

Women, Ischemic Heart Disease, Revascularization, and the Gender Gap

What Are We Missing?

Alice K. Jacobs, MD

Boston, Massachusetts

During the past three decades, numerous reports from single-center databases, multicenter registries, and a few randomized trials in patients with ischemic heart disease (IHD) undergoing revascularization with both coronary artery bypass grafting and percutaneous coronary intervention have noted remarkably consistent gender differences in clinical, angiographic, and procedural factors and an increased morbidity and mortality in women. Explanations such as alternative markers of atherosclerosis and novel risk factors in women, gender-specific measures of left ventricular function, and the relationship between disorders more common in women with IHD and adverse cardiovascular outcomes are beginning to unfold. (J Am Coll Cardiol 2006;47:63S-5S) © 2006 by the American College of Cardiology Foundation

This year, an estimated 150,000 women will undergo coronary artery bypass grafting (CABG) and 360,000 women will undergo percutaneous coronary intervention (PCI) for treatment of ischemic heart disease in the U.S. (1). Based upon numerous previous studies (2-4), it is anticipated that periprocedural mortality and morbidity will be significantly higher in women than in men. Most of this difference in outcomes following revascularization has been attributed to the older age in women and to the underlying gender differences in clinical, angiographic, and procedural factors.

In fact, much of what we have learned about the gender differences in patients with IHD has been gleaned from the numerous studies of patients undergoing coronary revascularization during the past three decades. Single-center databases, multicenter registries, and fewer randomized trials have all reported that when compared with men, women have a higher prevalence of risk factors, acute coronary syndromes, (angina) symptoms, and a higher prevalence of congestive heart failure, despite preservation of left ventricular (LV) systolic function, but a similar (or lesser) extent of epicardial coronary disease (5,6). Based upon emerging data from investigations such as the Women's Ischemia Syndrome Evaluation (WISE) study (7), explanations for these seemingly paradoxical observations between the sexes are beginning to unfold.

Have we been looking at the wrong measures of coronary atherosclerosis in women? The Coronary Artery Surgical Study (CASS) registry most clearly demonstrated that for a given extent of coronary artery disease (single, double, or triple vessel) measured by angiography, women were more symptomatic, had more functional (Canadian Cardiovascular Society) impairment, and more unstable symptoms than men (8). Initial skepticism about altered pain threshold and

psychologic factors operative in women has gained credence, and appropriate evaluation and treatment options are currently being evaluated (9). In addition, increased appreciation for syndrome X (chest pain, abnormal (ischemic) stress test, and normal coronary arteries) is based on the finding of abnormal coronary flow velocity reserve suggestive of microvascular dysfunction in women (10). Interestingly, endothelial dysfunction due to a higher prevalence of hypertension and hypercholesterolemia has been implicated as the basis for the increased chest discomfort in women and for the presence of chest pain in the absence of significant coronary artery disease (3). However, aging is associated with progressive endothelial dysfunction in both sexes, and this occurs, in fact, later in women than in men although there is a steep decline in endothelial function around menopause (11,12). These findings suggest a gender difference in the pattern of age-related vascular injury.

Have we been looking at the wrong risk factors for coronary disease in women? Despite a higher prevalence of traditional risk factors in women undergoing coronary revascularization, the extent of epicardial disease is similar to that seen in men (2-6). In fact, in many series, women have a lower prevalence of multivessel disease and fewer significant coronary stenoses. Whether the traditional risk factors are less potent in women (perhaps based on a protective effect of estrogen) or whether women have more diffuse coronary atherosclerosis is unclear. However, these findings have prompted the evaluation of other potential risk factors or markers of disease in women.

Reports from the WISE study investigators have noted that the metabolic syndrome but not obesity (defined by body mass index) is associated with significant coronary artery disease (13), that apolipoprotein E polymorphism is an independent risk factor for the presence and severity of coronary atherosclerosis (14), and that serum amyloid A is independently associated with coronary disease measured by angiography in women (15). Additionally, in patients with

From the Section of Cardiology, Boston University Medical Center, Boston, Massachusetts.

