

6

Sex Differences in Acute Coronary Syndrome

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Executive Summary

Sex differences have been identified in nearly every aspect of cardiovascular disease. Women presenting with acute coronary syndrome report more non-chest pain symptoms, more commonly have negative cardiac biomarkers, and are referred for cardiac catheterization less often. Women who do undergo angiography tend to have less obstructive coronary artery disease than men, although appropriate risk stratification may narrow this gap and help identify those women who will most benefit from an early invasive strategy. Despite having a lower incidence of ST-segment elevation myocardial infarction than men, women, particularly younger women, have a relatively higher morbidity and mortality. Some of this increased mortality can be attributed to women receiving less aggressive treatment, such as lower rates of PCI. Both primary PCI and glycoprotein IIb/IIIa inhibitors have been found to improve outcomes in women. Endothelial dysfunction, microvascular disease, and diffuse atherosclerosis are commonly identified as causes of ischemia in women without angiographic evidence of significant coronary artery disease, and are associated with an increased risk of future MI and death.

Introduction

There is an increasing awareness of sex differences in nearly all areas of cardiovascular disease (CVD). While women have a proportionally lower prevalence of disease and tend to develop it later in life, it remains underappreciated that every year more women than men die of CVD, and that it is the eventual cause of death in one out of every two women in the United States⁽¹⁾. What we know about CVD and how we treat it has grown out of a body of research focused primarily on men⁽²⁾. Whether or not these findings are always applicable to women remains unknown. A growing body of sex-based research, however, is beginning to shed some light.

Women Presenting with Acute Coronary Syndrome

Acute coronary syndrome (ACS) refers to any constellation of clinical symptoms that are compatible with acute myocardial ischemia. It encompasses unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI)⁽³⁾. Studies have consistently shown that compared to men, women presenting with ACS are older (by about 3 to 8 years), and have more diabetes, hypertension, and hyperlipidemia, but are less likely to smoke⁽⁴⁻⁷⁾. They are more likely to have had prior angina and prior congestive heart failure (CHF), but less likely to have had a prior myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). Women tend to present to the hospital later and are more likely to present with UA than a STEMI or NSTEMI. They also have a higher Killip class upon presentation despite a more preserved left ventricular function. This has been attributed to the steeper pressure/volume relationship (smaller left ventricular end-diastolic volume (LVEDV) for a similar left ventricular end-diastolic pressure (LVEDP)) seen in women and is consistent with their proportionally higher incidence of diastolic heart failure in the general population⁽⁸⁾.

In the setting of ACS, the most common symptom reported by both women and men is chest pain. Reports vary, but in general, women complain of symptoms that are considered typical, such as dyspnea, nausea, arm pain, and jaw pain, but are more likely than men to report multiple symptoms with women reporting a mean of 3.4 ± 1.8 symptoms and men reporting a mean of 2.5 ± 1.4 symptoms ($p=0.0002$)⁽⁹⁻¹¹⁾. Women with ACS are less likely than men to have elevation of typical cardiac biomarkers, including creatinine kinase-MB (CK-MB) and the troponins (TnT and TnI)⁽¹²⁾. They are also less likely to have obstructive coronary

artery disease (CAD). Among women undergoing angiography for UA, NSTEMI, and STEMI, 31%, 9%, and 10% are found to have no significant CAD, respectively⁽⁶⁾. When women are found to have significant CAD, they are just as likely as men to undergo revascularization, but they are more likely to have complications, particularly bleeding complications^(6,13).

Unstable Angina and Non-ST-Segment Myocardial Infarction

Women presenting with ACS are significantly less likely than men to receive coronary angiography^(6,13). The reasons for this are likely multiple, including older age, higher rates of comorbidities, and an "atypical" presentation, as well as physician experience with a lower incidence of obstructive CAD and a higher rate of periprocedural complications in women. While one might expect that these reasons justify the referral difference, that is not always the case.

