risk profile, women had a significantly decreased 5-year mortality risk, with no difference in the 5-year risk of mortality plus MI. The investigators concluded that female sex independently predicts increased 5-year survival.

Identified as potential contributors to favorable outcomes were the use of increased myocardial protection and greater use of arterial conduits during CABG surgery, and smaller guiding catheters and low-profile balloon catheters for PTCA. It should, however, be noted that this means only that gender, per se, does not impart increased risk; the findings should not be construed to mean that women do not have an increased procedural risk, since this analysis corrected for the higher prevalence of risk attributes in women. Comparing CABG and PTCA performed in women, while there were similar in-hospital mortality rates with both procedures, there was an excess of Q-wave MI, heart failure or pulmonary edema with CABG surgery versus PTCA.

While the clinical outcomes achieved with the newer transcatheter revascularizations, particularly stenting, are comparable in men and women, women are more likely to have complications—in particular, the need for vascular repair and transfusion, as well as coronary dissection and hypotension. This is likely related to the larger size of these newer devices relative to women's smaller coronary and peripheral access arteries.

The Potential for Improving Outcomes

Examination of potential contributors to the more adverse outcomes of MI in women might enable appropriate interventions. Women are older, which is a nonmodifiable risk factor, but their greater likelihood to have comorbidities, particularly diabetes and hypertension, offers promise that more aggressive comorbidity management could improve outcomes. Of particular concern is women's lesser eligibility for coronary thrombolysis, related predominantly to their late arrival to the hospital; this variable might be altered favorably if women receive intensive education regarding prompt response to MI symptoms. Also cause for concern is the potential for suboptimal use of medical therapies in women; there has been little

systematic comparative evaluation of antianginal drugs or other agents used in acute coronary syndromes in women, and dosages used in women (often older women) are derived from studies conducted predominantly or exclusively in middle-aged men. Furthermore, there is less use of standard therapies that improve survival with suspected acute MI in women, particularly thrombolytic drugs, beta-blocking drugs and aspirin.[11,12]

Clinician education is the key to ensuring that comparable therapies are provided for both genders. Further, until recently, there was less postinfarction risk stratification for women than for men, with resultant lesser likelihood that invasive diagnostic and therapeutic interventions would be employed. Once risk stratification is undertaken there is essentially comparable intervention by gender when CHD presence and severity have been ascertained. Even today, fewer women than men are referred to cardiac rehabilitation programs, in which exercise training can improve functional status and intensive coronary risk reduction can be undertaken. Clearly, this intervention can be encouraged.

The potential contributors to the less favorable outcomes of myocardial revascularization procedures in women include their greater likelihood of presenting with severe and unstable angina, with resultant increased likelihood of urgent or emergency intervention and its consequent excess morbidity and mortality. Clearly, risk stratification during the stable phase of angina pectoris can avert this problem. More intensive and aggressive therapy across the lifespan could help to address the problem of increased comorbidity, particularly diabetes and hypertension, as is the case with MI. Since women typically have greater functional impairment at referral for myocardial revascularization than do men, the question of whether there is undue delay or a requirement for increased severity of symptoms and impairment before women are considered for myocardial revascularization must be asked. Again, earlier assessment might provide benefit.

Given that CHD is, at least, an equal opportunity killer of women, remediation of the potential contributors to these less favorable outcomes is likely to improve the course of clinical CHD among women. ■

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Evolution of a Clinical Trial: The STOP-DUB Experience

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- Netting the Evidence (**www.shef.ac.uk/~scharr/ir/netting**) ■

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