

Angina and Cardiac Care Are There Gender Differences, and If So, Why?

Viola Vaccarino, MD, PhD

Differences in cardiac care according to gender have now been described for 20 years. As early as 1987, Tobin et al¹ reported that 40% of male patients with abnormal exercise radionuclide scans were referred for cardiac catheterization, whereas only 4% of the female patients were referred for future testing. Since then, many investigations have continued to describe a less aggressive management strategy for coronary artery disease (CAD) in women than in men in a variety of settings, but predominantly in patients with acute coronary syndromes.²⁻¹¹

Article p 490

Women are normally protected against CAD as compared with men until elderly age, but once they experience an acute myocardial infarction (MI), they have poorer outcomes than their male counterparts, particularly if they are younger than 60 years.^{12,13} It is possible that underrecognition and undertreatment of CAD in its early phase in women is a contributory factor. This may lead to 2 possible scenarios: (1) a more advanced or complicated disease at the time of MI due to lack of preventive treatment, and (2) referral bias due to the fact that only the most severely affected or the most symptomatic women with CAD are eventually diagnosed and treated.

Angina pectoris is the most common initial presentation of symptomatic CAD in women and therefore represents, in many cases, the starting point in the sequence of healthcare delivery events that may result in gender-related inequalities. If there is lower utilization of noninvasive diagnostic testing at this initial point of care, it may translate into delayed diagnosis, delayed initiation of therapeutic interventions, and ultimately worse outcomes. Recognition of such underutilization, therefore, would shed light on whether the more advanced level of symptom severity, comorbidity, and often worse outcomes of women at the time of an MI are due to earlier undertreatment or referral bias. Surprisingly, data are limited about referral patterns according to gender early in the course of CAD, perhaps because of the complexities of collecting a sufficiently large sample of these data in a systematic fashion.

The report by Daly et al¹⁴ in this issue of *Circulation* represents a useful step toward filling this gap. This multinational investigation is the largest evaluation of management and outcome of chronic stable angina according to gender in recent years. It reports on 2197 male and 1582 female patients who received a new diagnosis of stable angina by a cardiologist in 197 participating cardiology services in Europe. Clinical information on the patients and management strategies performed or planned were recorded, and patient follow-up was obtained at 1 year. The results of this study indicate a systematically lower utilization of treatments and diagnostic procedures in women than in men, even though both groups had received a diagnosis of angina pectoris from a cardiologist, and women had a higher angina class. At the initial assessment, women were less likely to be prescribed antiplatelet and statin therapy (despite similar rates of hyperlipidemia) and to be referred for further evaluation with exercise ECG (73% of women and 78% of men) and coronary angiography (31% of women and 49% of men). Adjustment for comorbidity, symptom characteristics, and other factors did not account for the gender differences in procedures, and observed management differences persisted almost unaltered at 1 year.

One obvious explanation for the lower referral of women for coronary angiography is the lower rate of positive stress tests in this group; however, among patients with a positive ECG stress test, a significantly lower proportion of women (56%) than men (65%) received coronary angiography at 1 year. Additionally, among patients with demonstrated CAD by angiography, women had 30% lower adjusted odds of receiving revascularization than men. Even differences in severity of CAD at angiography did not explain gender-based variations in revascularization when added to the model. The latter results are in contrast to other investigations showing that once coronary anatomy is defined by coronary angiography, gender is not an independent predictor of revascularization procedures.^{3,15,16}

A strength of the present study was the examination of patients' outcomes, because this may shed some light on the clinical implications of withholding appropriate patient care. In the entire population, there were no differences in angina symptoms and major cardiovascular events (death or MI) between men and women; however, among patients with confirmed CAD at angiography, women experienced worse outcomes. They continued to experience more angina and had approximately twice the rates of death or MI at 1 year as compared with men. There are 2 possible explanations of these results. First, differential referral by gender was appropriately due to the lower risk of women,¹⁷ but because women with confirmed CAD received fewer secondary prevention

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From Emory University School of Medicine, Division of Cardiology, Atlanta, Ga.

Correspondence to Viola Vaccarino, MD, PhD, Associate Professor of Medicine, Emory University School of Medicine, 1256 Briarcliff Rd, Suite 1N, Atlanta, GA 30306. E-mail viola.vaccarino@emory.edu (*Circulation*. 2006;113:467-469.)

© 2006 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>
DOI: 10.1161/CIRCULATIONAHA.105.602284

treatments than men, worse outcomes in this group were due to undertreatment of women. Surprisingly, however, adjustment for use of statin and antiplatelet medications at the initial assessment did not change the gender-related hazards ratio of death or MI, and adjustment for revascularization tended to widen rather than narrow the gender difference in outcome. A second and more likely explanation for the findings is that differential referral by gender was not appropriate and led to selection bias. Patients needed to undergo coronary angiography, with or without prior noninvasive testing, to confirm the diagnosis of CAD; the women selected for these tests were probably at higher risk than their male counterparts. Their higher-risk status may not have been accounted for completely in the statistical analysis and may have superseded any other factors that potentially contributed to the gender differences, such as treatment.

