Sex Differences in Response to Treatments for Chronic Coronary Artery Disease

Molly Szerlip, MD, Cindy L. Grines, MD, FACC, FSCAI

Department of Cardiovascular Medicine, William Beaumont Hospital, Royal Oak, MI

More women than men die of coronary artery disease (CAD) each year. In women, cardiovascular disease can present atypically and may be caused by small vessel disease rather than by major epicardial coronary luminal narrowing. Women with CAD tend to have more diffuse disease, endothelial dysfunction, and microvascular disease than men. In those studies that have looked at sex differences in treatment response, sex-specific physiologic, pharmacokinetic, and pharmacodynamic differences appear to be the cause. Women have smaller hearts, higher heart rates, shorter cardiac cycle lengths, and longer QT intervals than men. CAD medical treatments such as antiplatelet agents, anticoagulants, β-blockers, and antithrombin agents may have different effects in women and men. Only 30% of percutaneous coronary interventions are performed in women. Women are less likely than men to undergo diagnostic angiography and are more likely to experience delays in treatment.
[Rev Cardiovasc Med. *2009;10(suppl 2):S14-S23 doi: 10.3909/ricm10S20003*]

Key words: Coronary artery disease • Women's health • Antiplatelet agents • Anticoagulants • β-blockers • Antithrombin • Percutaneous coronary intervention

Cardiovascular disease is the leading cause of death in the United States, despite advances in cardiovascular research and technology. In the United States, as in many countries, women die of heart disease more often than their male counterparts. In women, cardiovascular disease often presents atypically and may be caused by small vessel disease rather than by major epicardial coronary luminal narrowing. Nevertheless, the disease can progress to cause chronic disability and adverse cardiovascular events.[1] Not only is the disease process different between the sexes, but in recent years, we have discovered that there may be sex differences in the response to treatments for

coronary artery disease (CAD). This article will discuss differences in the way men and women respond to medications and percutaneous approaches for the treatment of chronic CAD.

CAD in Women

The paradigm of treating CAD originated in the 1950s and was based on data gathered from middle-aged men with CAD. Large population studies such as the Framingham Study (started in 1948) were undertaken to learn how best to approach, treat, and prevent CAD. Up until the late 1980s, it was thought that only men suffered from this disease. It was eventually recognized, however, that women were dying from CAD more often than men were. Data from the Women's Ischemia Syndrome Evaluation (WISE) study were among the first to show pathophysiological differences in CAD between men and women. This large study from the National Heart, Lung, and Blood Institute (NHLBI) found that women tended to have more diffuse disease, endothelial dysfunction, and microvascular disease than men.[2]

Advances in imaging technology (intravascular ultrasound [IVUS], computed tomography [CT], magnetic resonance imaging [MRI], and retinal photography) have allowed a closer look into the characteristics of CAD. Women have smaller coronary arteries, even after adjusting for body surface area.[3] In the presence of cardiac risk factors, women appear to have a different vascular remodeling response to diffuse atherosclerosis. This characteristic is often not seen on plain angiography and can therefore be missed.[2] The available treatment options for CAD have been predominantly studied in large populations of white men. In recent years, with the increasing number of women enrolled in cardiovascular disease studies, it has been recognized that women respond differently to cardiovascular medications. Unfortunately, many of the studies that have enrolled a significant portion of women have not analyzed the data to identify differences between the sexes.

In those studies that have looked at sex differences in treatment response, sex-specific physiologic, pharmacokinetic, and pharmacodynamic differences appear to be the cause. Women have a lower body mass index, smaller organ size, and a higher proportion of body fat, differences that result in a smaller volume of distribution for specific medications.[4] Women also have smaller hearts, higher heart rates, shorter cardiac cycle lengths, and longer QT intervals than their male counterparts. These differences may cause diverging responses to therapies.[5,6] Although drug absorption does not appear to be significantly different between men and women, sex-specific differences in how enzymes metabolize drugs may be clinically relevant.[7] There have been conflicting studies on whether there truly is a difference in enzyme metabolism in men and women. Such differences, if present, could cause levels of drugs to be higher or lower in men or women than what would normally be expected. Furthermore, female-specific factors such as the menstrual cycle, pregnancy, and menopause can cause differences in drug activity.[8] For example, during the menstrual cycle, the cardiac cycle duration fluctuates. This fluctuation disappears if there is complete autonomic blockade.[5] Sex steroid concentrations themselves can change the pharmacokinetics of drugs. Exogenous estrogens and progestins have already been shown to interact with a number of cardiovascular drugs, and may cause drug levels to increase or decrease.[7] Although the ramifications of these differences are unclear, it has been shown that women are 50% to 70% more likely to have adverse reactions to medications, and differences in pharmacokinetics and pharmacodynamics may be the culprit.[9]

CAD Pharmacotherapy

There are many drugs that are used to treat chronic CAD. Just as CAD presents itself differently in men and women, it appears that the medications used to treat this disease may also manifest different responses. Furthermore, it appears that women are treated less often with medications (aspirin, β-blockers, and statins) for secondary prevention of CAD.[10] There are some sex-specific data on antiplatelet agents, anticoagulants, β-blockers, calcium channel blockers, statins, angiotensin-converting enzyme (ACE) inhibitors, antianginals, antithrombotics, and renin angiotensin system blockers. We will discuss a few of these below.