A post-hoc analysis of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial examined sex differences in the management and prognosis of 4,836 women and 7,726 men presenting with unstable angina and non-ST-segment myocardial infarction (UA/NSTEMI). Consistent with other studies, the women were older, had higher age-adjusted rates of diabetes, hypertension, and elevated cholesterol, and were significantly less likely to undergo coronary angiography than the men (25.4% vs. 29.5%, $p=0.0001$). Despite the lower rates of angiography, there were no sex differences in the incidence of cardiovascular death, recurrent MI, or stroke at 30 days or 9 months. Much of this may be attributed to the finding that of those who had angiography, women were more likely than men to have normal appearing coronary arteries (26.7% vs. 13.2%, $p=0.0001$) and less likely to have significant CAD (34.9% vs. 44.7%, $p=0.00001$). However, when patients were risk stratified into low-, intermediate-, and high-risk based on TIMI risk score, it was found that the decision to perform angiography was not linked to the risk status of the patient. Angiography rates were significantly lower among women of all risk strata even though high-risk women, unlike low- and intermediate-risk women, were equally likely to have significant CAD as similarly-risked men (60.8% vs. 59.4%, $p=0.68$). Once significant CAD was discovered, women were just as likely as men to undergo percutaneous or surgical revascularization. While the incidence of cardiovascular death, MI, and stroke was not increased among high-risk women compared to men, high-risk women did have an increased incidence of refractory angina and rehospitalization for chest pain, presumably because of underidentified and untreated CAD.

Early Invasive versus Conservative Therapy

Three recent randomized controlled trials investigating the value of early invasive versus conservative management in the treatment of UA/NSTEMI specifically examined outcomes in women. These included FRISC II (Fragmin and fast Revascularization during InStability in Coronary artery disease II), RITA 3 (Randomized Interventional Trial of unstable Angina 3), and TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy). When the results of FRISC II were published, the conclusion was that an early invasive strategy was superior to a conservative strategy in the treatment of patients with UA/NSTEMI⁽¹⁴⁾. However, a subanalysis found that in contrast to its benefit in men, an early invasive strategy did not reduce the risk of future events in women (15). In the conservative group, the incidence of the combined end point of death or MI was significantly less in women than men during 12 months of follow-up (10.5% vs. 15.8%, $p=0.005$), whereas women in the early invasive group had a worse outcome than their conservatively treated counterparts, particularly after adjusting for the presence of coronary stenosis (odds ratio [OR] 1.72, 95% confidence interval [CI] 1.11-2.65, $p=0.04$). Similarly, in RITA 3, men benefited from an early invasive strategy while women did not⁽¹⁶⁾.

TACTICS-TIMI 18, on the other hand, found that this lack of benefit with the early invasive strategy did not apply to all women equally⁽¹⁷⁾. There was a trend toward improved outcomes with the early invasive strategy in women with intermediate and high TIMI risk scores, as well as those who had ST-segment changes. Moreover, women with elevated levels of troponin T had a significant reduction in the primary combined endpoint of death, MI, and rehospitalization for ACS at 6 months with the early invasive strategy (adjusted OR 0.47, 95% CI 0.26-0.83). Similar to FRISC II and RITA 3, women with low TIMI risk scores and negative cardiac biomarkers had a positive trend of excess events with the invasive strategy (including higher rates of death, MI, and rehospitalization).

The implications of TACTICS-TIMI 18 are that low risk women do not benefit from an early invasive strategy, while higher risk women, particularly those with elevated cardiac biomarkers, do. The lack of benefit with the early invasive strategy in women seen in FRISC II and RITA 3 may have been because neither of these studies stratified their outcomes by risk and because both studies may have had an overall lower risk cohort than TACTICS-TIMI 18. Compared with TACTICS-TIMI 18, women in FRISC II had higher rates of normal appearing coronary arteries on angiography and women in RITA 3 had lower rates of death and MI at one year. In addition, TACTICS-TIMI 18

may have found a benefit because of having an earlier invasive approach. Patients were included in TACTICS-TIMI 18 if they had their index symptoms within 24 hours of enrollment while both FRISC II and RITA 3 included patients with symptoms occurring within 48 hours of enrollment. In TACTICS-TIMI 18, patients in the invasive group underwent cardiac catheterization within the first 48 hours of presentation, compared to a median of 3 days in RITA 3 and 4 days in FRISC II.