Manuscript received November 1, 2004, accepted December 21, 2004.

Abbreviations and Acronyms

| | |
|------|----------------------------------------|
| CABG | = coronary artery bypass grafting |
| CASS | = Coronary Artery Surgical Study |
| IHD | = ischemic heart disease |
| LV | = left ventricular |
| PCI | = percutaneous coronary intervention |
| WISE | = Women's Ischemia Syndrome Evaluation |

acute coronary syndromes, there is a differential expression of cardiac biomarkers by gender (16). Specifically, men are more likely to have elevated creatine kinase MB and troponins, whereas women are more likely to have elevated C-reactive protein and brain natriuretic peptide. These data suggest that there may be gender differences in the pathophysiologic mechanisms associated with acute coronary syndromes. Atherosclerotic plaque rupture, platelet-rich thrombus, and microembolization may be operative more often in men, whereas small-vessel disease, vascular inflammation, and congestive heart failure may be operative more often in women (16).

Have we been looking at the wrong measure of LV function in women with heart failure? The higher prevalence (and incidence) of congestive heart failure despite a lower prevalence of LV systolic dysfunction (consistent with fewer previous myocardial infarctions) in women in comparison to men undergoing both CABG and PCI has been attributed to diastolic dysfunction and hypertensive heart disease in women (3). In fact, a steeper LV pressure-volume relationship in women has been reported (17). It is noteworthy that heart failure is an independent predictor of mortality following revascularization in both genders (6). Although difficult to study because women are underrepresented in trials of heart failure, owing to older age and preserved LV function serving as exclusions for enrollment (18), several observations have increased our understanding of issues specific to women. In elderly patients hospitalized with (all-cause) heart failure, female gender is an independent predictor of preserved LV systolic function (19). Hypertension, diabetes, and obesity all impart a higher risk, although myocardial infarction appears to impart a lower risk of heart failure in women than in men (20). Furthermore, gender differences in postinfarction hypertrophy and cellular remodeling in end-stage failing hearts have been reported, with women exhibiting reduced hypertrophy (21).

Is there a relationship between the issues specific to women with IHD and outcome following coronary revascularization? Although our understanding of the gender differences in outcomes following coronary revascularization has increased, what is missing is a clear concept of how these gender paradoxes translate into increased morbidity and mortality in women. Recent reports suggest that impaired coronary vasomotor response to acetylcholine is independently linked to adverse cardiovascular outcomes regardless of the severity of coronary atherosclerosis (22), that the metabolic syndrome modifies the risk associated

with coronary artery disease measured by angiography (23), and that lower hemoglobin levels are associated with a higher risk for adverse outcomes in women undergoing evaluation for ischemic heart disease (24) and in patients undergoing PCI (with anemia more frequent in women) (25). It is also noteworthy that in patients with acute coronary syndromes (16), gender differences in the relationship between elevated biomarkers and outcomes have been noted. Elevated biomarkers are associated with a benefit from early coronary revascularization (compared with early conservative therapy) in both genders. However, the absence of at least one positive biomarker is associated with an increased incidence of adverse outcomes in the invasive compared with conservatively treated group of women, whereas there is no difference in outcomes between the two strategies in men. Finally, LV hypertrophy has been shown to be an independent predictor of mortality in patients with coronary artery disease. Although the relative risk of LV hypertrophy does not vary by race or gender, the attributable risk is greater in black patients and in women (26).