Aspirin

Aspirin is the most studied antiplatelet agent and one of the most studied cardiovascular drugs on the market today. It works by irreversibly inhibiting cyclooxygenase-1, which in turn prevents the conversion of arachidonic acid to thromboxane A2. This action inhibits platelet aggregation and prevents platelets from forming hemostatic plugs in atherosclerotic vessels.[11] Aspirin has well-documented benefits for both the primary and secondary prevention of cardiovascular disease, but these benefits may be different for men and women.[12,13]

Gender differences in platelet reactivity have been described since the early 1970s. Women have higher platelet reactivity than men do, and aspirin achieves greater inhibition of

platelets in men than in women. Furthermore, studies have shown that women are more likely than men to be aspirin-resistant or semiresponders.[14]

Clinically, aspirin plays an important role in the prevention of CAD. This too has shown sex-specific effects. For secondary prevention of myocardial infarction (MI), aspirin therapy consistently lowers mortality in both men and women when compared with placebo. For this reason, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend low-dose aspirin for the secondary prevention of MI.[13] One should keep in mind, however, that the studies recruited far more men than women and, therefore, decision-making on treatment of women is still limited. The significance of aspirin for women in primary prevention is less clear. A prospective, nonrandomized study showed a significant reduction in the risk of first MI in women taking aspirin in more than 6 years of follow-up. There was no effect on stroke.[15] Conversely, Ridker and colleagues[16] in the Women's Health Study showed that there was a reduction in ischemic stroke but not in MI or mortality in women randomized to low-dose aspirin versus placebo. Of note, however, in a subgroup of women ages 65 or older, there was a significant reduction of 26% in cardiovascular events and 30% in ischemic stroke. This benefit was counterbalanced by a 40% increase in gastrointestinal bleeding and a 24% increase in risk of hemorrhagic stroke.[16]

Clopidogrel

Clopidogrel works by preventing adenosine diphosphate–mediated thrombocyte activation and aggregation. Oxidation of clopidogrel by hepatic enzymes (CYP2B6, CYP34A, CYP2C19) and hydrolysis form the active metabolite, which inhibits platelet aggregation. There are no studies with clopidogrel alone that have analyzed the effect on women with established CAD. A few studies have examined the benefit of clopidogrel plus aspirin in women and men who were undergoing elective percutaneous coronary intervention (PCI) and who were at risk of acute coronary syndrome (ACS).[17] The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial studied patients who presented with non–ST-elevation myocardial infarction (NSTEMI) within 24 hours of symptoms. Women had a smaller relative risk reduction when given clopidogrel plus aspirin than men, and there were no differences in major bleeding episodes between men and women.[18] This finding was also seen in the PCI-CURE trial, in which the benefit of these 2 drugs was relatively greater in men than in women who were undergoing PCI for ACS.[19] In the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, patients undergoing elective PCI were given clopidogrel plus aspirin following PCI. This study showed a greater relative risk reduction in women than men for the 1-year combined endpoint of death, MI, or stroke. This reduction was associated with a nonsignificant increase in major bleeding.[20]

β-Blockers

Sex hormones can modulate β-adrenergic receptors in the heart and vasculature. In times of estrogen deficiency, β-1 receptors are upregulated. Hormone supplementation can attenuate this upregulation. It is logical then to assume that the pharmacodynamics and the pharmacokinetics of β-blockers would have sex-specific differences.[8] Cardioselective and noncardioselective β-blockers have been found to have sex-specific differences in their pharmacokinetics. For example, men have greater activity of the liver enzyme CYP2D6, which is known to metabolize some β-blockers, such as metoprolol. This increased activity, added to the significantly lower volume of distribution in women, may result in plasma concentrations that are more than 100% higher in women. These higher plasma concentrations can be further increased in women taking oral contraceptives. Clinically, this difference translates into a more pronounced decrease in heart rate and blood pressure, as well as an inability to increase exercise heart rates as compared with men.[21] Higher plasma concentrations may ultimately result in profound fatigue in women. Studies investigating the sex-specific benefits of β-blockers in secondary prevention after MI have produced conflicting results, primarily due to the low numbers of women that have been enrolled. A recent meta-analysis of 5 studies exploring metoprolol's effect on mortality after MI revealed no difference in the relative reduction of cardiac death between men and women.[22] Investigations of β-blocker therapy in the heart failure literature have provided conflicting results. The Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial demonstrated no differences in relative benefit for women compared with men, whereas the subgroup analysis from the Cardiac Insufficiency Bisoprolol Study (CIBIS II) suggested that women with chronic heart failure have a prognostic advantage (Figure 1).[8,22-24] Once again, the paucity of women in these studies hinders definitive interpretation of the data.

