

Sex Differences in Percutaneous Coronary Interventions

Juzar O. Lokhandwala · Kimberly A. Skelding

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Abstract Cardiovascular disease is the leading cause of mortality in women, and women have a higher cardiovascular mortality and morbidity associated with the treatment of cardiovascular disease compared to men. Percutaneous coronary intervention (PCI) is an important therapy for women with coronary artery disease particularly in acute coronary syndromes; however, only 33% of all PCIs are performed in women. The purpose of this review is to evaluate the evidence for PCI in women and demonstrate the unique aspects of therapy in regard to sex.

Keywords Percutaneous Coronary Intervention · Women · Sex Differences · Coronary Artery Disease

Epidemiology of Coronary Artery Disease in Women

Cardiovascular disease is the leading cause of death in women and is responsible for one in three deaths among women. One in every five women aged 40 years and above will die within the first year after having a heart attack. Cardiovascular disease is prevalent in 86% of women above the age of 80 years, in 73% of women between 60 and 79 years, and in 39% of women between 40 and 59 years. Of the 1.2 million percutaneous coronary interventions (PCI) being performed annually in the USA, women account for only 33% [20].

J. O. Lokhandwala · K. A. Skelding (✉)
Department of Cardiology, Geisinger Medical Center,
100 North Academy Lane,
Danville, PA 17822, USA
e-mail: kaskelding@geisinger.edu

J. O. Lokhandwala · K. A. Skelding
Henry Hood Center for Health Research,
Geisinger Medical Center,
Danville, PA, USA

Despite these staggering statistics, there is still a lack of appropriate awareness among women. While 57% of women were aware of heart disease as the leading killer, only 13% perceived it to be their greatest health problem [24]. We review the sex differences in the presentation and diagnosis of coronary artery disease (CAD), particularly acute coronary syndromes as well as the unique aspects of PCI in women with CAD.

Sex Differences in Diagnosis of CAD

Clinical Presentation

Women are less likely to present with typical angina, more likely to use different terms to describe their symptoms, and more likely to have more nonpain-related symptoms in addition to chest pain than men [10]. However, the definition of typical anginal symptoms was determined in a male cohort, and we may need a new set of contemporary definitions for women. In a recent study, while men and women presented equally with chest pain, among those patients that did not present with chest pain, jaw pain, and nausea were more frequent among women [11]. In a 26-year follow-up from the Framingham Study, 80% of women presented with angina without myocardial infarction (MI), whereas in 66% of men, angina evolved from myocardial infarction [23]. In addition to different clinical presentations which may delay treatment, women also tend to seek medical attention later than men after the onset of their chest pain [34].

Noninvasive Testing

Data regarding stress testing for the diagnosis of CAD in women is limited and is largely extrapolated from data

gathered from studies that have an underrepresentation of women. These early studies were performed prior to the realization of sex-based differences in heart disease. Women have higher false-positive rates of exercise-induced electrocardiographic changes. As a result, exercise-based stress testing for CAD, although useful on some patients, has only a moderate sensitivity and specificity in women [18]. Women undergoing an exercise stress test tend to have a lower functional capacity which limits the ability to induce myocardial ischemia and decreases the diagnostic value of the test. Women with exercise capacity less than five metabolic equivalents are at an increased risk of death and current guidelines recommend that women who are unable to achieve five metabolic equivalents be further evaluated with a pharmacologic stress test [25]. In a study of over 11,000 patients undergoing exercise or dobutamine stress echocardiography, it was found that qualitative resting left ventricular function and parameters obtained during stress provided accurate future risk stratification for men and women alike [30]. Other modalities like dobutamine stress cardiac magnetic resonance imaging have also been shown to be good predictors of future adverse events in women [37]. Therefore, despite the decreased sensitivity and specificity of noninvasive tests in women, they provide important prognostic information about future adverse events. In addition, when considering coronary computed tomography in premenopausal women, the increased risk of breast cancer due to radiation exposure must be carefully weighed into the clinical decision-making process [12].