Whether our increasing appreciation of the issues and novel risk factors operative in women will result in continued improvement in outcomes following both PCI and CABG remain speculative. What is clear, however, is that the gender gap in mortality in patients undergoing PCI with stable coronary disease (27), acute coronary syndromes (28), ST-segment elevation myocardial infarction (29), and cardiogenic shock complicating acute myocardial infarction (30) has narrowed and that the outcomes in women following both PCI and CABG have improved (4,27,31). Whether the remaining gender difference in outcomes is related to our inability to completely and correctly account for the inherent biologic differences between the genders has yet to be defined. The fact that stents (32,33) and newer surgical techniques, including minimal access approaches (34), have not eliminated the gender difference in mortality following these procedures suggests that periprocedural complications are not the major determinant of survival. Certainly, observations concerning risk-benefit ratios in women with acute coronary syndromes where the benefits of revascularization have been most apparent in those at high risk (28), in ST-segment elevation myocardial infarction where the benefit of primary PCI in comparison to fibrinolytic therapy has been demonstrated (35), and in cardiogenic shock where the benefit of revascularization was similar to that in men (30) will influence the recommendation of these therapies to women.

What is missing is a clear understanding of the relationship between symptoms and microvascular ischemia, of the gender differences in novel risk factors and particularly how they relate to the pathophysiology of acute coronary syndromes, of the independent relationship between heart failure and mortality following revascularization, and of the small but persistent gender difference in (adjusted) outcomes following both CABG and PCI. Fortunately, what is apparent is that the increasing awareness of the burden of

cardiovascular disease in women has resulted in ongoing studies such as those by the WISE study investigators that will address what is missing in our understanding of the gender gap and ultimately improve the care and outcomes in women with IHD.

Reprint requests and correspondence: Dr. Alice K. Jacobs, Section of Cardiology, Boston University Medical Center, 88 East Newton Street, Boston, Massachusetts 02118-2308. E-mail: alice.jacobs@bmc.org.

