Current challenges in the diagnosis and management of acute coronary syndromes in women

Jenan Awesat[1, 2], Merry Abitbol[1, 2], Shelly Vons[1, 2], Alon Eisen, Avital Porter[1]

[1]Department of Cardiology, Rabin Medical Center, Petach Tikva, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Correspondence to:
Avital Porter, MD,
Department of Cardiology,
Rabin Medical Center,
Derech Ze`ev Jabotinski 39,
Petah Tikva, 4941492, Israel,
phone: +972 504 065 491,
e-mail: avitalp@clalit.org.il

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ABSTRACT

Cardiovascular disease remains the leading cause of death among women nowadays. However, there is a persistent lack of awareness of the impact of different risk factors on women's cardiovascular health, in specific pregnancy-related complications, hormonal changes, and psychological aspects. Moreover, there is still not enough awareness of the importance of coronary artery disease (CAD) in women, which leads to a delay in the diagnosis and prompt treatment, particularly during emergent coronary scenarios. Although guidelines suggest the same treatment for women and men who present with acute coronary syndrome (ACS), women are still undertreated. Contemporary data show an improvement over time in the management of ACS in women, however, women are still less likely than men to receive revascularization and pharmacological treatments. Women have higher rates of complications and mortality, in particular the young population, in which all outcomes are still worse in women compared to men. In this review, we aim to emphasize the importance of women's risk factors, women-specific pathophysiology, and clinical presentation in the setting of ACS. This is a review of current challenges in the diagnosis and treatment of women with ACS.

Key words: acute coronary syndrome, women

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death among women [1]. In fact, a third of all women in their fourth decade will develop coronary artery heart disease [1]. Although there has been a decline in mortality from acute myocardial infarction (AMI) in both sexes, younger women, under the age of fifty-five still have the highest mortality rate with no significant improvement in the last two decades [1, 2]. Sex-related differences in women presenting with ACS are well known. Women with ACS have different clinical presentations, they are older and have multiple comorbidities compared with men.

Despite the updated current recommendations on CVD prevention of women [3], a nationwide survey demonstrated that although 74% of women had one or more CVD risk factors, only 16% of the women were informed that they were at risk of heart disease. Additionally, only 22% of primary care physicians and 42% of cardiologists felt well-prepared to assess CVD in women [4]. The persistent lack of awareness about the importance of CAD in women leads to a delay in the diagnosis and prompt treatment, particularly during emergent scenarios [5, 6].

RISK FACTORS

Women have both traditional and women-specific CAD risk factors. While traditional risk factors are widely known, the fact that their impact on CVD outcomes differs between sexes is less known. Moreover, specific CAD risk factors are often overlooked (Table 1).

Hypertension prevalence is the same in women and men. However, the incidence of hypertension increases 2-3-fold in women taking oral contraception. Furthermore, hypertension has a more profound impact on CVD in women over the age of 60 compared with men [7].

Diabetes mellitus is a strong risk factor for CVD, and its impact on the risk of coronary death is significantly greater for women than

Table 1. Coronary artery disease risk factors

Traditional risk factors	Sex-specific risk factors
Hypertension	Age of menarche
Diabetes mellitus	Preterm delivery
Dyslipidemia	Pregnancy related conditions: gestational hypertension, sever preeclampsia, eclampsia, amniotic fluid embolism, postpartum hemorrhage, low birth weight, placental abruption, and stillbirth.
Smoking	Polycystic ovary syndrome
	Endometriosis
	Breast cancer

men. In a meta-analysis addressing sex differences in the outcomes of diabetic patients, the relative risk of coronary death from diabetes was 2.58 (95% confidence interval [CI], 2.05–3.26) for women compared to 1.85 (1.47–2.33) for men ($P = 0.045$) [8].

Dyslipidemia is common in women. The risk of CVD increases greatly after menopause and in some studies, the increase in risk was found to be related to a change in the lipid blood profile and especially to the increase in total cholesterol and low-density lipoprotein cholesterol (LDL-C) amongst premenopausal women [9]. A study, which explored the changes during menopausal transition, found an increase in total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A-I (ApoA1) around the onset of menopause. The greatest increase in HDL-C and ApoA1 levels occurred within a year after the onset of menopause and then leveled off or declined, suggesting that HDL-C may be paradoxically associated with an increase in atherosclerosis progression in the postmenopausal phase [10].

Smoking is the leading preventable cause of cardiovascular death in the general population. Although women smoke less than men [11], smoking in women is probably more harmful than in men because female smokers have a significantly increased risk of ST-segment elevation myocardial infarction (STEMI) than men, with the greatest risk in women aged 18 to 49 years old [12].

A history of menarche before the age of ten and delayed menarche after the age of twenty-five are associated with an increased risk of CVD [13].