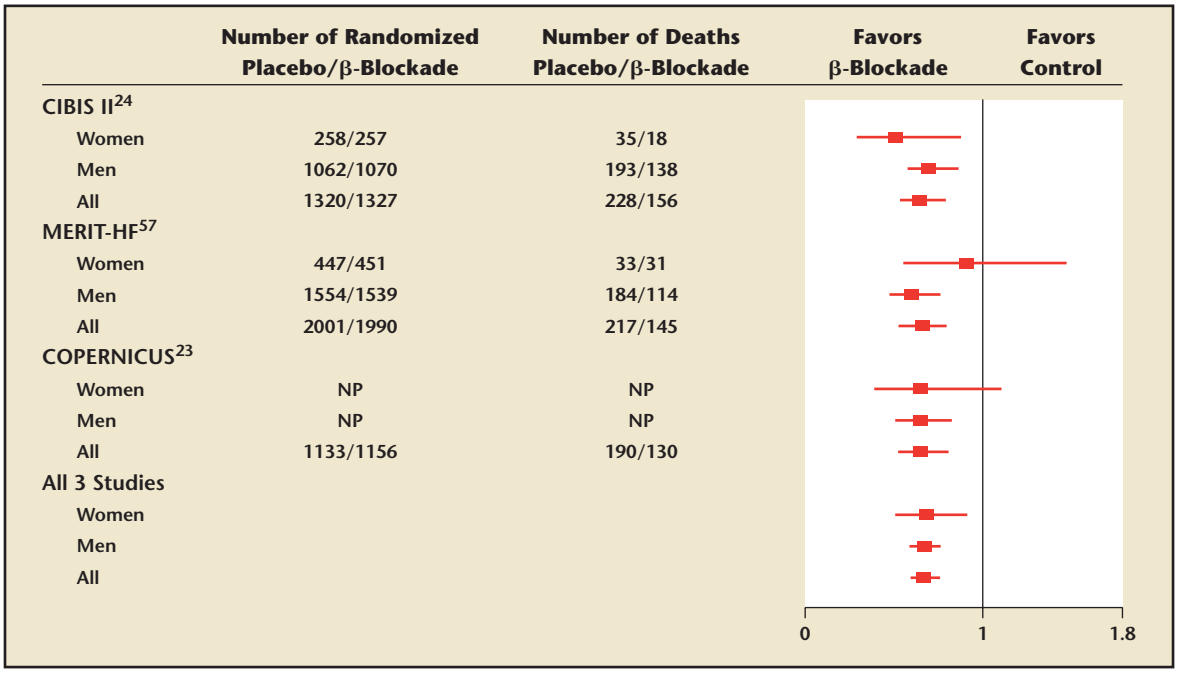

Figure 1. *Relative risk ratios and 95% confidence intervals for total mortality in women and men, in studies evaluating the impact of β-blockade in heart failure. CIBIS II, Cardiac Insufficiency Bisoprolol Study; MERIT-HF, Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; NP, not provided. Reprinted from Jochmann N et al. Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases.* European Heart Journal. *2005;26:1585-1595[8] by permission of the European Society of Cardiology. Adapted with permission from Ghali JK et al. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF).* Circulation. *2002;105(13):1585-1591.[57]*

Statins

Statins are used for primary and secondary prevention of CAD. They are competitive inhibitors of HMG-CoA reductase, resulting in a reduction in intrahepatic cholesterol, an increase in low-density lipoprotein–receptor turnover, and a reduction in overall low-density lipoprotein cholesterol. Some statins increase high-density lipoprotein cholesterol as well, although this increase is modest at best.[25] Statins show only a small pharmacokinetic difference between men and women. Although statin levels are slightly increased in women, the increase is so small that there have not been any recommendations for dose adjustment.[8] Clinically, there do not appear to be differences in statin effect between men and women. In a study of patients who experienced a recent cerebrovascular accident or transient ischemic attack, treatment with atorvastatin 80 mg reduced stroke and cardiovascular events equally in men and women.[26] This effect was seen again in a meta-analysis of 10 studies of patients who were taking statins. The relative risk of severe coronary events was 0.73 for men and 0.77 for women.[27] Despite the equally beneficial effects in primary and secondary prevention of CAD in men and women, women are still treated less frequently with statins.

ACE Inhibitors

Estrogens reduce ACE and renin activity through negative feedback regulation by elevating angiotensin II. Thus, premenopausal women have lower ACE levels than postmenopausal women, although this difference is eliminated by hormone replacement therapy.[28] Whether this decrease affects the activity of ACE inhibitors has not been elucidated. The only study looking at ACE inhibitors and CAD that also analyzed sex differences was the Heart Outcomes Prevention Evaluation (HOPE) study. In this trial, cardiovascular deaths were decreased by 38% (P = .0068) in both men and women.[29] Two other studies evaluating coronary disease and ACE inhibitors, the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA) and the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) study, did not include enough women to make a statement as to whether there were sex differences.[30,31] The PEACE trial of 8290 patients found no benefit of ACE inhibition in either men or women. Frequency of ACE inhibitor side effects, such as angioedema and urticaria, does not appear to differ between men and women.

Ranolazine

Ranolazine is the newest antianginal medication in the CAD armamentarium.

