Coronary Intervention in 2009
Are Women No Different Than Men?

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Cardiovascular disease remains the leading cause of death in the United States in both women and men, and each year for more than 2 decades, more women than men have died (Figure 1). In 2006, 41.3 million women (34.9%) and 38.7 million men (37.6%) were living with cardiovascular disease, reflecting mortality in 454.6 thousand women and 409.9 thousand men in 2005, with coronary heart disease responsible for 1 of every 5 deaths overall. In fact, the lifetime risk of developing coronary heart disease after age 40 is 49% in men and 32% in women. Furthermore, it is estimated that in 2009, cardiovascular disease and stroke will cost the nation $475.3 billion.1

Despite these sobering statistics, marked disparities in cardiovascular health and care, and specifically in the delivery and outcomes of coronary revascularization therapy, persist between women and men. Of the 1.3 million percutaneous coronary intervention (PCI) procedures performed in 2006, only 35% were performed in women,1 despite the known benefits of this treatment, particularly in high-risk women with acute coronary syndromes (ACS)2 and ST-segment elevation myocardial infarction (STEMI).3,4 Moreover, for those women treated with PCI, unadjusted mortality (Figure 2) and (vascular and bleeding) complication rates (Figure 3) remain significantly higher than in men.5,6

Whether these sex differences are explained by pathophysiology by impaired access to guideline-recommended therapies, by biology or bias, by lack of a robust evidence base in women, or by the artificial comparison between women and men as their control group, continues to be actively debated. Certainly, the seemingly paradoxical findings of a higher prevalence of risk factors, more severe angina symptoms but a similar (or lesser) extent of epicardial coronary disease, and of a higher prevalence of congestive heart failure despite better of left ventricular systolic function in women compared with men undergoing coronary revascularization, are likely based on underlying sex differences in vascular and myocardial physiology, structure, and function.7 Given the increasing awareness by patients, the public, and healthcare providers of the prevalence and impact of coronary heart disease in women, it is timely to review the current status and issues concerning coronary intervention in women,8,9 focusing on biology and pathophysiology, access to care, and outcomes across the spectrum of coronary disease acuity. A greater understanding of the basis for the ongoing sex disparities in patients undergoing PCI may serve as a platform to improve the overall quality of cardiovascular health care in women.

Sex-Related Differences in the Biology and Pathophysiology of Cardiovascular Disease

Whether the increased mortality after PCI and MI in women in comparison with men can be explained by factors inherent to the female sex is unclear. However, several vascular abnormalities more prevalent in women including vasospastic disorders, Raynaud phenomenon, various forms of vasculitis, and migraine headaches underlie the concept of sex differences in the pathophysiology of ischemic vascular disease. In addition, the macro- and microvasculature is smaller and stiffer, with more diffuse atherosclerosis and endothelial as well as smooth muscle dysfunction in women as compared with men.10 Of note, impairment of coronary flow reserve, as assessed by intracoronary response to adenosine, has served as a marker of microvascular smooth muscle cell dysfunction and has been shown to be an independent predictor of adverse cardiovascular outcomes in women.11

Many of these differences in the vasculature have been attributed to female sex steroid hormones and their fluctuations throughout the life cycle in women; the expression of sex steroid hormone receptors and aromatase (which converts testosterone to estrogen in specific tissues) in blood vessels is well recognized but how the expression of these proteins in cardiovascular cells varies with vascular bed, the presence of cardiovascular risk factors, or sex is unknown.12 Sex steroid hormones have been implicated in control of vascular tone and blood pressure. Estrogens have been shown to cause vasodilatation through both rapid increases in nitric oxide production and the induction of nitric oxide synthase genes.13 Vasodilatation and blood pressure are both affected by changes in circulating estrogen levels during the menstrual cycle, pregnancy, or estradiol replacement.14 Sex steroid hormones and hormone replacement therapy regulate lipid abnormalities, primarily by way of hepatic effects on lipoprotein metabolism.15 Moreover, several genes coding for proteins involved in hemostasis are regulated by sex hormones and suggest a molecular mechanism for the observation that estrogens increase the risk of venous thrombosis.16 However, the relevance of this finding to arterial thrombosis is not well
explored. Importantly, aspirin decreases platelet reactivity to a similar extent in women and men (although it is not as effective in the primary prevention of MI in women). Yet, despite these biological explanations for many of the sex differences in clinical manifestations of cardiovascular disease, notably, there is no abrupt rise in the prevalence of disease in women in comparison with men at the time of menopause.

