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WOMEN AND ISCHEMIC HEART DISEASE (E. JACKSON, SECTION EDITOR)

Acute Coronary Syndromes: Differences in Men and Women

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Abstract
Purpose of Review Increased awareness of cardiovascular disease in women has prompted studies to investigate gender-related disparities in acute coronary syndromes (ACSs). In this review, we discuss findings from current literature on the clinical presentation, pathophysiology, diagnosis, and management of ACS in women as compared to men.
Recent Findings Emerging data show that cardiovascular disease (CVD) continues to be the leading cause of death in women and the annual mortality rate from CVD remains higher in women compared to men. Recent studies demonstrate sex-specific differences in patients presenting with ACS. Comorbidities, especially diabetes, are more common in young women compared with age-matched men who develop acute myocardial infarction (AMI). Women are more likely to have atypical symptoms and nonobstructive coronary disease on angiography. Women are less likely to receive guideline-based therapies. They have higher rates of periprocedural complications with PCI and are less likely to be referred to cardiac rehabilitation.
Summary Awareness of differences in the underlying pathophysiology of coronary disease in women compared to men may lead to improved gender-based diagnostic and treatment modalities. However, until more studies are performed, efforts should be directed toward improving delivery of current, gender-neutral guidelines in women just as in men.

Keywords Acute coronary syndrome · Women · Nonobstructive coronary disease · Gender differences · Myocardial infarction

Introduction

Despite the increased awareness of cardiovascular disease (CVD) in women over the last two decades, it remains the leading cause of death in women in the USA and accounts for more deaths than cancer, chronic lower respiratory disease, and diabetes combined [1]. Since 1984, the annual CVD mortality rate has been greater in women than men [2]. Regardless of age, within 1 year of a first acute myocardial infarction (AMI), more women than men will die, and the median survival time after a first myocardial infarction (MI) is significantly lower for women [2]. Despite the immense burden of CVD on women, they are historically underrepresented in cardiovascular disease trials. This has resulted in gaps in knowledge with regard to sex-specific differences of acute coronary syndrome (ACS). Over the last decade, emerging findings have revealed important information regarding the clinical presentation, pathophysiology, diagnosis, and management of ACS in women. Identified risk factors in women with ACS differ from men. Women have a higher incidence of nonobstructive coronary disease, are less likely to be treated with guideline-based therapies, and have more complications with reperfusion interventions compared to men.

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Awareness

Over the past two decades, there has been a reversal in the perception that cancer causes more deaths in women than heart disease [3, 4]. Mosca et al. conducted a cross-sectional survey of 2300 women in the USA who were at least 25 years old and compared results from similar surveys conducted in 1997, 2000, 2003, and 2006. Awareness among women that CVD is the leading cause of death was 30 % in 1997. Although this percentage has increased, only 56 % of women in 2012 recognized CVD as the leading cause of death. The level of awareness increased among racial and ethnic minorities but at a lower rate compared to white women. African-American women have the highest CVD mortality rate among ethnic minority groups but substantially lower awareness. Increased awareness among women is attributed to the success of national educational programs and has been linked to preventative action taken by women. However, this rising awareness has plateaued since 2006 [4].

Presentation and Risk Factors

Sex-differentiated risk factors identified in women presenting with ACS include multiple comorbidities, age, and race/ethnicity. Women are more likely than men to have multiple comorbidities at initial ACS [5, 6, 7•, 8]. Obesity, smoking, depression, hypertension, and chronic kidney disease have been found more frequently in women compared to men with ACS [9–12]. These comorbidities were more frequent in women <55 years old, and these differences were less pronounced as age increased [12, 13]. Diabetes is especially prevalent in young women with ACS. The INTERHEART study was a global case–control study of more than 6700 women from 52 countries, which revealed that women with diabetes were 4.3 times more likely to develop an MI than women without diabetes. By contrast, men with diabetes were 2.7 times more likely to develop an MI compared to men without diabetes [5].

Hormonal differences and ACS in women have been studied but are not fully understood. It is widely believed that postmenopausal women lose the protective effects of endogenous estrogen on the vascular endothelium, leading to an increased risk of CAD [14]. However, both the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) concluded that estrogen plus progestin therapy does not reduce the rate of CHD events [15, 16]. In fact, the absolute excess risks of CHD events, strokes, pulmonary embolism, and breast cancer were higher in the estrogen plus progestin group in the WHI trial [16]. Replacement of combined postmenopausal hormones is not recommended for primary or secondary prevention of coronary events and should be discontinued in women who present with ACS. Oral contraceptives that included ethinyl estradiol were also shown to increase the risk of myocardial infarction. The risk was increased in patients using contraceptives with higher ethinyl estradiol doses and in patients with increased age [17]. None of the progestin-only products, including the levonorgestrel-releasing IUD and the subcutaneous implants, significantly increased the risk of thrombotic stroke or myocardial infarction [17].