It is used to treat stable angina and has been very effective. It works by reducing sodium entry into cardiac cells, thus maintaining sodium and calcium hemostasis. This action prevents ischemia-induced diastolic dysfunction.[32] There have been 4 large studies evaluating ranolazine: Monotherapy Assessment of Ranolazine in Stable Angina (MARISA), Combination Assessment of Ranolazine in Stable Angina (CARISA), Efficacy of Ranolazine In Chronic Angina (ERICA), and Ranolazine Clinical Study #080 (RAN080).[33-36] Wenger and colleagues[37] summarized sex comparisons of the efficacy and safety of this medication in these studies. Because the designs were different for each study, a meta-analysis was not performed, and each study was individually assessed in reference to sex-specific differences. Ranolazine, in all studies, worked equally as well in reducing angina in men and women. In MARISA, CARISA, and RAN080, ranolazine improved exercise performance in women less frequently than in men. The study investigators believed that this finding suggested only that exercise treadmill tests were a less sensitive indicator of ranolazine efficacy in women.[37]

Antithrombin Agents

Unfractionated heparin (UFH) is used routinely in patients with CAD who are undergoing PCI or coronary artery bypass grafting (CABG). UFH is a thrombin inhibitor, which inactivates Factor Xa by binding both thrombin and antithrombin. Low-molecular-weight heparin (LMWH) is similar, although it binds to antithrombin and has a lesser effect on thrombin due to its size.[38] Conversely, fondaparinux does not bind to thrombin. Heparin has a narrow therapeutic window, and may be associated with bleeding at high doses or clotting at subtherapeutic doses. Women have been shown to have higher heparin levels following equivalent heparin doses than men, especially if they are older. Men and women are at higher risk of bleeding when heparin is used in conjunction with aspirin, glycoprotein (GP) IIb/IIIa inhibitors, or fibrinolysis. This finding has led to weight-based heparin protocols of an intravenous bolus of 60 to 70 U/kg with an infusion of 12 to 15 U/kg/h. The ACC/AHA guidelines recommend lower doses of heparin for women, particularly those who are receiving concomitant GP IIb/IIIa inhibitors.[39] A significant side effect of heparin is heparin-induced thrombocytopenia (HIT). HIT is a drug-induced immune reaction affecting platelets. Large, retrospective studies have found that women are more likely to experience HIT than men are. This finding was again seen in a large German study that looked at multiple databases of medical and surgical patients receiving UFH and LMWH. Women were twice as likely to have HIT (OR, 2.37; 95% confidence interval, 1.37-4.09) than their male counterparts.[40] LMWH as compared with UFH has more bioavailability, more predictable dose response, and less HIT. There is no difference in efficacy and safety in LMWH between men and women for PCI, although there may be a slight increase in bleeding overall.[41]

Bivalirudin is a direct antithrombin with a short half-life that acts on both clot-bound and circulating thrombin. This drug has been shown in multiple studies to reduce the incidence of major bleeding when compared with UFH for use in PCI.[42,43] This finding was also specifically confirmed in women as well. There was a reduction in major and minor bleeding from 34.1% with UFH to 19.7% with bivalirudin. However, despite treatment with bivalirudin, women still have significantly higher risk of bleeding than men.

GP IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors work by binding to the platelet GP IIb/IIIa receptor, which inhibits platelet aggregation. When platelet activation occurs, these receptors are expressed on the platelet surface where they bind to fibrinogen and other protein ligands, forming a bridge between 2 platelets. This activity promotes platelet aggregation. The GP IIb/IIIa inhibitors bind to the receptor and inhibit the platelets from binding to each other. A few studies have looked at sex differences with GP IIb/IIIa inhibitors with respect to nonurgent PCI. A pooled analysis of 3 trials (Evaluation of c7E3 for the Prevention of Ischemic Complications [EPIC], Evaluation in PTCA to Improve Long-Term Outcome With Abciximab GP IIb/IIIa Blockade [EPILOG], and Evaluation of Platelet Inhibition in Stenting [EPISTENT]) examined sex differences with the use of abciximab and heparin in PCI.[44] Abciximab reduced the composite endpoint of death, MI, or urgent revascularization in both men and women at 30 days and 6 months (30 days: from 11.3% to 5.8% in men and from 12.7% to 6.5% in women; 6 months: from 14.1% to 8.3% in men and from 16% to 9% in women). At 1 year, mortality was decreased from 2.7% to 1.9% in men and 4.0% to 2.5% in women. Major and minor bleeding were increased in women with and without abciximab.[44]

The Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy (ESPRIT) trial examined use of heparin and eptifibatide in PCI. Although women were at higher risk, there were no differences between men and women in

absolute benefit of reducing death, MI, urgent revascularization, or "bail-out" GP IIb/IIIa inhibitor use at 48 hours (from 14.5% to 6.0% in men and from 28.9% to 20% in women). Nor was there any difference in men and women in the combined endpoint of death, MI, and target-vessel revascularization at 1 year (from 9% to 6.8% in men and from 19.5% to 16.6% in women). There was, however, an increase in bleeding events in women, especially with eptifibatide.[45]