Risk Stratification

The findings of TACTICS-TIMI 18 corroborate the findings of the CURE trial, highlighting the point that risk stratifying women with UA/NSTEMI prior to angiography may help identify those women who will actually benefit. These trials used TIMI risk score, ST-segment changes, and elevated troponin levels, but the optimal method of risk stratification remains unknown. While troponin elevation in TACTICS-TIMI 18 identified those women who most benefited from invasive management, a substudy of TACTICS-TIMI 18 found a sex difference in cardiac biomarkers of those presenting with UA/NSTEMI⁽¹²⁾. Specifically, men were more likely to have elevated CK-MB, TnT, and TnI, while women were more likely to have elevated high-sensitivity C-reactive protein (hs-CRP) and brain natriuretic peptide (BNP), and elevated biomarkers predicted adverse outcomes in both sexes. TIMI risk scores and ST-segment deviations did not differ between the sexes. Using several biomarkers identified a greater proportion of high-risk women, as well as those who would benefit from an invasive strategy. Both women and men with at least one positive biomarker had significantly improved outcomes (death or MI) with an invasive compared to conservative strategy. In contrast, women with no positive biomarker had a significantly worse outcome with the invasive strategy, while men with no positive biomarker fared similarly regardless of which strategy was used. This suggests that using multiple biomarkers may help identify those women who have a sufficiently low risk to benefit from a conservative approach or a sufficiently high risk to benefit from an invasive approach, but further studies are needed to validate this method of risk stratification.

ST-Segment Elevation Myocardial Infarction

Despite having a lower incidence of STEMI than men, women have been found to have a higher morbidity and mortality associated with STEMI when it does occur. Factors attributed to this higher mortality include women having more comorbidities, presenting to the hospital later, and being sicker upon presentation. In addition, women appear less likely to rapidly

receive certain modes of treatment known to provide a mortality benefit in the setting of STEMI.

Less Aggressive Treatment

A large database analysis of 138,956 patients (49% women) presenting with STEMI showed that compared with men, women were significantly older, had more coexisting conditions (including diabetes, hypertension, CHF, and stroke), were more likely to delay seeking treatment, and had a longer wait before undergoing electrocardiography⁽⁴⁾. Women were significantly less likely to undergo catheterization, particularly older women, but after undergoing catheterization, women and men were referred for revascularization at similar rates. Even when they were identified as ideal candidates, women were significantly less likely to receive a thrombolytic agent within the first hour after arrival to the hospital, as well as at any time during hospitalization. They were also significantly less likely to receive an aspirin. The unadjusted 30-day mortality rate was significantly worse for women than men (27% vs. 17%, hazard ratio [HR] 1.24, 95% CI 1.21-1.28). This sex difference was attenuated with adjustment for demographic characteristics, severity of illness, coexisting conditions, and adverse events in the hospital, but remained significant (HR 1.04, 95% CI 1.01-1.07). It was only with adjustment for in-hospital intervention that the mortality difference between women and men disappeared. This indicates that even after adjusting for age and comorbidities, there remains a sex-based difference in treatment strategy that has an effect on outcome.

Indeed, a more recent study evaluated a database of 74,389 patients presenting with acute MI and then used microsimulation models to identify potential contributions to sex differences in PCI and mortality rates (18). Essentially, the models estimated the PCI and mortality rates that women would experience if they were “treated like men” and then compared them to actual PCI and mortality rates. Similar to the previous study, they found that women had a higher rate of hospital mortality than men (14.8% vs. 6.1%, $p < 0.0001$) and a lower rate of PCI (14.2% vs. 24.4%, $p < 0.001$). The simulations showed that while much of the mortality disparity could be accounted for by sex differences in age and comorbidities, approximately one quarter of the excess mortality in women was attributed to lower rates of PCI than were experienced by men with similar characteristics. Interestingly, while they found that women would likely have a mortality benefit from a more liberal use of PCI, they also found that women would ultimately still not derive as much benefit as men. The reason for this lower benefit from PCI in acute MI in women was not readily apparent, but is speculated to be secondary to various anatomic and biological differences⁽¹⁹⁾.