Women present with ACS on average ~10 years later than men in all regions of the world [5, 6, 18], likely related to the hormonal changes of menopause. With regard to younger women, the trend of declining cardiovascular events in the overall population has not been seen in this subgroup over the past decade. From 2001 to 2010, women demonstrated either no change (in women 30–34 and 35–39 years of age) or a slight absolute increase (in women 40–44 and 45–49 years) in hospitalization rates for acute myocardial infarction (AMI) [19••]. Furthermore, young women <55 years of age have longer lengths of stay, higher hospital readmission rates, and higher in-hospital mortality, as compared to young men [12, 19••, 20].

The first study to investigate sex differences in veterans undergoing cardiac catheterization showed that women had higher rates of depression and posttraumatic stress disorder compared to men [21••]. Shah et al. illustrated that depressive symptoms predict CAD presence and increases risk of death in young women aged ≤55 years [22]. The Women's Health Initiative also showed that depression is a risk factor for CVD among older women, even after controlling for established CVD risk factors [23]. Numerous studies have correlated depression with increased morbidity and mortality after ACS [22, 24, 25]. A systematic literature review including 53 studies and 4 meta-analyses demonstrated robust evidence that depression after ACS is a risk for all-cause and cardiac mortality [24]. Studies evaluating CVD during disasters such as earthquakes, wars, and major sporting events showed that acute mental stress has been linked to cardiovascular mortality [25]. More than 80 % of patients presenting with stress (takotsubo) cardiomyopathy are women, and these patients have a higher prevalence of psychiatric disorders [26].

Morbidity and mortality in racial and ethnic minorities have not improved as vigorously as in white women and have worsened in certain subgroups. Non-Hispanic black women have a higher prevalence of MI, present with MI at a younger age, have more comorbidities, and increased mortality within 1 and 5 years after a first MI [2, 27]. The reduction in hospitalization for AMI or fatal CHD from 1987 to 2011 decreased less in black women compared to white women [2]. There are documented disparities in rates of referral of black women to coronary angiography and reperfusion compared with white women and black men [28]. Surprisingly, CHD mortality rates

in Asian-Indian women were higher in 2010 than in 2003 [29]. Similarly, American-Indian women have increasing coronary events, and this is associated with a significantly higher prevalence of diabetes [30].

Pathophysiology

The differences in presenting age and preexisting comorbidities in women with ACS suggest an underlying sex-specific pathophysiology of ischemic heart disease. Although plaque rupture is the leading cause of coronary thrombus and MI in men, this is a much less common cause among women. One striking gender difference is that women presenting with ACS have a higher incidence of nonobstructive CAD and plaque erosion as a cause of coronary thrombus formation [31–37]. In fact, plaque rupture is especially rare in premenopausal women. It has been postulated that estrogen may cause plaque to be more stable [38••]. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study utilized three-vessel multimodality intracoronary imaging (quantitative coronary angiography [QCA], grayscale intravascular ultrasound (IVUS) imaging, and radiofrequency virtual histology (VH) IVUS in patients presenting with ACS. The study showed that plaque rupture was less common in women (6.6 vs. 16.3 %; $p = 0.002$) [8]. Thin-capped fibroatheromas (TCFA) are known to be vulnerable to rupture. In contrast, eroded plaques are more fibrous and have an intact plaque cap and less necrotic cores. The thrombi overlying eroded plaques are more organized, reflecting longer existence (up to 7 days) before presentation with clinical symptoms [31]. Also, the degree of stenosis from plaque erosion is smaller compared to ruptured plaques. More women than men may be symptomatic with plaque erosion, due to smaller vessel lumen diameters. The longer period of thrombus existence seen in plaque erosion also provides greater opportunities for distal embolization. Microvascular embolization and microvascular occlusion have been shown to cause focal myocardial necrosis [39]. Plaque erosion is clearly a distinct, primarily endothelial pathology compared to plaque rupture, which is an inflammatory process [31]. Therefore, utilizing intracoronary image-guided plaque characterization to differentiate plaque erosion versus rupture as a cause of coronary thrombus and ACS may lead to improvement in diagnoses and tailored treatments.