Invasive Therapy

PCI

Sex-based differences in the outcomes of PCI have decreased since the advent of contemporary treatment with drug-eluting stents (DES). Despite the well-established benefit of PCI, and data showing that more women than men die of cardiovascular disease each year, only 30% of the 1.2 million PCIs performed annually in the United States are in women. Women are less likely to be sent for diagnostic angiography and are more likely to experience delays in treatment. This disparity exists despite growing evidence suggesting that outcomes after PCI are similar in men and women. Many reasons have been cited for the lack of referrals to PCI for women. Some of these include small body size, small coronary vessels, older age, increased risk profile, and atypical symptoms. Recent advances in equipment and devices have allowed optimal treatment in these less optimal circumstances.[41]

In 2008, Singh and colleagues[46] published data gathered from the Mayo Clinic experience with PCI from 1979 to 1995 and 1996 to 2004. They found that women were more likely to have diabetes, hypertension, and hyperlipidemia. Women also had higher absolute adverse event rates. After adjustment for risk factors, however, the 30-day and long-term mortality rates from 1994 onward were similar between men and women.[46] Glaser and coworkers[47] echoed these findings with data from the NHLBI-sponsored Dynamic Registry, which included 20 centers. In this study, investigators examined 1-year major adverse cardiac event (MACE) outcomes of PCI in stable angina versus non–ST-elevation acute coronary syndromes (NSTACS) in women compared with men. In the stable angina cohort, outcomes were similar in both men and women, but outcomes were higher for women in the NSTACS group.[47] In a study by Lansky and colleagues[41] of risk-adjusted outcomes of elective PCI in 15 studies, there was an increase in in-hospital mortality in women compared with men, but no difference in outcomes of late mortality (Figure 2).

There have been many studies exploring sex differences with the type of stent (DES vs bare-metal stent [BMS]) deployed. Prior to the stenting era, angioplasty studies reported higher rates of angiographic success, lower incidence of procedural complications, and better long-term outcomes in men compared with women.[48] With the advent of stents, specifically DES, 1-year MACE rates and target-vessel revascularization in men and women seem to be similar. Earlier BMS study subgroup analyses showed conflicting results on whether MACE rates were comparable between men and women. There have been 2 more recent studies of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) comparing outcomes in men and women. The first looked at data derived from the TAXUS IV trial. This trial demonstrated the safety and efficacy of PES versus BMS in elective PCI. Women with PES had higher rates of ischemia-driven target-vessel revascularization and target-lesion revascularization than men with PES. When the data were adjusted for confounding factors (diabetes, vessel size, and body surface area), there was no difference between men and women.[49] Similar observations have been made with SES. Solinas and colleagues[50] published their data on 1748 patients (1251 men and 497 women) who were randomized to SES or BMS. Compared with men, women were more likely to have diabetes, hypertension, and congestive heart failure. Treatment with SES had comparable outcomes in all endpoints between men and women. Women with an SES had an 86% reduction in in-lesion binary restenosis and a 92% reduction in in-stent binary restenosis as compared with women who received a BMS. Men with an SES had an 82% reduction in in-lesion binary restenosis and a 93% reduction in in-stent binary restenosis as compared with men who received a BMS. Overall, there was a 66.7% reduction in 1-year MACE. Unlike in TAXUS IV, women did not have a significant difference in the unadjusted data. This finding may be due to the differences in drugs and polymers that have been seen in SES and PES.[50]

As mentioned earlier, women tend to be offered PCI less often than men are. One of the reasons for this difference is the increase in vascular complications in women compared with men. Although vascular complication rates have decreased over time, women still have a 1.5 to 4 times higher risk of vascular complications than their male counterparts. This finding is illustrated by Applegate and colleagues,[51] who evaluated 20,645 patients undergoing 31,000 diagnostic catheterizations or PCIs from the femoral approach between the years 1998 and 2005. As seen in other studies, the

Study	N	Unadjusted Mortality Rate: Women (%)	Men (%)	*P* Value
Watanabe[58]	82,783	35	1.1	0.5	<.0001
Alfonso[59]	981	16	6.0	2.0	.01
WHC[60]	7372	28	1.39	0.66	<.002
Malenka[61]	12,232	NA	1.64	0.7	<.001
Bell[62]	3557	27	4.2	2.7	.005
NHLBI[63]	2136	26	2.6	0.3	<.001
NCN*[64]	150,918	33	1.8	1.0	–
Mehilli†[65,66]	4264	24	3.1	1.9	.02
Welty[67]	5989	35	1.2	0.52	.017
Malenka[68]	33,666	33	1.2	1.1	.1
NHLBI[69]	2524	35	2.2	1.3	–
NCN[70]	109,708	33	1.8	1.0	<.001
Arnold[71]	5000	25	1.1	0.3	.001
NACI[72]	2855	34	1.4	1.1	NS
Weintraub[73]	10,785	26	0.7	0.1	<.001