Poorer Outcomes in Younger Women

We have known for almost a decade now that there is a complex interaction between sex and age contributing to differences in early mortality after MI. Vaccarino and colleagues published data from the National Registry of Myocardial Infarction 2 (NERMI 2) in 1999 concluding that after MI, younger women, but not older women, had higher rates of in-hospital death than men of the same age⁽⁷⁾. Younger women were more likely than younger men to have a history of diabetes, CHF, and stroke, to present late, and to be sicker upon presentation. They were also more likely to have complications such as hypotension, heart failure, cardiogenic shock, and major bleeding, and were less likely to undergo cardiovascular procedures such as coronary angiography and revascularization than their younger male counterparts. The mortality rate during hospitalization was higher among women than men (16.7% vs. 11.5%, OR 1.54, 95% CI 1.51-1.57), but this mortality rate varied by age such that women who were less than 50 years of age had a greater than 2x chance of in-hospital mortality compared to men less than 50 years of age. This mortality differences between the sexes decreased with increasing age and was no longer significant after the age of 74. Differences in medical history, the clinical severity of the infarction, and early management accounted for only about one third of the difference in risk, and even after adjusting for these factors, women still had a higher risk of death for every five-year decrement in age.

A more contemporary study investigated whether this sex-age interaction continues to exist in the modern era of treating acute MI with primary PCI⁽²⁰⁾. In this study, in-hospital mortality rates were twice as high for women compared to men, but after adjusting for age, comorbid conditions, and hemodynamic status, there was no longer a mortality difference. However, among patients <75 years of age, women had a 37% increased adjusted risk of in-hospital mortality (adjusted OR 1.37, 95% CI 1.01-1.98, $p = 0.04$), whereas there was no significant difference in mortality between women and men ≥ 75 years of age. Using a finer breakdown of age (<65, 65 to 74, 75 to 85, and >85), women had an increased in-hospital mortality risk of 68% ($p \geq 0.006$), 48% ($p = 0.02$), 17% ($p = 0.37$), and 16% ($p = 0.75$), respectively. These findings have been extended to long-term outcomes in women and men presenting with acute MI⁽²¹⁾. Five-year adjusted survival rates are lower in younger women compared to younger men. Progressively over time this sex differential diminishes, and at about the age of 70, the survival rates become progressively better for women than men.

Outcomes with Fibrinolysis, Glycoprotein IIb/IIIa inhibitors, and CABG

In 2005, the AHA made a statement emphasizing the overall benefit of primary PCI over fibrinolytic therapy in women with STEMI⁽²²⁾. Evidence supporting this was demonstrated in a sex-based analysis of the GUSTO II-B PTCA (Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes II-B Angioplasty) Substudy, which was originally designed to evaluate the relative benefit of direct PTCA over thrombolytic therapy⁽²³⁾. Women and men presenting with STEMI were randomized to receive either direct PTCA or thrombolytic therapy with accelerated tissue plasminogen activator (t-PA). Women treated with direct PTCA had lower rates of the combined 30-day endpoint (death, nonfatal MI, and nonfatal disabling stroke) than women treated with t-PA (15.9% vs. 19.8%), as did men (7.5% vs. 12%). Results indicated that women derive a similar relative benefit from treatment with PTCA in acute MI as men, and may derive a larger absolute benefit given the higher absolute event rates seen in women. It was estimated that 56 events could be prevented for every 1,000 women treated with PTCA over fibrinolytic therapy, compared with only 42 events for every 1,000 men.

Concerns have been raised about the use of glycoprotein (GP) IIb/IIIa inhibitors in women, particularly because of their consistently increased risk of bleeding complications in the setting of PCI^(6,24,25). A subset analysis of the CADILLAC (Results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial investigated the use of GP IIb/IIIa inhibitor with primary PCI in women presenting with acute MI⁽²⁶⁾. Overall, women had significantly lower door-to-balloon times (2.18 hours vs. 1.95 hours, $p<0.001$), higher in-hospital, 30-day, and 1-year mortality rates, and significantly increased rates of moderate/severe bleeding at all time points compared with men. At PCI, the addition of a weight-adjusted GP IIb/IIIa (abciximab) resulted in a significantly reduced ischemic target vessel revascularization (TVR) at 30 days (0.8% vs. 5.1%, $p=0.03$) without causing an increased risk of major bleeding (7.4% vs. 6.6%, $p=0.74$). This finding was consistent with previous data showing that despite higher overall rates of bleeding complications, women undergoing elective PCI for stable angina and ACS have a similar benefit to men with GP IIb/IIIa inhibitor use in terms of decreased rates of death, MI, and urgent revascularization at 30 days⁽²⁷⁾. Attention to appropriate dosing may lead to a reduction in overall bleeding complications for women⁽²⁸⁾.