Invasive Coronary Angiography

Women were less likely to be referred for diagnostic catheterization after a stress test when compared to men in a study of over 3,000 consecutive patients undergoing nuclear stress testing (7.1% versus 10.6%, $p<0.001$). This sex difference disappeared when stratification was done according to extent of the abnormality in the stress test, leading many to believe that stress testing may not be sufficiently sensitive in the detection of single vessel CAD in women. When the abnormality on the stress testing was large, women were referred more frequently than men to cardiac catheterization. Despite this, women with a markedly abnormal stress test had a significantly higher 1-year event rates regardless of referral for invasive evaluation (17.5% versus 6.3%, $p<0.0001$) [15].

In the Women's Ischemia Syndrome Evaluation (WISE) study which enrolled women referred for coronary angiography, the observed rates of CAD at angiography were much lower than the estimated probability of CAD. This may be indicative of the diffuse nature of atherosclerosis in women, and coronary angiography may underestimate the degree of CAD and its subsequent morbidity and mortality

in women [31]. In a subgroup of 163 women in the WISE study who were referred for invasive angiography and also underwent testing for coronary microvascular dysfunction, only 25% of the total number of women had $>50\%$ stenosis in the coronary arteries. However, adverse cardiovascular outcomes including death occurred in 36% of the 163 women on follow-up. In this study, coronary microvascular dysfunction was an independent predictor of adverse cardiovascular outcomes after adjusting for traditional cardiovascular risk factors and CAD severity [36]. In another substudy, coronary microvascular dysfunction was seen in 47% of women who presented with chest pain without obstructive disease on coronary angiography, suggesting that this is more ubiquitous and needs to be factored into our evaluation for CAD in women [29]. Coronary microvascular dysfunction plays an important role in women with chest pain and an abnormal stress perfusion imaging, even in the presence of nonobstructive CAD by angiography, and unfortunately carries an adverse prognosis in women.

Percutaneous Coronary Intervention in Women

Invasive Treatment Approach to CAD

In the Systolic Hypertension in the Elderly Program study cohort, among the 432 patients with CAD, 26% of men and 9.1% of women ($p<0.001$) underwent surgical or percutaneous revascularization. It suggested that even with identified CAD, women were treated less aggressively than men. In patients younger than 75 years, the percentages of revascularization were 31.1% for men and 12.3% for women ($p<0.001$). In patients above 75 years of age, the percentages of revascularization were 19.5% for men and 5.9% for women ($p=0.005$). Therefore, women and older patients underwent less intensive cardiovascular interventions irrespective of comorbid conditions, socioeconomic status, and social support. But importantly, women underwent revascularization less often, regardless of their age, refuting the fact that age alone accounts for less aggressive therapy [8]. Similarly, a later study involving more than 74,000 patients with acute myocardial infarction found that women had a lower rate of PCI when compared to men (14.2% versus 24.4%). Their analyses concluded that while two thirds of this sex difference in PCI rates can be explained by adjustments for age and comorbidities, the remaining one third was related solely to disparity in treatment based on sex [26].

Periprocedural Risk

In 118,548 PCI procedures, women had a twofold increase in same-admission mortality and increased rates of coro-

nary artery bypass grafting following PCI. A significantly increased risk remained after multivariate adjustment for differences in baseline characteristics in women undergoing PCI without an acute myocardial infarction [38]. Many reasons for this increased risk have been discussed. Women tend to have a lower body surface area and are therefore likely to receive inadvertent higher doses of anticoagulants which leads to an increased risk of bleeding [3]. Bleeding and blood transfusions increase cardiovascular morbidity and mortality consistently regardless of other risk factors, particularly in women [28]. For women undergoing PCI, accurate dosing of anticoagulants based on calculated estimated glomerular filtration rate and body surface area is critical in decreasing periprocedural risks of PCI. Women also tend to have a 1.5 to fourfold increased risk of vascular access complications. Interestingly, although women have been shown to have a higher risk of in-stent restenosis which has been attributed to a higher incidence of comorbidities associated with restenosis, they are at a lower risk of stent thrombosis in some studies [2, 20]. When comparing PCI outcomes for women from the National Heart, Lung and Blood Institute (NHLBI) registries between 1985–1986 and 1993–1994 to the NHLBI Dynamic Registry from 1997 to 1998, there was a higher angiographic and procedural success rate and a lower repeat revascularization rate at 1 year in the Dynamic Registry despite the older age and higher comorbidities among women in the Dynamic Registry. After adjusting for baseline differences between women in the registries, the time period of the Dynamic Registry was associated with an approximately 50% decrease in 1 year mortality in comparison with the 1985–1986 registry time period. This indicates that contemporary outcomes for women undergoing PCI have improved, leading to a decrease in sex differences in mortality from PCI [17, 32]. More recently, in an unselected population undergoing PCI as part of the National Heart, Lung, and Blood Institute Dynamic Registry, drug-eluting stents were found to reduce clinically driven revascularization equally in men and women [1].