On the basis of the observation that many therapeutic drugs affect women and men differently, and that adverse drug reactions tend to occur more often in women (such as a higher incidence of hemorrhagic stroke after fibrinolytic therapy and of QT prolongation and torsades de pointes), biological and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics are being explored. Biological factors that influence differences in pharmacokinetics include a lower body weight but higher body fat in women. In addition, sex differences in gastric emptying, acidity, and enzymes, in the activity of several isoenzymes in the liver, and in the glomerular filtration rate have been reported.

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 to account for the observation that despite a higher prevalence of traditional risk factors in women undergoing coronary revascularization, the extent of epicardial disease detected by angiography is similar to that seen in men is unclear. However, these findings have lead to the evaluation of other potential risk factors or markers of disease in women.

It has been reported that in women, the metabolic syndrome but not obesity is associated with significant coronary artery disease, that serum amyloid A is independently associated with coronary disease measured by angiography, and that apolipoprotein E polymorphism is an independent risk factor for the presence and severity of coronary atherosclerosis. In addition, in patients with ACS, there is a differential expression of cardiac biomarkers by sex. Specifically, elevated C-reactive protein and brain natriuretic peptide are more likely to be elevated in women whereas creatine kinase-MB and troponins are more likely to be elevated in men. These data suggest that there may be sex differences

**Figure 1.** Cardiovascular mortality trends for males and females in the United States, 1979 to 2005. Reproduced with permission from Ref. 1, Copyright © 2009 American Heart Association.

**Figure 2.** In-hospital and late mortality rates in women versus men after PCI. NACI indicates New Approaches to Coronary Intervention; NCN, National Cardiovascular Network; NHLBI, National Heart, Lung, and Blood Institute; WHC, Washington Hospital Center. Reproduced with permission from Reference 53.
in the pathophysiologic mechanisms associated with ACS. Small-vessel disease, vascular inflammation, and congestive heart failure may occur more often in women whereas atherosclerotic plaque rupture, platelet-rich thrombus, and microembolization may occur more often in men. In fact, in the Global Use of Strategies to Open Occluded Coronary Arteries in ACS (GUSTO) IIb, even after adjustment for baseline differences between the sexes, women were significantly less likely to present with the syndrome associated with occlusive thrombus, STEMI. Furthermore, sex-based differences in serum cardiac troponin I have been reported in patients after cardiac surgery where men had significantly higher values than women although they were case matched with respect to age and risk factors. Taken together, these data support the concept that there may be sex-related differences in the myocardial response to ischemia and reperfusion injury or intrinsic differences between the male and female myocardium.

Finally, compelling evidence implicates a higher incidence of hypertensive heart disease, a steeper pressure-volume relationship, and more diastolic dysfunction to explain the consistent observation of a higher incidence of congestive heart failure despite better left ventricular function (with fewer previous infarctions) in women in comparison with men undergoing coronary intervention. Reports of sex differences in molecular remodeling in pressure overload hypertrophy and in cardiac adaptation to isolated systolic hypertension support these findings. In addition, it is postulated that sex steroid-mediated changes in the levels and regulation of myocardial calcium contractility coupling proteins in the heart are responsible for the effects of these hormones on myocardial hypertrophy and heart failure. Sex differences in these relationships are difficult to study because women are underrepresented in trials of heart failure based on their older age and preserved left ventricular function that serve as exclusions for enrollment. However, it has been reported that in elderly patients hospitalized with (all cause) heart failure, female gender was an independent predictor of preserved left ventricular systolic function.

Figure 3. Meta-analysis of vascular complications in women versus men undergoing PCI. BOAT indicates Balloon Versus Optimal Atherectomy; CAVEAT, Coronary Angioplasty Versus Excisional Atherectomy; NACI, New Approaches to Coronary Intervention; NCN, National Cardiovascular Network; NHLBI, National Heart, Lung and Blood Institute; STARS, Stent Antithrombotic Regimen Study; WHC, Washington Hospital Center. Reproduced with permission from Reference 53.

