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Sex Revisited
Alice K. Jacobs, MD

During the past 3 decades, numerous and remarkably consistent studies have reported sex differences in the epidemiology, prevention, diagnosis, and clinical manifestations of coronary artery disease.\(^1\) and, especially noteworthy, in the sex differences in patients undergoing coronary revascularization, where a disturbingly higher mortality rate has been noted in women.\(^2,3\) In fact, multiple paradoxes have been observed. Differences between women and men in the extent of epicardial coronary artery disease in relation to risk factors and the degree of stable and unstable angina, in the relationship between congestive heart failure and left ventricular systolic function, and recently, in the higher in-hospital mortality after revascularization in younger but not older women in comparison to men have been noted.\(^4\) It has been suggested that improvements in procedural technology and technique, particularly the increasing performance of off-pump procedures and use of heparin bonded circuits, and the widespread use of stents and adjunctive pharmacotherapy in patients undergoing both coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) would improve outcomes in women. Therefore, it is timely to review the current status and issues concerning coronary revascularization in women.

Clinical, Angiographic, and Procedural Characteristics

Virtually all single-center and large-scale multicenter registries have reported that in comparison to men, women undergoing CABG or PCI have more comorbid disease, are older, are smaller in size, and have a higher prevalence of hypertension, diabetes mellitus, hypercholesterolemia, peripheral vascular disease, and unstable angina, as well as more severe (Canadian Cardiovascular Society class III–IV) angina. Despite a lower prevalence of previous myocardial infarction and left ventricular dysfunction than men, they have more congestive heart failure.\(^2–6\) Yet, the extent of epicardial coronary artery disease, as measured by angiography, is similar (or less) in women in comparison to men, a finding that refutes the hypothesis that women are referred for coronary angiography less often or later in the course of their disease than men. Although the reasons for this sex difference in the degree of symptoms and risk factors in relation to the extent of angiographic disease are unclear, microvascular dysfunction, abnormal vasomotor tone, and endothelial dysfunction in women are often implicated. Despite smaller vessel size in women, coronary lesion morphology and distribution is similar to that in men, except that women tend to have more ostial lesions.\(^5\)

For patients undergoing CABG, the increased incidence of incomplete revascularization in women is no longer apparent, although women receive fewer internal mammary artery conduits than men.\(^2,5\) A difference unexplained by unstable symptoms or the prevalence of diabetes. In patients undergoing contemporary PCI, stent usage is similar in women and men after adjusting for vessel size.\(^6\) In comparison with men, however, women tend to be treated less often with platelet glycoprotein IIb/IIIa receptor antagonists, despite similar efficacy in women and men,\(^7\) perhaps because of the increased incidence of bleeding noted in women.\(^6\)

In-Hospital Mortality

Despite improvements in myocardial protection and advances in surgical technique, sex differences in in-hospital mortality after CABG have persisted and have been notably consistent over the past 20 years. On average, in-hospital mortality is 2 times higher in women in comparison with men, and stratification according to age reveals a more pronounced difference in younger women.\(^4,8\) In addition, women have a higher incidence of periprocedural morbid events, such as stroke and bleeding, in comparison with men.\(^2,8\) Despite similar procedural success rates, albeit higher vascular and bleeding complication rates in women, in-hospital mortality also remains higher in women than in men undergoing contemporary PCI, although the magnitude of the sex difference in unadjusted mortality has decreased considerably.\(^1,6,9\) The reason for this persistent mortality difference between women and men remains speculative, but older age, co-morbid disease, a higher incidence of urgent procedures in women with unstable symptoms, smaller vessel size, and hypertensive heart disease have been implicated.

In fact, in the majority of recent studies, after adjustment for the increase in overall risk in women undergoing both CABG and PCI, in-hospital mortality is similar to that in men, particularly when body surface area (a surrogate for coronary vessel size) is added into the multivariate model.\(^5,6,9\) Relationship between body surface area and in-hospital mortality after revascularization has been consistently demonstrated in patients undergoing CABG, where mortality is inversely related to body surface area in both women and men.\(^2,10\) During CABG, smaller vessel size may impose more technical difficulties and may be associated with a higher incidence of graft failure. During PCI, higher incidence of
coronary dissection, abrupt vessel closure, and device-vessel size mismatch have been reported to occur with increased frequency in small vessels.\textsuperscript{11}