Although there is evidence of significant improvement in short-term mortality for women undergoing coronary artery bypass grafting (CABG), women continue to have higher mortality rates than men (3.6%

vs. 2.0%, $p<0.001$)⁽²⁹⁾. This may be particularly true for women presenting with STEMI and undergoing CABG. A recent retrospective observational study found that among patients undergoing CABG for STEMI, more nonsurvivors were women (58% vs. 23%, $p<0.01$) and that female sex was an independent predictor of in-hospital death⁽³⁰⁾.

Platelet Function and Plaque Erosion

Among young survivors of MI, women have more platelet aggregability to adenosine diphosphate and less platelet inhibition to prostacyclin than men⁽³¹⁾. Thrombi found at autopsy in women who died of sudden cardiac death are more often associated with erosion of a proteoglycan-rich plaque rather than rupture of a lipid-rich plaque with a thin fibrous cap, as is more commonly seen in men⁽³²⁾. Women who die from plaque erosion tend to be younger and are more likely to smoke, whereas women who die from plaque rupture tend to be older and hypercholesterolemic⁽³³⁾. In addition, younger age and plaque erosion are both associated with a lesser degree of luminal narrowing at the plaque site, as well as a lesser overall extent of CAD. This may indicate an underestimation of risk by angiography, particularly in younger women.

Ischemia and Non-Obstructive Coronary Artery Disease

There is a growing body of evidence that women commonly experience ischemia in the absence of obstructive CAD. The majority of this data comes from the WISE (Women's Ischemia Syndrome Evaluation) study, a sex-specific study that prospectively evaluated over 900 women referred for elective coronary angiography because of suspected myocardial ischemia. WISE investigators found that over half of the women they tested had evidence of endothelial dysfunction and/or microvascular disease despite the majority of them having no or minimal epicardial disease. In addition, the presence of these vascular derangements was associated with future cardiovascular events, including CHF, MI, stroke, and death even after controlling for the degree of CAD and multiple cardiac risk factors^(34,35). Coronary endothelial dysfunction is defined as a blunted epicardial vasodilatory response (by quantitative coronary angiography, QCA) to an endothelial-dependent vasodilator delivered intracoronary, such as acetylcholine. The presence of microvascular disease can be diagnosed by a diminished coronary flow reserve (CFR) or index of microcirculatory resistance (IMR) using a coronary PressureWire[®] (Radi Medical Systems, Wilmington, MA). In the WISE study, CFR was measured using a Doppler-tipped guidewire (0.014-inch FloWire, JOMED/Cardiometrics, Mountain View, CA)^(36,37).

WISE investigators have also found that women without significant epicardial disease by angiography often have diffuse atherosclerosis by intravascular ultrasound (IVUS)⁽³⁸⁾. Such pathology may lead to ischemia. It has been demonstrated by using a coronary pressure wire and calculating fractional flow reserve (FFR) during a slow pullback that diffusely diseased epicardial vessels without angiographic evidence of a focal stenosis often have a graded continuous loss in pressure along the arterial length, and that the presence and/or severity of this coronary pressure gradient cannot be predicted from the angiogram alone⁽³⁹⁾.

Conclusion

A growing body of sex-based research in cardiovascular disease is increasingly elucidating differences between women and men. Many of these differences can be attributed to age, prevalence of comorbidities, and even varying treatment practices, but underlying variations in biology likely remain underappreciated and undiscovered. Adoption and application of new knowledge regarding sex differences will hopefully lead to improved outcomes. Future investigations into sex differences in cardiovascular disease need to continue to probe deeper than clinical observations by including more randomized controlled trials and basic science research.

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