Gender Differences in Access to Evidence-Based Therapy: Biology or Bias?
In its broadest sense, the term “health disparities” refers to preventable differences in the indicators of health of different population groups, usually defined by race, ethnicity, socioeconomic status, geographic location of residence, education level, and sex. Interestingly, these disparities have been documented for nearly 2 centuries. Whether sex differences in the biological and pathophysiologic manifestation of cardiovascular disease translate into differences in access to and delivery of evidence-based therapies is not well defined. During the past 2 decades, several reports have indicated that women experience greater delays to intervention and are referred for diagnostic catheterization less frequently than men. Although women’s older age, differences in symptoms and pain perception, and a higher prevalence of comorbidities, lower predictive accuracy of noninvasive testing, and an increased risk for an adverse procedural outcome in women have been proposed as explanations for these observations, there is some evidence to suggest a potential gender and racial bias. Yet increasingly it has been recognized that socioeconomic and cultural factors and lack of awareness of the prevalence and implications of coronary heart disease in women have played an important role. Because the clinical manifestations of coronary disease in women lag behind those in men, within populations presenting for revascularization, women are always older than men. However, with the recognition that the average lifetime
risk of cardiovascular disease is high and that atherosclerosis is not a “have” or “have not” condition but rather that women are on a continuum of risk, there is an increased focus on the prevention of disease. In addition, the role of newer imaging modalities in the detection of preclinical coronary atherosclerosis may have particular importance in women. Unfortunately, there is evidence to suggest that at the time of an acute coronary event, women delay in seeking care and have a longer time from symptom onset to hospital presentation than men. Indeed, it has been reported that longer delays are associated with reduced likelihood of receiving primary reperfusion therapy and that even among those treated, late presenters had significantly longer door-to-balloon times.

Despite the recognition of the adverse impact of sex disparities in access to and delivery of evidence-based care in women and the Institute of Medicine’s report *Exploring the Biological Contribution to Human Health: Does Sex Matter?*, marked disparities continue to exist for women in need of coronary intervention and have been most frequently studied in patients with ACS. Within the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology (ACC) and American Heart Association (AHA) Guidelines (CRUSADE) National Quality Improvement Initiative, 40,912 patients with non-STEMI ACS at 391 hospitals in the United States between 2000 and 2002 were evaluated. Although women were older with a higher prevalence of risk factors, they were less likely to receive cardiac catheterization and revascularization than men; among patients with significant coronary disease, PCI was performed in a similar proportion of women and men. Women were also less likely to receive IIb/IIIa platelet receptor antagonists.

In aggregate, these data suggest that the ongoing sex disparities in access to and delivery of evidence-based guideline recommended revascularization (and medical) therapies for patients with ACS and STEMI represent potential opportunities to improve care and outcomes, particularly in women.

Outcomes of Coronary Intervention in Women Across the Spectrum of Coronary Artery Disease

**Trends in Overall Outcomes**

During the past 3 decades, numerous single- and multicenter registries and fewer randomized trials have reported remarkably consistent sex differences in patients undergoing PCI. As noted earlier, in comparison with men, women are older and smaller with a higher prevalence of hypertension, diabetes mellitus, hypercholesterolemia, peripheral vascular disease and unstable angina in addition to more severe (Canadian Cardiovascular Society Class III–IV) angina. In addition, despite a lower prevalence of previous MI and left ventricular dysfunction than men, women have more congestive heart failure. Moreover, procedural success is similar in women and men, although women are less likely to receive IIb/IIIa platelet receptor antagonists.
What has changed, however, is that despite the fact that patients undergoing contemporary PCI are older with more comorbid disease and complex coronary anatomy, outcomes have improved overall, and the sex difference in-hospital mortality has decreased.\(^6\) Of note, among women, outcomes have also improved.\(^{52}\)

Vascular complications (such as access-site hematomas, retroperitoneal bleeds, and bleeding requiring transfusion) have also improved over time in women with less aggressive anticoagulation regimens, the increasing use of weight-adjusted heparin dosing, smaller sheath size, and early sheath removal.\(^{53}\) Yet, there remains a significant increase in vascular and bleeding complications in women,\(^5\) which serves to emphasize the importance of considering biological and clinical factors specific to women. Although IIb/IIIa platelet receptor antagonists have been shown to be equally effective in preventing ischemic complications in women and men treated with PCI, women experience more bleeding complications whether or not they are treated with these agents.\(^{54}\)

