Gender Differences in the Treatment for Acute Myocardial Infarction
Bias or Biology?

R. David Anderson, MD; Carl J. Pepine, MD

A ccumulating evidence over the last several decades regarding the treatment and outcomes for coronary artery disease reveals disparities that have a clear relationship to gender. It had previously been thought that these differences were related to gender bias in physicians’ approach to treatment; thus, the term Yentl syndrome was coined in 1991.1 As the volume of literature expanded and clinical studies included more women, it became clear that outcomes after treatment for coronary artery disease, particularly acute myocardial infarction, were different for women compared with men. Women have a well-documented higher mortality after acute myocardial infarction.2 Much of this disparity has been attributed to differences in age and attendant comorbidities. Female patients with coronary artery disease typically are older, have a higher prevalence of risk factors, and have a lower functional status than their male counterparts.3,4 Additionally, women appear to be at higher risk than men when diabetes, hypertriglyceridemia, and metabolic syndrome are present. The underuse of revascularization procedures in women has been suggested as an explanation, but it has not been uniformly demonstrated to explain increases in mortality. Some studies have suggested a link to less aggressive hospital care of female patients, including the underuse of revascularization, as an explanation for their increased mortality.5 Other studies have indicated age and comorbidity as the primary factors leading to mortality differences.6 Still other studies suggest no evidence of undertreatment.7,8

Gender differences in the clinical outcome of patients with acute myocardial infarction may be explained in part by the female status. Several conditions found only in women hint at differences in the pathophysiology of ischemic vascular disease between the sexes. Such female-specific conditions include early menopause, gestational diabetes, peripartum vascular dissection, preeclampsia and eclampsia, polycystic ovarian syndrome, low-birth-weight children, and hypothalamic hypoestrogenemia. Several of these states, most of which occur at a younger age, carry an increased risk for ischemic heart disease later in life.9 Women also have a higher prevalence of vascular abnormalities such as Raynaud’s phenomenon, migraines, vasospastic disorders, and other vasculitides. There is also evidence that sex hormones play a role in the pathophysiology of vascular disease. Over a woman’s lifetime, her vascular bed experiences a significant fluctuation in hormonal influence. Changes in estrogen and androgen balance occur during pregnancy, during the peripartum period, and with the use of oral contraceptives or hormone replacement therapy. Additionally, the aging process heralds a reduction in estrogen to about 1/10th premenopausal levels. The predominant source of estrogen before menopause is estradiol. After menopause, a lower level of estrogen is produced primarily from the conversion of androgens to estrone in adipose tissue.10 These variations have implications for the differences in ischemic heart disease between the sexes and are coincident with the rise in risk for women that occurs after menopause. It is supported by the fact that younger women with endogenous estrogen deficiency have a >7-fold increase in coronary artery risk.11

Further evidence that may help to explain variations in coronary artery disease outcome are gender differences in vascular structure. Women typically have smaller and less compliant conduit arteries than men. This is true even after adjustment for differences in height, weight, and blood pressure.12 Age-related stiffening of the aorta appears more prominent in diabetic women than men.13 Changes in arterial size have been documented to occur during pregnancy. These were previously considered physiological manifestations. In the presence of the peripartum pathology noted above, however, the possibility that this represents pathological remodeling has not been excluded. Additional evidence for sex-related differences in arterial size and remodeling comes from data on transplant and transgender patients. When a female-to-female heart transplantation occurs, there is little evidence of changes in the caliber of the coronary arteries over time. When a female heart is transplanted to a man, there is progressive enlargement of the coronaries after accounting for body habitus and left ventricular hypertrophy.14 Women who have been taking androgens have been found to have larger arteries than control subjects, whereas androgen-deprived men had smaller arteries than control men. A study of transsexual brachial arteries has demonstrated a reduction in size when genetic men have been taking estrogen. Increased brachial artery size also has been linked to an
increased risk of coronary artery disease.\textsuperscript{15} These data support the concept of differences in vascular physiology based on sex hormone status. There appears to be enlargement with androgens, consistent with positive remodeling. The latter may itself be an independent marker of vascular disease. Women who present with acute coronary syndromes have a higher incidence of nonobstructive coronary artery disease (the Figure). In the Women’s Ischemia Syndrome Evaluation (WISE) study, those patients with nonobstructive coronary artery disease also had a higher event rate.\textsuperscript{16}

In addition to the structural differences in vasculature noted above, function alterations may help to explain the higher risk and more severe disease in women. The same hormonal fluctuations that can lead to macrovascular changes can also lead to microvascular alterations. The endothelium may be affected, and $\geq 50\%$ of women in the WISE study had an abnormal response to acetylcholine. This abnormal response to intracoronary acetylcholine proved to be an independent marker of adverse outcomes.\textsuperscript{17} Over time, the normal endothelial repair processes likely become inadequate as a result of multiple factors, including aging, change in hormonal status, oxidative stress of metabolic syndrome, hypertension, and obesity. Bone marrow–derived endothelial progenitor cells have been shown to be important in vascular repair. Estrogen exerts antiapoptotic effects, thereby increasing circulating endothelial progenitor cells.\textsuperscript{18} The loss of estrogen later in life, associated with other risk conditions such as aging, leaves women vulnerable to a decreased ability to sustain adequate vascular repair; this may be linked to an increased risk of ischemic heart disease.