REFERENCES

1. American Heart Association. Heart Disease and Stroke Statistics—2005 Update. Dallas, TX: American Heart Association, 2005.
2. Fox AA, Nussmeier NA. Coronary artery bypass graft surgery in women. *J Cardiothorac Vasc Anesth* 2004;18:344-52.
3. Jacobs AK. Coronary revascularization in women in 2003: sex revisited. *Circulation* 2003;107:375-7.
4. Malenka DJ, Wennberg DE, Quinton HA, et al. Gender-related changes in the practice and outcomes of percutaneous coronary interventions in northern New England 1994 to 1999. *J Am Coll Cardiol* 2002;40:2092-101.
5. Edwards FH, Carey JS, Grover FL, et al. Impact of gender on coronary bypass operative mortality. *Ann Thorac Surg* 1998;66:125-31.
6. Jacobs AK, Kelsey SF, Brooks MM, et al. Better outcome for women as compared to men undergoing coronary revascularization: a report from the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1998;98:1279-85.
7. Bairey 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;33:1453-61.
8. Davis KB, Chaitman B, Ryan T, Bittner V, Kennedy JW. Comparison of 15-year survival for men and women after initial medical or surgical treatment for coronary artery disease: a CASS registry study. *J Am Coll Cardiol* 1995;25:1000-9.
9. Rosen SD. Hearts and minds: psychological factors and the chest pain of cardiac syndrome X. *Eur Heart J* 2004;25:1672-4.
10. Reis SE, Holubkov R, Smith AJC, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. *Am Heart J* 2001;141:735-41.
11. Celermajer DS, Sorensen KE, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Deanfield JE. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. *J Am Coll Cardiol* 1994;24:471-6.
12. Benjamin EJ, Larson MG, Keyes MJ, et al. Clinical correlates and heritability of flow-mediated dilation in the community. The Framingham Heart Study. *Circulation* 2004;109:613-9.
13. Kip KE, Marroquin OC, Kelly 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;109:706-13.
14. Chen Q, Reis SE, Kammerer CM, et al. APOE polymorphism and angiographic coronary artery disease severity in the Women's Ischemia Syndrome Evaluation (WISE) study. *Atherosclerosis* 2003;169:159-67.
15. Johnson BD, Kip KE, Marroquin OC, et al. Serum amyloid A as predictor of coronary artery disease and cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004;109:726-32.
16. Wiviott SD, Cannon CP, Morrow DA, et al. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST elevation myocardial infarction. A TACTICS-TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18) substudy. *Circulation* 2004;109:580-6.
17. Mendes LA, Davidoff R, Cupples LA, Ryan TJ, Jacobs AK. Congestive heart failure in patients with coronary artery disease: the gender paradox. *Am Heart J* 1997;134:207-12.
18. Wenger NK. Women, heart failure, and heart failure therapies. *Circulation* 2002;105:1526-8.
19. Masoudi FA, Havranek EP, Smith G, et al. Gender, age, and heart failure with preserved left ventricular systolic function. *J Am Coll Cardiol* 2003;41:217-23.
20. Petrie MC, Dawson NF, Murdock DR, Davie AP, McMurray JJV. Failure of women's hearts. *Circulation* 1999;99:2334-41.
21. Crabbe DL, Dipla K, Ambati S, et al. Gender differences in post-infarction hypertrophy in end-stage failing hearts. *J Am Coll Cardiol* 2003;41:300-6.
22. Von Mering GO, Arant CB, Wessel TR, et al. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004;109:722-5.
23. Marroquin OC, Kip KE, Kelley DE, et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women. A report from the Women's Ischemia Syndrome Evaluation. *Circulation* 2004;109:713-21.
24. Arant CB, Wessel TR, Olson MB, et al. Hemoglobin level is an independent predictor for adverse cardiovascular outcomes in women undergoing evaluation for chest pain: results from the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation study. *J Am Coll Cardiol* 2004;43:2009-14.
25. Nikolsky E, Mehran R, Aymong ED, et al. Impact of anemia on outcomes of patients undergoing percutaneous coronary interventions. *Am J Cardiol* 2004;94:1023-7.
26. East MA, Jollis JG, Nelson CL, Marks D, Peterson ED. The influence of left ventricular hypertrophy on survival in patients with coronary artery disease: do race and gender matter? *J Am Coll Cardiol* 2003;41:949-54.
27. Jacobs AK, Johnston JM, Haviland A, et al. Improved outcomes for women undergoing contemporary percutaneous coronary intervention: a report from the National Heart, Lung, and Blood Institute Dynamic Registry. *J Am Coll Cardiol* 2002;39:1606-14.
28. Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. *JAMA* 2002;288:3124-9.
29. Vakili BA, Kaplan RC, Brown DL. Sex-based differences in early mortality of patients undergoing primary angioplasty for first acute myocardial infarction. *Circulation* 2001;104:3034-8.
30. Wong SC, Sleeper LA, Monrad ES, et al. Absence of gender differences in clinical outcomes in patients with cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK trial registry. *J Am Coll Cardiol* 2001;38:1395-1401.
31. Ferguson TB, Hammill BG, Peterson ED, et al. A decade of change: risk profile and outcomes for isolated coronary artery bypass grafting procedures, 1990-1999: a report from the STS National Database Committee and the Duke Clinical Research Institute. Society of Thoracic Surgeons. *Ann Thorac Surg* 2002;73:480-9.
32. Wantanabe CT, Maynard C, Ritchie JL. Comparison of short-term outcomes following coronary artery stenting in men versus women. *Am J Cardiol* 2001;88:848-52.
33. Mehilli J, Kastrati A, Dirschinger J, Bollwein H, Neumann F, Schömig A. Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. *JAMA* 2000;284:1799-805.
34. Petro KR, Dullum MK, Garcia JM, et al. Minimally invasive coronary revascularization in women: a safe approach for a high-risk group. *Heart Surg Forum* 2000;3:41-6.
35. Stone GW, Grines CL, Browne KF, et al. Comparison of in-hospital outcome in men versus women treated by either thrombolytic therapy or primary coronary angioplasty for acute myocardial infarction. *Am J Cardiol* 1995;75:987-92.