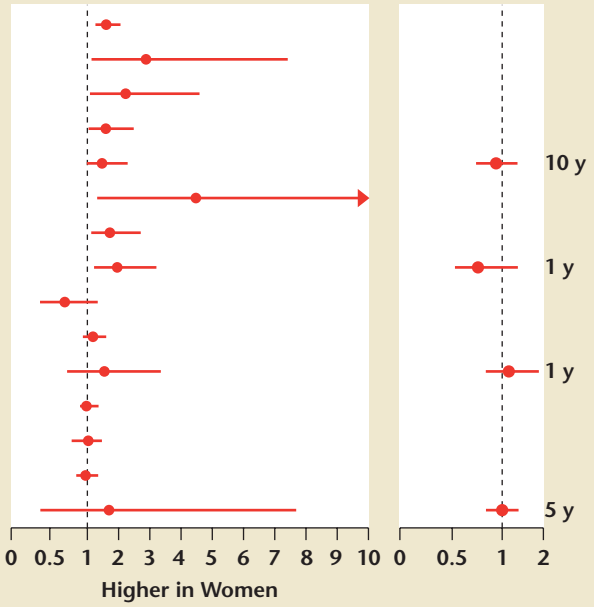

Figure 2. *In-hospital and late mortality rates in women versus men after percutaneous coronary interventions that were mostly elective. *The adjusted OR is for women younger than 50 years. †The in-hospital figures are for death and myocardial infarction. OR, odds ratio; CI, confidence interval; WHC, Washington Hospital Center; NHLBI, National Heart, Lung, and Blood Institute; NCN, National Cardiovascular Network; NACI, New Approaches to Coronary Intervention. Reprinted with permission from Lansky AJ et al. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association.* Circulation. *2005;111(7):940-953.*[41]

incidence of vascular complications did decrease over time in both sexes, although at the end of this study, there was still a higher incidence in women than in men. This higher incidence persisted even after rates were adjusted for confounding variables. Predictors of vascular complications for both men and women included closure device failure, history of renal failure, age, peripheral vascular disease, and sheath size.[51] Decreasing vascular complication rates in women have been attributable to reduction in levels of periprocedural anticoagulation and an increase in bivalirudin use. Although the transradial approach has reduced complications in men, women still have higher hematoma rates than men with the use of this access approach.[52]

Coronary Artery Bypass Grafting

There have been mixed results on outcomes of women undergoing CABG. In earlier trials, operative mortality in women seemed to be higher than in men, although long-term mortality seemed to be similar. Many theories have been explored as to why women may have higher operative mortality. Women have increased comorbid factors including smaller body surface area, smaller coronary arteries, and older age, and they are less likely to receive internal mammary grafts.[53] More recently, in the Bypass Angioplasty Revascularization Investigation (BARI) trial, in-hospital mortality was similar between men and women (1.3% vs 1.4%). In this study, women had a higher rate of pulmonary edema, congestive heart failure, and Q-wave MI. These results were not specifically attributable to sex differences, but instead reflected the increased risk profile among women.[54]

A recent meta-analysis of 23 studies between 1985 and 2005 involving outcomes with CABG reported conflicting results. In this study, women had higher in-hospital mortality, although after adjusting for comorbidities, the magnitude of risk decreased.[55] The data have been more consistent regarding long-term mortality rates between men and women. There does not seem to be a difference between men and women in regard to long-term mortality rates. This similarity was most recently seen in the Arterial Revascularization Therapies Study II (ARTS II).[56] In this study, patients were randomized to an SES or CABG. Follow-up was performed at 1, 6, and

12 months, and at 3 and 5 years. There was no difference between men and women for major adverse cardiac and cerebrovascular events at any of the follow-up time points.[56]

Conclusion

There are still many unanswered questions regarding differences in the ways men and women with CAD respond to treatment. Most of the data analyses are retrospective and involve very few women. More studies specifically looking at treatment differences between men and women must be performed. More women should be enrolled into cardiovascular disease studies, and the reasons why women do not receive evidence-based treatment should be elucidated. Only then will we be able to win the war on cardiovascular disease. ■

Acknowledgment: Drs. Szerlip and Grines have no real or apparent conflicts of interest to report.

References

1. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *J Am Coll Cardiol*. 2007;49:1230-1250.
2. Bairey Merz CN, Shaw LJ, Reis SE, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol*. 2006;47(3 suppl):S21-S29.
3. Sheifer SE, Canos MR, Weinfurt KP, et al. Sex differences in coronary artery size assessed by intravascular ultrasound. *Am Heart J*. 2000;139:649-653.
4. Meibohm B, Beierle I, Derendorf H. How important are gender differences in pharmacokinetics? *Clin Pharmacokinet*. 2002;41:329-342.
5. Burke JH, Goldberger JJ, Ehlert FA, et al. Gender differences in heart rate before and after autonomic blockade: evidence against an intrinsic gender effect. *Am J Med*. 1996;100:537-543.
6. Legato MJ. Gender and the heart: sex-specific differences in normal anatomy and physiology. *J Gend Specif Med*. 2000;3:15-18.
7. Schwartz JB. The influence of sex on pharmacokinetics. *Clin Pharmacokinet*. 2003;42:107-121.
8. Jochmann N, Stangl K, Garbe E, et al. Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. *Eur Heart J*. 2005;26:1585-1595.
9. Rademaker M. Do women have more adverse drug reactions? *Am J Clin Dermatol*. 2001;2:349-351.
10. Enriquez JR, Pratap P, Zbilut JP, et al. Women tolerate drug therapy for coronary artery disease as well as men do, but are treated less frequently with aspirin, beta-blockers, or statins. *Gend Med*. 2008;5:53-61.
11. Maree AO, Fitzgerald DJ. Aspirin and coronary artery disease. *Thromb Haemost*. 2004;92:1175-1181.
12. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation*. 2002;106:388-391.
13. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113:2363-2372.
14. Zuern CS, Lindemann S, Gawaz M. Platelet function and response to aspirin: gender-specific features and implications for female thrombotic risk and management. *Semin Thromb Hemost*. 2009;35:295-306.
15. Manson JE, Stampfer MJ, Colditz GA, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. *JAMA*. 1991;266:521-527.
16. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005;352:1293-1304.
17. Grines C, Cho L. Atherothrombotic disease and the role of antiplatelet therapy in women. *J Womens Health (Larchmt)*. 2008;17:35-46.
18. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
19. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527-533.
20. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411-2420.
21. Luzier AB, Killian A, Wilton JH, et al. Gender-related effects on metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. *Clin Pharmacol Ther*. 1999;66:594-601.
22. Olsson G, Wikstrand J, Warnold I, et al. Metoprolol-induced reduction in postinfarction mortality: pooled results from five double-blind randomized trials. *Eur Heart J*. 1992;13:28-32.
23. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation*. 2002;106:2194-2199.
24. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Circulation*. 2001;103:375-380.