Smooth muscle cell dysfunction also is implicated and more frequent in women than men. This is suggested by the increased frequency of coronary artery spasm, Raynaud’s disease, and other vascular abnormalities, as previously mentioned. The impairment of smooth muscle cell function also has been linked to an increased risk of ischemic heart disease. Impairment of coronary flow reserve, as measured by the intracoronary Doppler response to adenosine, has been suggested as a marker of microvascular smooth muscle cell dysfunction. This was seen in many of the women tested in the WISE and was an independent predictor of adverse outcomes over 5 years of follow-up.\textsuperscript{19} Recent work with estrogen receptor-$\alpha$ has suggested a relationship with smooth muscle cell differentiation. This could be a potential link between estrogen receptor-$\alpha$ and vascular health. It suggests that the activational state of estrogen receptor-$\alpha$ could influence smooth muscle cell phenotype and possibly the production of extracellular matrix that is responsible for maintaining a healthy vascular wall.

In this issue of Circulation, Milcent et al\textsuperscript{20} describe a large series of patients ($n=74\,389$) from the French healthcare system who were treated for an acute myocardial infarction in 1999. The goal was to evaluate gender differences in hospital mortality and to determine the individual contributions of patient comorbidities, use of percutaneous coronary intervention (PCI), and benefit of PCI. The authors used microsimulation models as a technique to tease out these various different contributions on the basis of a hypothetical set of events. The first model predicted the expected rate of PCI for women using the probability (rate of PCI) for men with the same set of comorbidities. The second model initially simulated the expected mortality of women using the same PCI rates for men and then was used to predict expected hospital mortality of women using the PCI rates and comorbidities of men and their expected response to PCI.

The crude hospital mortality rate was 14.8\% for women and 6.1\% for men (odds ratio, 2.65; 95\% CI, 2.52 to 2.79). After adjustment for age, the absolute difference in hospital mortality was 1.95\%. The rate of PCI for women was 14.2\% compared with 24.4\% in men. The expected rate of PCI in women when modeled using the same rate as in men was 17.5\%. Thus, Milcent et al calculated an absolute 3.4\% higher rate of PCI expected in women if they had been treated with the same rate of PCI as their male counterparts. The authors concluded that approximately one third of the difference in the rate of PCI use is attributable to “gender disparity,” whereas the remaining two thirds can be explained by differences in age and comorbidities.

The mortality model suggested that the expected mortality in women would be 14.32\% (versus 14.78\%) if they had...
experienced the same rate of hospital PCI as men, leading to a 0.46% difference. This suggests that about one quarter of the mortality difference (absolute mortality difference, 1.95%) could be explained by the difference in the rate of use of PCI. Second, their microsimulation model revealed an expected mortality for women of 12.55% (versus 14.78%) if they had undergone similar rates of PCI with the expected outcomes of men. The authors propose that this accounts for >90% of the gender difference in adjusted hospital mortality. The difference was thought to be explained by characteristics not available for study. Finally, they presented a comparison of observed and expected age-adjusted mortality, suggesting a decrease if women had the same rate of PCI use and outcomes as men.

The authors confirm the higher hospital mortality in women treated for an acute myocardial infarction from a very large cohort of patients. This remained true even after adjustment for more advanced age and clustering of comorbidities. They further document differences in the rate of PCI use and estimate its effect on mortality. The differences in the observed and expected mortalities are complex. They did not find any contribution to this difference related to hospital volume, which had previously been linked to outcome. They were unable to extract data on ethnicity and other variables that may have partially explained the differences reported. Medium- and long-term outcomes were unavailable. A large part of the difference in observed and expected mortality is explained by the older age and clustering of risk factors in women. Although the lower rate of PCI use in women may explain part of the observed mortality difference, the issue is likely much more complex because of several or many of the previously noted differences between the sexes. As Milcent et al point out, angiographic data regarding differences in anatomy were not available and could have explained in part less PCI use in women. Smaller vessels could lead to a lower rate of PCI use. Additionally, as noted above, women with acute coronary syndromes are more often found to have nonobstructive coronary artery disease (the Figure), which also could lead to a lower rate of intervention. Although they documented overall higher rates of angiography and PCI in men compared with women, there was heterogeneity in the patient population >75 years of age. Despite an overall lower rate of angiography and PCI in women treated for acute myocardial infarction, other healthcare systems could benefit from such a large and complete data set. Despite the more advanced age and risk profile of women, after adjustment, the authors have shown that there is still disparity. Some of this discordance may be due to bias or underuse of aggressive therapy. It is likely that given the complexities in gender differences, biology also plays a role. The findings in the present study advance our knowledge base in gender-specific treatment of ischemic heart disease. Because women make up at least 50% of our patient population, we must be more vigilant and continue to search for explanations for these disparities and new treatment options.

Disclosures

None.

References


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