Nonobstructive disease or coronary microvascular dysfunction (CMD) (previously known as syndrome X) is far more common in women compared to men [35, 40–43, 44•]. Progression of CMD in parallel with worsening glucose intolerance in the setting of insulin resistance has been recognized in several studies [45–47]. In a study of asymptomatic diabetics, impaired coronary flow reserve (CFR) was associated with a rate of cardiac death comparable to that for nondiabetic patients with known CAD (2.8 vs 2.0 %/year; $p = 0.33$) [48]. Myocardial blood flow improves with insulin infusion in healthy patients, increasing the threshold for ischemia [49, 50]. The strong association of diabetes and CMD likely explains the high incidence of nonobstructive coronary disease in young women with diabetes.

Other less common causes of ACS that are more prevalent in women than men include coronary vasospasm, spontaneous coronary artery dissection, and stress-related (takotsubo) cardiomyopathy. These entities are beyond the scope of this review but should be considered in the differential diagnosis of any woman presenting with an acute coronary syndrome, particularly in the presence of factors predisposing to these entities. It is interesting to note that coronary microvascular dysfunction has been strongly suggested as the underlying etiology of stress cardiomyopathy [51].

The possibility of a sex-specific pathophysiology of ACS may explain some of the differences in the manifestation of symptoms between men and women. Although chest pain is the most common symptom of ACS in both men and women, presentation without chest pain or with atypical symptoms is more frequent among women [52–54]. Atypical symptoms include jaw pain, shoulder pain, arm pain, nausea, fatigue, weakness, dyspnea, and indigestion [52].

Evaluation and Management

Delay in Presentation

Data from 125,161 patients taken from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) and the ACTION-GWTG registries showed a longer median time to hospital presentation in women (3 h) than in men (2.8 h; $p < 0.001$) [18]. Although, increased awareness from national awareness campaigns in women has been linked to more preventative action, time to presentation remains unchanged, and a significant gender gap persists. This may be due to the reluctance of women to seek emergency evaluation, as only 53 % of women stated they would call 9-1-1 if they thought they were having symptoms of a heart attack [18]. Delay in presentation among women may also be related to restricted access to care, inaccurately assessed personal risk of heart disease, and variability in prodromal symptoms [55].

Diagnosis

Cardiac troponin (cTnI) is the most widely used and specific marker of cardiomyocyte injury. Baseline concentrations of troponin are lower in women than in men, which may be due to smaller cardiac mass in women [56]. Slagman et al.

evaluated sex differences in troponin and showed a lower positive predictive value (PPV) for women (53.5 %; 95 % CI 42.4–64.3) as compared to men (60.8 %; 95 % CI 54.1–67.2) and a slightly higher negative predictive value (NPV) for women with 97.1 % (95 % CI 96.0–97.9) vs. 96.3 % (95 % CI 95.2–97.2) in men [57•]. However, there are no current sex-related differences in cutoff points for cardiac troponin in diagnosing ACS. Although not readily available in the USA, high-sensitivity assays for cardiac troponin (hsTnI) have emerged, and these levels have also been found to be lower in women than men. This assay may improve sensitivity in women and specificity in men. Shah et al. used sex-based thresholds for hsTnI (men 34 ng/L, women 16 ng/L) in patients presenting with suspected ACS in the UK. This resulted in double the number of ACS diagnoses in women. Specificity was unchanged in men and only slightly lower in women, suggesting that noticeable improvements in diagnostic sensitivity would not be offset by reductions in specificity [58]. In contrast, a study including patients from two tertiary centers in Australia and New Zealand found an increased number of female patients with increased troponin I concentrations using hs-cTnI compared to cTnI, but this was not associated with an increased number of women with AMI diagnoses. It was thought that outcomes were not improved with lower cutoff values for women, because the performance of serial cTnI measurements increased sensitivity [59]. It is clear that a higher level of troponin is associated with increased mortality and recurrent MI in both sexes. [60]. There are other proposed novel biomarkers, including proneurotensin, that have been shown to be predictive of cardiovascular disease (as well as breast cancer) in women [56]. More prospective clinical studies are needed to further investigate sex-dependent cutoff values for current and novel biomarkers.

As mentioned, women more frequently than men have plaque erosion and coronary microvascular dysfunction-associated ACS. Lee et al. assessed endothelial function, microvascular resistance, CFR, and fractional flow reserve (FFR) and performed intravascular ultrasound in patients with nonobstructive coronary artery disease, as well as discovered occult coronary abnormalities [44•]. This study concluded that comprehensive invasive assessment of these patients at the time of coronary angiography can be performed safely and provide important diagnostic information that may affect treatment and outcomes. Murthy et al. used positron emission testing (PET) myocardial perfusion imaging to show that CFR was an incremental predictor of major adverse cardiac events (MACE) at a median follow-up of 1.3 years in patients with CAD [61]. Optic coherence tomography (OCT) is another promising modality to diagnose plaque erosion, and OCT erosion is more frequent in younger patients with non-ST elevation (NSTE)-ACS [62]. Wider adoption of these diagnostic modalities may allow clinicians to better diagnose ACS stemming from causes other than plaque rupture. This may lead to improved diagnosis and management of nonobstructive coronary disease, which is more prevalent in women.