Management of Unstable Angina and Non-ST Elevation Myocardial Infarction in Women

Numerous clinical trials focusing on the treatment of acute coronary syndromes exist to guide the clinician. However, women are frequently underrepresented in these clinical trials, making these data far from generalizable [22]. Women are less likely to meet the inclusion criteria for entry into clinical trials due to multiple factors including late presentation after onset of symptoms, increased comorbidities, and being sicker on presentation. Data from the National Registry of Myocardial Infarction showed that

women younger than 75 years who had a myocardial infarction had a much higher short-term mortality when compared to men. For every 5-year decrease in age, the odds of death during hospitalization of women relative to men increased 11.1% (95% confidence interval, 10.1% to 12.1%). This difference was not seen in women greater than 75 years of age. This indicates that premature CAD in women carries a worse prognosis or that we may not look hard enough for CAD in younger women to treat them appropriately [34].

When analyzing results of trials by sex, randomized clinical trials regarding choosing an early invasive approach versus a conservative approach in patients with acute coronary syndromes other than ST elevation MI have had conflicting results for women. In the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC II) trial, women with unstable CAD were older but were less likely to have prior infarctions, left ventricular dysfunction, and elevated troponin at presentation. There was no difference seen in death or risk of recurrent myocardial infarction when comparing women in the invasive and noninvasive groups, but when compared to men in the invasive group, women in the invasive arm had an increased risk of death or MI, suggesting that there is something other than the choice of therapy that leads to the increased risk [19]. Possibly, a much higher surgical mortality in women undergoing surgical revascularization in the FRISC II trial may have resulted in the latter finding. Similarly, in the Randomized Intervention Trial of Unstable Angina (RITA3), no benefit of early invasive therapy was seen in women as opposed to the increased benefit seen in men [13]. In the Treat Angina with Aggrastat and Determine Cost of Therapy with Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) trial, a similar benefit of early invasive therapy was seen in women and men [14]. A possible explanation for disparate findings in these trials is that the FRISC II and RITA3 trial included women with low risk, leading to imbalance between the benefit from the procedure and procedural risk which is elevated in women. Additional supportive data are seen in the TACTICS-TIMI 18 trial where women with TIMI risk scores between 0 and 2, and no elevation in serum troponin had a trend toward worse outcome with early invasive therapy, albeit not statistically significant [14].

Current guidelines for the management of unstable angina or non-ST elevation myocardial infarction state that there should be no sex difference in management. When risk adjusted, women have a similar benefit from an early invasive strategy within the first 48 h to their male counterparts. They also similarly recommend usage of antiplatelet agents like aspirin and clopidogrel as well as glycoprotein IIb/IIIa inhibitors in all troponin-positive

patients [5]. Despite these recommendations, women less frequently receive guideline recommended strategies that decrease cardiovascular mortality and morbidity, including percutaneous coronary interventions.