Main Points

- In women, cardiovascular disease presents atypically and may be caused by small vessel disease rather than by major epicardial coronary luminal narrowing.
- Women are treated less often than men with medications (aspirin, β-blockers, and statins) for secondary prevention of coronary artery disease.
- Women have higher platelet reactivity than men, and aspirin achieves greater inhibition of platelets in men than in women.
- Women have a smaller relative risk reduction when given clopidogrel plus aspirin than men do.
- Women have been shown to have higher heparin levels with equivalent doses than men do, especially if they are older.
- Of the 1.2 million percutaneous coronary interventions performed annually in the United States, only 30% are performed in women.

25. Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science*. 2001;292:1160-1164.
26. Goldstein LB, Amarenco P, Lamonte M, et al. Relative effects of statin therapy on stroke and cardiovascular events in men and women: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study. *Stroke*. 2008;39:2444-2448.
27. Cheung BM, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *Br J Clin Pharmacol*. 2004;57:640-651.
28. Schunkert H, Danser AH, Hense HW, et al. Effects of estrogen replacement therapy on the renin-angiotensin system in postmenopausal women. *Circulation*. 1997;95:39-45.
29. Lonn E, Roccaforte R, Yi Q, et al. Effect of long-term therapy with ramipril in high-risk women. *J Am Coll Cardiol*. 2002;40:693-702.
30. Fox KM; for the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782-788.
31. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058-2068.
32. Belardinelli L, Shryock JC, Fraser H. Inhibition of the late sodium current as a potential cardioprotective principle: effects of the late sodium current inhibitor ranolazine. *Heart*. 2006;92(suppl 4):iv6-iv14.
33. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol*. 2004;43:1375-1382.
34. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA*. 2004;291:309-316.
35. Stone PH, Gratsiansky NA, Blokhin A, et al. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol*. 2006;48:566-575.
36. Rousseau MF, Pouleur H, Cocco G, Wolff AA. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. *Am J Cardiol*. 2005;95:311-316.
37. Wenger NK, Chaitman B, Vetrovec GW. Gender comparison of efficacy and safety of ranolazine for chronic angina pectoris in four randomized clinical trials. *Am J Cardiol*. 2007;99:11-18.
38. Campbell NR, Hull RD, Brant R, et al. Different effects of heparin in males and females. *Clin Invest Med*. 1998;21:71-78.
39. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). *J Am Coll Cardiol*. 2004;44:E1-E211.
40. Warkentin TE, Sheppard JA, Sigouin CS, et al. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. *Blood*. 2006;108:2937-2941.
41. Lansky AJ, Hochman JS, Ward PA, et al. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2005;111: 940-953.
42. Kastrati A, Neumann FJ, Mehilli J, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med*. 2008;359:688-696.
43. Lincoff AM, Kleiman NS, Kereiakes DJ, et al. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA*. 2004; 292:696-703.
44. Cho L, Topol EJ, Balog C, et al. Clinical benefit of glycoprotein IIb/IIIa blockade with Abciximab is independent of gender: pooled analysis from EPIC, EPILOG and EPISTENT trials. Evaluation of 7E3 for the Prevention of Ischemic Complications. Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stent. *J Am Coll Cardiol*. 2000; 36:381-386.
45. Fernandes LS, Tcheng JE, O'Shea JC, et al. Is glycoprotein IIb/IIIa antagonism as effective in women as in men following percutaneous coronary intervention? Lessons from the ESPRIT study. *J Am Coll Cardiol*. 2002;40: 1085-1091.
46. Singh M, Rihal CS, Gersh BJ, et al. Mortality differences between men and women after percutaneous coronary interventions. A 25-year, single-center experience. *J Am Coll Cardiol*. 2008;51:2313-2320.
47. Glaser R, Selzer F, Jacobs AK, et al. Effect of gender on prognosis following percutaneous coronary intervention for stable angina pectoris and acute coronary syndromes. *Am J Cardiol*. 2006;98:1446-1450.
48. Kelsey SF, James M, Holubkov AL, et al. Results of percutaneous transluminal coronary angioplasty in women. 1985-1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry. *Circulation*. 1993;87: 720-727.
49. Lansky AJ, Costa RA, Mooney M, et al. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. *J Am Coll Cardiol*. 2005;45:1180-1185.