Reperfusion Strategies

Non-ST Elevation Myocardial Infarction

In patients with stable angina, trials including Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) showed that optimal medical therapy (OMT) was equally beneficial as an initial strategy compared to revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in both women and men [63–65]. There are conflicting outcomes with regard to gender differences in the treatment of NSTE-ACS with OMT versus revascularization. Women in the Framingham and Fast Revascularization during Instability in Coronary artery disease (FRISC II) study had less advantage with an early invasive strategy, compared with men [66]. However, this study included women with unstable angina and the absence of cardiac biomarker elevation. A meta-analysis showed that in women with elevated biomarkers (creatine kinase MB or troponin), an invasive strategy significantly decreased the odds of death, MI, or rehospitalization with ACS [67]. There was less benefit for an invasive strategy in women in the absence of biomarker elevation, and an early invasive approach potentially increased the risk of death or MI, as shown in TACTICS-TIMI 18 [60]. Therefore, an early invasive strategy should be reserved for women with NSTE-ACS and high-risk features (e.g., troponin positive) [68]. Despite the benefit of early invasive strategy in this subgroup, it has been clearly shown that women are less likely to receive coronary interventions [7•, 69, 70, 71•, 72]. Of the women who underwent PCI, the use of second-generation drug-eluting stent (DES) was higher among men in the first 1.5 years after its introduction, but DES use increased in women and there were no differences thereafter [73]. Newer-generation DESs (including everolimus- and zotarolimus-eluting stents with durable polymers and biolimus- and sirolimus-eluting stents with a biodegradable polymer) were associated with lower 3-year MACE rates in women with ACS compared with early-generation DESs (sirolimus- and paclitaxel-eluting stents) [74•].

ST-Elevation Myocardial Infarction

Women with ST-segment elevation myocardial infarction (STEMI) present later after symptom onset are less likely to receive aspirin or beta blockers within 24 h of presentation and have delayed door-to-balloon time compared to men [75]. The CRUSADE registry found that female sex was one of the strongest factors associated with not attempting reperfusion among the eligible population [76]. Fibrinolytic therapy is

recommended for the treatment of STEMI with symptom onset within 12 h and if primary PCI cannot be performed within 120 min from first medical contact regardless of gender [77]. However, women have a higher risk of mortality with fibrinolysis [78]. In addition to increased mortality, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial showed that women have more nonfatal complications such as shock, heart failure, reinfarction, recurrent ischemia, bleeding, and stroke compared with men [79]. Analysis of the primary angioplasty in patients transferred from general community hospitals to specialized PTCA Units with or without emergency thrombolysis (PRAGUE) 1 and 2 studies demonstrated that long-distance transportation of women with STEMI from a community hospital to a tertiary PCI center is a significantly more effective treatment strategy than on-site fibrinolysis [78].

Complications

Peri-procedural complications from PCI are higher in women, especially vascular and bleeding complications [68, 75]. After adjustment for baseline demographics, comorbidities, clinical presentation, and lesion characteristics, female gender was associated with an increased risk of in-hospital death, vascular complications, blood transfusion, stroke, and MACE [43].

It has been suggested that bleeding complications appear to be driven by access site complications and sheath size. Closure techniques also play a role in complications experienced by women [80, 81]. Radial artery access has been shown to reduce bleeding complications, especially in women [82–84]. However, this technique is dependent on operator experience, and adoption of radial access cardiac catheterization in the USA has been slower than elsewhere in the world.

Coronary Artery Bypass Grafting

Women referred for CABG are older and have more comorbidities. These predisposing factors are reflected in higher rates of peri-procedural mortality, bleeding, stroke, wound infection, cardiogenic shock, and renal failure [85]. They also experience longer stays in the intensive care unit and hospital and longer recovery times [68]. A retrospective analysis from the Nationwide Inpatient Sample database from 2003 to 2012 reported that female gender remains an independent predictor of mortality after multivariate adjustment across all age groups. Proposed mechanisms to explain poorer surgical outcomes in women include a higher incidence of comorbidities, smaller diameter of coronary arteries, and decreased internal mammary artery (IMA) grafting in women. Although women continue to have poorer outcomes after CABG compared to men, outcomes are improving overall, and the difference in outcomes between women and men is decreasing. This may be attributed to advancement in surgical techniques. IMA use in women was less than men in 2003 (77.4 vs 81.9 %; $p < 0.001$), but there has been a significant uptrend that closed this gap by 2012. Using off-pump CABG has also resulted in reduced mortality rates in women from 4.1 % on-pump to 2.3 % off-pump [86].