An example of this is seen in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines registry, which enrolled 41% women. In this registry, women were on average 13 years older than men at presentation and were more likely to have diabetes and hypertension. But despite their high risk, they were less likely to receive appropriate medical therapy, including heparin on initial evaluation, angiotensin-converting enzyme inhibitor, and statins at discharge. More importantly, the use of diagnostic angiography and revascularization, both percutaneous and surgical, was lower in women. Women were also less likely to undergo cardiac catheterization in the first 24 h. Subsequently, on evaluating unadjusted in-hospital clinical outcomes, women were more likely to have postadmission myocardial infarction, cardiogenic shock, congestive heart failure, stroke, red blood cell transfusions, and death. After adjustment for baseline characteristics, these differences disappeared except for an increased need for blood transfusions. This less invasively treated population of women had about 15–20% higher rates of adverse events and death following their less frequent treatment with guideline-recommended medical and interventional strategies [9]. Similarly, the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial showed that women with acute coronary syndromes were less likely to undergo revascularization when compared to men (47.6% versus 60.5%; $p=0.0001$). While women did not have excess death, myocardial infarction, or stroke, they were more likely to develop refractory ischemia and to be rehospitalized for chest pain. This was particularly seen in women with high risk features at presentation. This again underlines the importance of early invasive approach in the management of women with high risk acute coronary syndromes [4].

In a cohort study involving 1,450 consecutive patients with acute coronary syndrome where PCI was performed in over 50% of patients, which was five times larger than the number of patients who underwent coronary artery bypass surgery, women had a much better long-term outcome than men with early invasive therapy [27]. This contrasts with the FRISC II and TACTICS-TIMI 18 study where the ratios of PCI to coronary artery bypass surgery in patients that underwent any form of revascularization were 1:1 and 2:1, respectively. The sole difference is that in the latter trials, more women went to coronary artery bypass surgery as their form of revascularization, which may have contributed to their higher mortality.

Evidence for Primary PCI in Women

Women presenting with ST-elevation myocardial infarction have higher rates of in-hospital mortality and cardiogenic shock [35]. In older studies, this has been found to be largely related to women presenting later and being older and sicker on presentation [6,7]. But not all studies are in agreement. One study showed that women had a 2.3-fold higher risk of death compared to men following primary PCI, despite adjustment for baseline characteristics with multivariate logistic regression analysis [35]. More contemporary data demonstrate that the gap is narrowed with primary PCI. In the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes Angioplasty study, the relative benefit of primary balloon angioplasty when compared to thrombolysis was similar in men and women. Women had a larger absolute benefit considering their higher absolute event rates compared to men [33]. In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial, women who received primary stenting had a significant reduction in major adverse cardiovascular events and target vessel revascularization at 1 year when compared to balloon angioplasty only. However, when compared to men, women had a higher mortality rate. The difference in mortality disappeared after adjusting for baseline comorbidities and lower body surface area in women but the higher rate of bleeding and 1 year major adverse cardiac events in women persisted [21]. In the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock trial which included patients with acute myocardial infarction and cardiogenic shock, early revascularization significantly improved 1-year survival compared to initial medical stabilization including thrombolysis. In one of the prespecified subgroup analyses of this trial, there was no difference in the benefit derived from early revascularization based on sex [16].

Future Directions

Cardiovascular disease outcomes in women are improving but are not yet at parity. Clinical trial results demonstrate a decrease in the gender gap when therapies have been provided in a sex neutral fashion. However, the underrepresentation of women in clinical trials often does not allow us to determine the true benefit of therapy for women since it does not allow an appropriately powered statistical comparison between the subgroups of women who receive versus do not receive the studied therapy. We need to encourage more enrollment in clinical trials of female patients. Likewise, we need to encourage prespecification of sex-related outcomes in clinical trials and development

of sex-specific guidelines for the treatment of women with acute coronary syndromes and myocardial infarction similar to the prevention guidelines recently released for women. It is also necessary to better define the pathophysiology of CAD in women. This requires advances in basic and translational research, in addition to clinical research. A better understanding of the pathophysiologic differences such as the role of microvascular dysfunction may help guide the choice of therapy, PCI versus medical therapy only, in women with CAD. We also need to continue to educate women about the symptoms of myocardial infarction to encourage early presentation for primary PCI in order for them to receive proper life-saving therapies.

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