Within CRUSADE, women treated with IIb/IIIa platelet receptor antagonists were more likely to receive excess doses (with similar serum creatinine levels but lower creatinine clearance in women). Excess dosing was associated with increased risk of bleeding in both women and men although the bleeding risk attributable to dosing was much higher (25\% versus 4.4\%) in women in comparison with men.\(^{55}\) An interaction of sex and age on contrast-induced acute renal injury (defined as 25\% increase in baseline serum creatinine or overall increase of $>0.5$ mg/dL) postprocedure has also been reported with rates higher in women compared with men in the groups $>65$ years.\(^{56}\)

### Coronary Stents
In patients undergoing contemporary PCI using both bare-metal\(^{57}\) and drug-eluting (with sirolimus\(^{58}\) and paclitaxel\(^{59}\)) stents,\(^{60}\) the benefits of reduction in restenosis and repeat target lesion and target vessel revascularization are independent of gender (Figure 4). However, the hope that stents would eliminate the difference in mortality in women and men following the procedure has not been realized. For patients treated with stents, the sex difference in in-hospital\(^{61}\) and 30-day\(^{62}\) mortality has persisted in the setting of both acute MI and elective/urgent procedures (Figure 5).

### Acute Coronary Syndromes
In several randomized trials in patients with ACS (unstable angina or non-STEMI), assignment to a routine invasive strategy involving coronary angiography and revascularization compared with a more conservative strategy with referral for acute intervention only for recurrent or inducible ischemia was associated with a reduction in death, MI, and rehospitalization.\(^{63}–^{65}\) However, in those trials that reported sex-specific outcomes, the invasive strategy seemed to be beneficial only in high-risk (defined as elevated troponin) women (Figure 6); and moreover, in women overall, there was a signal for harm (Figure 7).\(^{66},^{67}\) These data led to sex-specific ACC/AHA guideline recommendations: For women with high-risk features, recommendations for the invasive strategy are similar to those of men (class I, level of evidence B); in women with low risk features, a conservative strategy is recommended (class I, level of evidence B), Figure 8.\(^{68}\) A subsequent meta-analysis evaluating the 2 treatment strategies in women and men provided further support for the new guideline recommendations reporting that the invasive strategy has comparable benefit in men and high-risk women for reducing the composite end point of death, MI, or rehospitalization with ACS.\(^3\) It should be noted, however, that data from the

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**Figure 5.** Difference in mortality rates by sex after balloon angioplasty and stent placement. AMI indicates acute myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty. Reprinted from *American Journal of Cardiology*, vol 88, Watanabe CT, Marynard C, Ritchie JL. Comparison of short-term outcomes following coronary artery stenting in men vs. women. Pages 848–852, Ref. 61 © 2001, with permission from Elsevier.

**Figure 6.** Death, MI, and rehospitalization for ACS in women and men with elevated troponin T levels, by strategy. Reproduced with permission from Ref. 66, Copyright © 2002, American Medical Association. All rights reserved.
National Heart, Lung and Blood Institute Dynamic Registry revealed that women undergoing PCI in the setting of ACS have a higher risk of major adverse cardiac events (death, MI, cardiac rehospitalization) at 1-year than men or women undergoing PCI with stable angina.69

ST-Segment Elevation Myocardial Infarction

Although mortality after MI has been higher in women in comparison with men before and after the advent of reperfusion therapy70 and in most studies in patients undergoing primary PCI,71 the benefits of primary PCI as the preferred reperfusion strategy are apparent in both sexes.3,72 In fact, for patients treated within GUSTO IIb, because women had a higher event rate than men, the absolute number of major events prevented when treating women with primary PCI was higher than when treating men.4 Moreover, rates of hemorrhagic stroke are significantly reduced in patients treated with primary PCI. However, as previously noted, women with STEMI are less likely to receive timely primary PCI and guideline recommended medical therapy.37

Cardiogenic Shock Complicating Acute MI

Female sex is an independent risk factor for the development of cardiogenic shock complicating acute MI.73 Age is an additional risk factor for the development of this complication, such that elderly women are at substantial risk of cardiogenic shock. Once shock develops, however, female sex is not independently related to outcome.74 In-hospital mortality and the benefit of early revascularization are similar in women and men. According to the ACC/AHA guidelines for the treatment of STEMI, early revascularization with PCI or coronary bypass surgery is recommended for shock patients aged 75 years old who are suitable for revascularization, and early revascularization is reasonable for selected shock patients aged 75 years or older.75 These guidelines are not sex specific.