50. Solinas E, Nikolsky E, Lansky AJ, et al. Gender-specific outcomes after sirolimus-eluting stent implantation. *J Am Coll Cardiol*. 2007;50: 2111-2116.
51. Applegate RJ, Sacrinty MT, Kutcher MA, et al. Vascular complications in women after catheterization and percutaneous coronary intervention 1998-2005. *J Invasive Cardiol*. 2007;19:369-374.
52. Tizón-Marcos H, Bertrand OF, Rodés-Cabau J, et al. Impact of female gender and transradial coronary stenting with maximal antiplatelet therapy on bleeding and ischemic outcomes. *Am Heart J*. 2009;157:740-745.
53. Mikhail GW. Coronary revascularisation in women. *Heart*. 2006;92(suppl 3)iii19-iii23.
54. Jacobs AK, Kelsey SF, Brooks MM, et al. Better outcome for women compared with men undergoing coronary revascularization: a report from the bypass angioplasty revascularization investigation (BARI). *Circulation*. 1998;98:1279-1285.
55. Kim C, Redberg RF, Pavlic T, Eagle KA. A systematic review of gender differences in mortality after coronary artery bypass graft surgery and percutaneous coronary interventions. *Clin Cardiol*. 2007;30:491-495.
56. Vaina S, Voudris V, Morice MC, et al. Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularisation in patients with multivessel coronary artery disease: insights from ARTS I and ARTS II. *EuroIntervention*. 2009; 4:492-501.
57. Ghali JK, Piña IL, Gottlieb SS, et al. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). *Circulation*. 2002;105:1585-1591.
58. Watanabe CT, Maynard C, Ritchie JL. Comparison of short-term outcomes following coronary artery stenting in men versus women. *Am J Cardiol*. 2001;88:848-852.
59. Alfonso F, Hernandez R, Bañuelos C, et al. Initial results and long-term clinical and angiographic outcome of coronary stenting in women. *Am J Cardiol*. 2000;86:1380-1383.
60. Lansky AJ, Mehran R, Dangas G, et al. New-device angioplasty in women: clinical outcome and predictors in a 7,372-patient registry. *Epidemiology*. 2002;13(3 suppl):S46-S51.
61. Malenka DJ, O'Connor GT, Quinton H, et al. Differences in outcomes between women and men associated with percutaneous transluminal coronary angioplasty. A regional prospective study of 13,061 procedures. Northern New England Cardiovascular Disease Study Group. *Circulation*. 1996;94(9 suppl):II99-II104.
62. Bell MR, Holmes DR Jr, Berger PB, et al. The changing in-hospital mortality of women undergoing percutaneous transluminal coronary angioplasty. *JAMA*. 1993;269:2091-2095.
63. Kelsey SF, Miller DP, Holubkov R, et al. Results of percutaneous transluminal coronary angioplasty in patients greater than or equal to 65 years of age (from the 1985 to 1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry). *Am J Cardiol*. 1990;66: 1033-1038.
64. Abramson JL, Veledar E, Weintraub WS, Vaccarino V. Association between gender and in-hospital mortality after percutaneous coronary intervention according to age. *Am J Cardiol*. 2003;91:968-971.
65. Mehilli J, Kastrati A, Dirschinger J, et al. Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. *JAMA*. 2000;284:1799-1805.
66. Mehilli J, Kastrati A, Bollwein H, et al. Gender and restenosis after coronary artery stenting. *Eur Heart J*. 2003;24:1523-1530.
67. Welty FK, Lewis SM, Kowalker W, Shubrooks SJ Jr. Reasons for higher in-hospital mortality >24 hours after percutaneous transluminal

coronary angioplasty in women compared with men. *Am J Cardiol*. 2001;88:473-477.
68. Malenka DJ, Wennberg DE, Quinton HA, et al. Gender-related changes in the practice and outcomes of percutaneous coronary interventions in Northern New England from 1994 to 1999. *J Am Coll Cardiol*. 2002;40:2092-2101.
69. 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;39:1608-1614.
70. Peterson ED, Lansky AJ, Kramer J, et al. Effect of gender on the outcomes of contemporary percutaneous coronary intervention. *Am J Cardiol*. 2001;88:359-364.
71. Arnold AM, Mick MJ, Piedmonte MR, Simpfendorfer C. Gender differences for coronary angioplasty. *Am J Cardiol*. 1994;74:18-21.
72. Robertson T, Kennard ED, Mehta S, et al. Influence of gender on in-hospital clinical and angiographic outcomes and on one-year follow-up in the New Approaches to Coronary Intervention (NACI) registry. *Am J Cardiol*. 1997;80:26K-39K.
73. Weintraub WS, Wenger NK, Kosinski AS, et al. Percutaneous transluminal coronary angioplasty in women compared with men. *J Am Coll Cardiol*. 1994;24:81-90.