Pharmacologic Strategies

The 2014 AHA/ACC guidelines recommend that women with non-ST elevation acute coronary syndromes (NSTE-ACS) should be managed with the same pharmacological therapies as men for acute care. Women derive the same treatment benefit as men from aspirin, clopidogrel, anticoagulants, beta blockers, ACE inhibitors, and statins for secondary prevention [68]. Despite worse outcomes, women with NSTE-ACS are underprescribed guideline-directed pharmacological therapy, both during the acute illness and at discharge [6, 21••, 68, 80, 87]. The review of the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR), which included more than 55,000 women, showed that women were less likely to receive aspirin or glycoprotein IIb/IIIa inhibitors and were less often discharged on aspirin or a statin [80]. It was further shown that women <55 years are significantly less likely to be on optimal therapy by the end of 1 year after discharge, which is driven by a sex disparity in treatment initiation and not differences in treatment adherence [12, 88••].

Women with nonobstructive coronary disease are less likely to receive secondary prevention medication prescriptions at hospital discharge, as compared to patients with obstructive CAD [89]. However, despite normal-appearing coronary arteries on angiography, these patients are four times more likely than men to be readmitted for ACS and chest pain within 180 days [90, 91•]. This may indicate that secondary prevention with medical management is essential in this group.

The safety of antiplatelet and antithrombotic agents in women has been established. Several large studies including CRUSADE, Acute Catheterization and Urgent Intervention Triage strategy (ACUITY), Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38, Platelet Inhibition and Patient Outcomes (PLATO), and Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention (CHAMPION PHOENIX) demonstrated no significant interactions between sex and antithrombotic therapy with regard to bleeding risk [92–97]. Although there is no evidence-based indication for sex-based antithrombotic therapy, close attention should be devoted to avoiding excess dosing by measuring actual body weights and calculating weight-adjusted creatinine clearance for female patients [98].

Cardiac Rehabilitation

Multiple randomized controlled trials have shown improvements in mortality and morbidity outcomes as a result of participation in cardiac rehabilitation (CR). Medicare provides coverage for up to three weekly outpatient CR sessions for 3 months after AMI, CABG, or stable angina pectoris. An evaluation of national use patterns and predictors of CR showed that men were more likely to receive CR than women (22.1 vs 14.3 %) [99]. Similarly, the French registry of Acute ST elevation or non-ST elevation Myocardial Infarction (FAST-MI) study showed that fewer women were referred to CR at hospital discharge [100•]. Minority women are less likely than white women to be referred to cardiac rehabilitation, despite having a worse prognosis after ACS [101].

As noted previously, there is a higher prevalence of depression in women with CHD and depression is a risk factor for morbidity and mortality after ACS. Depression is also associated with decreased CR adherence [102]. One study demonstrated that a modified, gender-tailored CR program reduced depressive symptoms and increased CR adherence and completion when compared to a traditional program [102].

Conclusions

Enrollment of women in clinical trials to investigate and prevent heart disease has increased over the last two decades. However, gender-related disparities continue to exist, and coronary heart disease mortality in women remains substantial. Several factors, including disease awareness, comorbidities, and race, are strong risk factors for the incidence of ACS in women. Awareness of CHD among women has plateaued. Ethnic minorities are especially deficient in their awareness of ACS and have not shown robust improvement in mortality and reduction in comorbidities associated with ACS. Educational efforts should focus on this population, especially African-American women, as they have decreased awareness and higher risk of CHD compared to white women. Education should also focus on the importance of seeking medical attention immediately for ACS, as this will improve the delay in time to treatment in women. Diabetes is a significant risk factor in young women and should be treated aggressively to prevent ACS and future events. Secondary prevention is important for women with nonobstructive coronary disease in order to prevent recurrent symptoms and hospitalizations. Further studies are needed to determine whether sex-based diagnostic modalities and therapy can improve the morbidity and mortality of women presenting with ACS. Until this question is answered, the goal of achieving equality in guideline-based treatments should be reinforced. Providing guideline-based reperfusion therapy, pharmacologic therapy, and cardiac rehabilitation to women will improve outcomes for women with acute coronary syndromes.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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