What accounts for gender differences in the management of chronic angina? One factor likely to play a role is uncertainty about the diagnostic value of exercise stress testing in women, a problem that has been known for quite some time.^{18,19} The lower prevalence of obstructive CAD in women results in lower diagnostic accuracy with a higher rate of false-positive results²⁰; in addition, women's poorer physical performance as compared with men's at the time of testing further limits the value of the test in many cases.²¹ In contrast to exercise stress testing, stress imaging studies are highly accurate for the detection of CAD in women, and pharmacological stress can be used in patients who cannot exercise.²² Thus, if a perception of lower accuracy of treadmill testing was a factor in the study by Daly et al,¹⁴ one would have expected a preferential use of stress cardiac imaging in women. This, surprisingly, was not the case; cardiac imaging studies were used infrequently in both men and women. Despite the limitations of exercise treadmill testing, a recent American Heart Association consensus statement has concluded that evidence is insufficient to remove this test as a first-line evaluation for symptomatic women at intermediate or high pretest likelihood of CAD who are able to exercise. For women who cannot exercise, or who have an abnormal rest ECG, stress cardiac imaging is more appropriate.²²

Another possible explanation for gender differences in the management of angina is the perception that women are at lower risk than their male counterparts, which may translate into a lack of attention to early symptoms and signs of CAD in women. Indeed, a current study shows that physicians are more likely to classify women at a lower-risk category for cardiovascular disease than men despite similar calculated risk,²³ although this was not the finding of an earlier study.¹⁷ The origins of this misconception may go back to epidemiological data that indicate that chronic angina in women has a favorable prognosis as compared with men.^{24,25} With the publication of the Coronary Artery Surgery Study (CASS) data, however, it became clear that 50% of the women referred for coronary angiography for chest pain did not have significant CAD, compared with 17% of the men.²⁶ Thus, many women with chest pain clinically compatible with angina have no significant coronary narrowing, and this may explain why angina in women has been described as a benign

condition. It follows that clinical history alone is not adequate for the diagnosis of angina in women, and confirmatory testing is particularly important, rather than less important, in women with chest pain.

The results of the study by Daly et al¹⁴ are based on European cardiology practices, and their generalizability to other settings is unknown. In addition, it is unclear whether participant cardiologists were truly representative of all cardiologists in the general community. Yet, a population-based study in the United States appears to support these findings by showing a lower utilization of stress testing in women than in men at all ages,²¹ although procedure appropriateness could not be verified. Smaller investigations in Britain also support the notion of less aggressive diagnosis and management of angina in women than in men.^{27,28} In general, despite the plethora of studies of management disparities in patients with acute coronary syndromes, such data are limited in reference to the management of chest pain. In this setting, the results of the study by Daly et al¹⁴ are valuable because they point out the inadequate recognition of coronary heart disease in women at the time of initial manifestation, when preventive strategies could be most effective.

Because of the challenges in the initial diagnosis of CAD in women and the adverse consequences of this disease, at least the same attention should be paid to appropriately investigate chest pain in women as in men. The results of this study indicate that we need to continue striving toward the improvement of the cardiac care of women. Two key areas include the use of appropriate noninvasive diagnostic techniques in women with chest pain and a better education of clinicians toward risk assessment and management of women with suspected or confirmed CAD. It is crucial that an effective diagnostic strategy for women with chest pain be disseminated, leading to interventions aimed at preventing MI in women.

Disclosure

Dr Vaccarino has served as an advisory board member for CV Therapeutics.

References

1. Tobin J, Wassertheil-Smoller S, Wexler JP, Steingart RM, Budner N, Lense L, Wachspress J. Sex bias in considering coronary bypass surgery. *Ann Intern Med.* 1987;107:19–25.
2. Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary heart disease. *N Engl J Med.* 1991;325:221–225.
3. Steingart RM, Packer M, Hamm P, Coglione ME, Gersh B, Geltman EM, Sollano J, Katz S, Moyé L, Basta LL, Lewis SJ, Gottlieb SS, Bernstein V, McEwan P, Jacobson K, Brown EJ, Kukin ML, Kantrowitz NE, Pfeffer MA. Sex differences in the management of coronary artery disease. *N Engl J Med.* 1991;325:226–230.
4. Shaw LJ, Miller DD, Romeis JC, Kargl D, Younis LT, Chaitman BR. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. *Ann Intern Med.* 1994;120:559–566.
5. Yarbzebski J, Col N, Pagley P, Savangeau J, Gore J, Goldberg R. Gender differences and factors associated with the receipt of thrombolytic therapy in patients with acute myocardial infarction: a community-wide perspective. *Am Heart J.* 1996;131:43–50.
6. Kudenchuck PJ, Maynard C, Martin JS, Wirkus M, Weaver WD. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (the Myocardial Infarction Triage and Intervention Registry). *Am J Cardiol.* 1996;78:9–14.

7. Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of acute myocardial infarction and 30-day mortality among women and men. *N Engl J Med*. 2000;343:8–15.
8. Kostis JB, Wilson AC, O'Dowd K, Gregory P, Chelton S, Cosgrove NM, Chirala A, Cui T, for the MIDAS Study Group. Sex differences in the management and long-term outcome of acute myocardial infarction. *Circulation*. 1994;90:1715–1730.
9. Vaccarino V, Rathore SS, Wenger NK, Frederick PD, Abramson JL, Barron HV, Manhapra A, Mallik S, Krumholz HM, the National Registry of Myocardial Infarction Investigators. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. *N Engl J Med*. 2005;353:671–682.
10. Anand SS, Xie CC, Mehta S, Franzosi MG, Joyner C, Chrolavicius S, Fox KA, Yusuf S, CURE Investigators. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. *J Am Coll Cardiol*. 2005;46:1845–1851.
11. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, Brogan GXJ, Boden WE, Roe MT, Ohman EM, Gibler WB, Newby LK, CRUSADE Investigators. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol*. 2005;45:832–837.
12. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. *N Engl J Med*. 1999;341:217–225.
13. Vaccarino V, Krumholz HM, Yarzebski J, Gore JM, Goldberg RJ. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med*. 2001;134:173–181.
14. Daly C, Clemens F, Lopez Sendon JL, Tavazzi L, Boersma E, Danchin N, Delahaye F, Gitt A, Julian D, Mulchay D, Ruzyllo W, Thygesen K, Verheugt F, Fox KM. Gender differences in the management and clinical outcome of stable angina. *Circulation*. 2006;113:490–498.
15. Bell MR, Berger PB, Holmes DRJ, Mullany CJ, Bailey KR, Gersh BJ. Referral for coronary artery revascularization procedures after diagnostic coronary angiography: evidence for gender bias? *J Am Coll Cardiol*. 1995;25:1650–1655.
16. Ghali WA, Faris PD, Galbraith PD, Norris CM, Curtis MJ, Saunders LD, Dzavik V, Mitchell LB, Knudtson ML, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Sex differences in access to coronary revascularization after cardiac catheterization: importance of detailed clinical data. *Ann Intern Med*. 2002;136:723–732.
17. Mark DB, Shaw LK, DeLong ER, Califf RM, Pryor DB. Absence of sex bias in the referral of patients for cardiac catheterization. *N Engl J Med*. 1994;330:1101–1106.
18. Sketch MH, Mohiuddin SM, Lynch JD, Zencka AE, Runco V. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. *Am J Cardiol*. 1975;36:169–173.
19. Detry JM, Kapita BM, Cosyns J, Sottiaux B, Brasseur LA, Rousseau MF. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary heart disease. *Circulation*. 1977;56:756–761.
20. Weiner DA, Ryan TJ, McCabe CH, Kennedy JW, Schloss M, Tristani F, Chaitman BR, Fisher LD. Exercise stress testing: correlations among history of angina, ST-segment response and prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). *N Engl J Med*. 1979;301:230–235.
21. Roger VL, Jacobsen SJ, Pellikka PA, Miller TD, Bailey KR, Gersh BJ. Gender differences in use of stress testing and coronary heart disease mortality: a population-based study in Olmsted County, Minnesota. *J Am Coll Cardiol*. 1998;32:345–352.
22. Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS, Wenger NK. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation*. 2005;111:682–696.
23. Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, Fabunmi RP, Kwan J, Mills T, Simpson SL. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation*. 2005;111:499–510.
24. Kannel WB, Feinleib M. Natural history of angina pectoris in the Framingham Study; prognosis and survival. *Am J Cardiol*. 1972;29:154–163.
25. Orenca A, Bailey K, Yawn BP, Kottke TE. The effect of gender on long-term outcome of angina pectoris and myocardial infarction/sudden unexpected death. *JAMA*. 1993;269:2392–1397.
26. Kennedy JW, Killip T, Fisher LD, Alderman EL, Gillespie MJ, Mock MB. The clinical spectrum of coronary artery disease and its surgical and medical management, 1974–1979: the Coronary Artery Surgery Study. *Circulation*. 1982;66(suppl III):III-16–III-23.
27. Spencer I, Unwin N, Pledger G. Hospital investigation of men and women treated for angina. *BMJ*. 1995;310:1576.
28. Richards H, McConnachie A, Morrison C, Murray K, Watt G. Social and gender variation in the prevalence, presentation and general practitioner provisional diagnosis of chest pain. *J Epidemiol Community Health*. 2000;54:714–718.

KEY WORDS: Editorials ■ angina ■ prevention ■ prognosis ■ sex