As noted earlier, for patients undergoing PCI, the incidence of heart failure is higher in women than men and congestive heart failure has been shown to be an independent predictor of in-hospital mortality in both women and men undergoing revascularization.51 Interestingly, although women usually account for 25% to 30% of patients in both registries and trials of coronary revascularization, in the Should we emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK) trial Registry, women represented 36% of the study population.76

Relationship Among Sex Differences in Biology, Physiology, and Outcomes After PCI

In addition to access to and delivery of evidence-based therapies for women with ischemic heart disease, it is becoming increasingly clear that inherent sex differences in biology and physiology are related to outcomes after PCI. Although much of the longstanding excess in periprocedural mortality in women is explained by intrinsic sex differences at baseline, the remainder is likely due to our inability to completely account for biological factors specific to women.77 Yet, the impact of certain sex-related characteristics is being defined. It is likely that the smaller, stiffer vasculature in women is related to the higher incidence of vascular and bleeding complications and anemia and bleeding requiring transfusion (both more prevalent in women) are associated
with a higher risk for adverse outcomes in patients undergoing PCI. Smaller size and lower glomerular filtration rates in women predispose to excess dosing of potent adjunctive anticoagulant therapies and contrast agents resulting in subsequent bleeding and contrast-induced nephropathy. Smaller and stiffer hypertrophied hearts are less able to withstand the volume shifts and transient periods of ischemia experienced during PCI and periprocedural heart failure is a potent predictor of mortality in both women and men. Finally, the observation that in women with ACS, only those at high-risk, defined by elevated biomarkers, benefit from revascularization and that there is a sex-related difference in the distribution of biomarkers, underscores the importance of tailoring therapies to the risk status in women.

The Future

During the past two decades, since the publication of a report by the United States Public Health Service Task Force on Women’s Health Issues prompted the National Institutes of Health to announce a policy recommending the inclusion of women in federally funded clinical research, sex differences in patients with cardiovascular disease have slowly gained increased attention. Reports from the Institute of Medicine advocating a better understanding of the differences in disease between the sexes and a reemphasis of the existing federal requirements by the National Institutes of Health for analyses of outcomes by sex have contributed the development of sex-specific information. Yet, the American Medical Women’s Association Position Paper on Sex- and Gender-Specific Medicine noted a study reporting that although 80% of research studies evaluated included women, only 25% of outcomes data were analyzed by sex.

For patients undergoing coronary revascularization, numerous studies during the past 3 decades have reported on the sex-differences in baseline characteristics and outcomes. The hazards of subset analyses notwithstanding, these studies are beginning to inform our practice guidelines with sex-specific recommendations. The challenge is not only to deliver the message, but to translate the findings into clinical practice. To do so will require numerous strategies that include educating the healthcare provider in addition to patients and the public about the importance and consequences of coronary heart disease in women and that in certain settings, PCI in women may be lifesaving. Only then, we will be able to move through the “Cycle of Quality,” a framework adapted by the Duke Clinical Research Institute Think Tank to improve the quality of care for women with heart disease. Moreover, ongoing evaluation of newer technologies and devices in adequate numbers of women is essential, realizing that certain strategies such as intracoronary, local delivery of pharmacological and therapeutic agents may have their greatest potential in women.

In 2009, women undergoing coronary intervention are, and will likely continue to be, different than the men with whom they are compared. Sex difference in basic biology assures us that this is true. However, the expanding evidence based has allowed an increased understanding of biological and socioeconomic factors specific to women and to narrow the difference in mortality and adverse outcomes related to the procedure. Yet to be determined is the impact of prevention and early detection of coronary atherosclerosis and of the development of new technology in addition to systems of care for patients with STEMI, on the quality of care and outcomes in women treated with coronary intervention.

Disclosures

None.

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