The most provocative explanation for the sex difference in in-hospital mortality in patients undergoing coronary revascularization relates to the higher incidence of left ventricular hypertrophy and hypertensive heart disease in women compared with men. In multiple randomized trials and registries, women have been reported to have a higher incidence of congestive heart failure despite better left ventricular function (with fewer previous infarctions) than men.\textsuperscript{2–6,9} This is best illustrated in the Bypass Angioplasty Revascularization Investigation (BARI), in which, despite the similar incidence of in-hospital death and myocardial infarction, there was a significantly higher incidence of congestive heart failure or pulmonary edema after both CABG and PCI in women compared with men.\textsuperscript{5} For patients undergoing CABG, congestive heart failure has been shown to account for the excess mortality in women,\textsuperscript{2} and congestive heart failure is an independent predictor of mortality in both women and men in BARI and other revascularization studies.\textsuperscript{5,6} Compelling evidence implicates a higher incidence of hypertensive heart disease, a steeper pressure-volume relationship, and more diastolic dysfunction\textsuperscript{12} in women in comparison with men and is supported by reports of sex differences in molecular remodeling in pressure overload hypertrophy\textsuperscript{13} and in cardiac adaptation to isolated systolic hypertension.\textsuperscript{14} It has been postulated that the hypertrophied left ventricle is less able to withstand transient periods of ischemia and volume shifts and comparatively higher contrast loads (corrected for smaller size in women) associated with revascularization. Furthermore, it is noteworthy that although 25% to 30% of patients undergoing revascularization are women, in the randomized SHould we emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK) trial, women comprised 36% of the study population.\textsuperscript{15}

Most puzzling is the recent evidence that younger women undergoing CABG are at higher risk of in-hospital death than men, but this difference in risk decreases with age, when women become more like men. Interestingly, similar observations have been made for patients hospitalized with acute myocardial infarction.\textsuperscript{16} The reasons for this observation are unknown, but lack of normal protective factors, ovarian dysfunction, abnormalities of the estrogen receptor, and ascertainment and referral bias have been postulated to occur in women with premature coronary artery disease.\textsuperscript{17}

**Improved Outcomes in Women**

Fortunately, because of a number of very large databases, we can now focus on the changing outcomes in women, particularly as both CABG and PCI are being performed in older patients with more advanced disease and complex coronary anatomy. Despite the older age and higher prevalence of risk factors and co-morbid disease in women in the 1997 to 98 Dynamic Registry compared with women in the 1985 to 86 and 1993 to 94 Percutaneous Transluminal Coronary Angioplasty Registries, in-hospital and 1-year mortality was similar in women in the Dynamic and earlier registries. In addition, compared with the 1985 to 86 registry time period, the Dynamic registry time period was an independent predictor of lower mortality at 1 year after adjusting for baseline differences in women in the 2 registries.\textsuperscript{6} Similar findings have been reported from the Society of Thoracic Surgeons National Database.\textsuperscript{18}

**Is There an Optimal Revascularization Strategy?**

Reports of long-term outcomes of patients after revascularization have been limited. After hospital discharge, adjusted survival at 5 years after CABG\textsuperscript{19} and adjusted survival at 1 and 4 years after PCI have been shown to be similar in women and men.\textsuperscript{5,6} In BARI, survival at 5 years was no different in women and men overall and was no different in women treated with CABG or balloon angioplasty.\textsuperscript{5} Interestingly, preliminary studies in patients undergoing off-pump surgical revascularization have noted a lower in-hospital mortality in women in comparison with women treated in standard operative fashion. In fact, the mortality rate for women operated on without cardiopulmonary bypass dropped to the rate typically seen in men.\textsuperscript{20} Although platelet glycoprotein IIb/IIIa receptor antagonists and stents have been shown to have similar benefit in women and men treated with PCI,\textsuperscript{7} the promise that stents would eliminate the difference in mortality between women and men has not been realized. For patients treated with stents (and other devices), the sex difference in mortality has persisted in the setting of both acute myocardial infarction and elective procedures.\textsuperscript{21}

**Are the Paradoxes Beginning to Vanish?**

Advances in coronary revascularization techniques and adjunctive pharmacotherapy have allowed the extension of surgical and percutaneous procedures to older patients at higher risk for adverse outcomes. Notwithstanding, adjusted rates of peri-procedural mortality have improved in both women and men. Although mortality remains higher in women, much of the excess is due to inherent sex differences at baseline, and the remainder is perhaps due to our inability to accurately and completely account for biological factors specific to women. Despite our incomplete understanding of the influence of smaller size, diastolic dysfunction, and the increase in the sex difference in mortality in younger women that is far from being intuitively clear, several concepts have emerged. Certainly, overall inferences concerning sex-treatment effects will need to account for not only age but also for whether sex effects differ according to age at presentation. It is likely that continued improvements in myocardial protection and surgical techniques, including an increase in the performance of off-pump and minimal access procedures, in addition to the earlier detection of coronary atherosclerosis by noninvasive imaging and the potential to use drug-eluting stents in more moderate disease, will narrow the sex difference in outcomes after revascularization. Yet to be further explored are the biological and pathophysiological bases for the difference in the angiographic extent of disease in relation to the degree of symptoms and risk factors in women in comparison to men, as well as the impact of this difference on morbidity and mortality in women. For now, the paradoxes will no doubt persist and will require continued
attention and vigilance when women undergo CABG and PCI. However, what is clear in 2003 is that sex should no longer be a significant factor in decisions regarding revascularization.

References