Pregnancy is a unique period in the woman's life in which several medical conditions may predict an increase in the risk of future cardiovascular events. Preterm delivery, which is defined as births before 37 weeks of gestation, is associated with an increased maternal risk of future cardiovascular events, cardiovascular death, CHD, CHD death, and stroke [14]. The adjusted risk ranged between 1.4- and 2-fold compared with those without a history of preterm birth. This increased risk is greatest in preterm births that occur before 32 weeks of gestation [14]. Gestational hypertension of any sort was found to increase the risk of CVD, including heart failure, myocardial injury, stroke, and mortality [15]. Pregnancy may be complicated with severe maternal morbidity which includes severe preeclampsia, eclampsia, amniotic fluid embolism, postpartum hemorrhage, and obstetric shock, which are considered life-threatening during pregnancy [16]. A comprehensive review of the literature on the relationship between severe maternal morbidity and CVD demonstrated a higher future risk of any cardiovascular disease in women who suffer severe maternal morbidity during pregnancy [16]. Gestational diabetes increases both the risk of future diabetes and CVD [17].

Other pregnancy complications with an increased risk of subsequent CVD include low birth weight, placental abruption, and stillbirth [18].

Fertility treatment is not considered an independent risk factor for CVD, but studies demonstrate that women who have failed this treatment are at more risk of CVD [19]. Moreover, no association is reported between CVD and contraceptive usage in healthy women [20].

Polycystic ovary syndrome is a condition in which the ovaries produce an abnormal amount of androgens. It is strongly associated with metabolic syndrome and diabetes mellitus, eventually increasing the risk of CVD in an indirect way [21]. However, it is unclear whether it poses an independent risk factor for CVD [22].

Endometriosis is a common gynecologic condition in which endometrial tissue is present outside the uterine cavity [23]. A retrospective cohort study investigating the cardiovascular risk among women with endometriosis demonstrated a higher composite of CVD (ischemic heart disease IHD, cerebrovascular accident (CVA), and heart failure) in this group compared with women without endometriosis, 1.03% and 0.75% respectively [24]. Similar results were reported by other studies investigating the role of endometriosis in CVD [25].

Breast cancer history is associated with increased CVD risk through several mechanisms, including mainly breast cancer treatment [26, 27]. Medications commonly used such as anthracycline and trastuzumab have potential for direct cardiac injury. Studies investigating these medications demonstrate an increased risk of developing heart failure: 32.1% when treated with trastuzumab and 41.9% when treated simultaneously with both medications. Radiation therapy, a mainstay treatment of breast cancer, also increases the risk of CVD by 7.4%. The increase in risk begins within a few years of exposure and lasts for approximately twenty years [26, 27].

PATHOGENESIS OF ISCHEMIC HEART DISEASE (IHD) AND ACS

Sex hormones play a key role in the pathophysiology of CAD in women [28]. Specific hormone-related receptors in the cytosol and nuclear compartments of various cell types (including the endothelium and vascular smooth muscle) have been identified through their effect on vascular function reactivity, tone, and structure [28]. Moreover, women undergo intense hormonal changes during their lifetime exposing the vascular bed to radical changes.

Although plaque rupture is the leading cause of AMI in both sexes, it is responsible for only 55% of cases in women [29]. Several studies demonstrated a higher prevalence of plaque erosion in women presenting with ACS, especially in young premenopausal women [29–31], suggesting a possible protective effect of estrogen [32]. Moreover, atherosclerosis is usually found to be less extensive in women [33, 34]. A study investigating coronary angiograms demonstrated that nearly one-third of women presenting with ACS had no obstructive CAD [33]. In coronary plaque assessment using coronary computed tomography angiography (CTA), women had significantly fewer atherosclerotic plaques; however, as with men, a low-attenuation plaque burden predicted future myocardial infarction [34].

The Women's Ischemia Syndrome Evaluation (WISE) study demonstrated that 50% of women presenting with chest pain with the absence of an obstructive CAD had coronary artery dysfunction [35]. The study also demonstrated that an abnormal response to acetylcholine (ACH) was found to be an independent predictor of adverse cardiovascular events, including hospitalization for worsening angina, AMI, congestive heart failure, stroke, revascularization, other vascular events, and death [36]. It is important to mention that vascular dysfunction can be detected early in several pregnancy-associated conditions such as hypertensive disorder in pregnancy – HDP [37]. Recent studies suggest that endothelial dysfunction is a marker for early atherosclerosis even before structural changes to the vessel have occurred [36, 38–41].

Epicardial coronary arteries in women are smaller than in men, regardless of their body size [28, 41]. These differences are also attributed to sex hormones as demonstrated in several studies of transsexuals where brachial artery size in genetic men taking estrogens is smaller compared with the control group of men [43, 44]. Furthermore, women taking androgens show larger arteries than the control group of women [45]. In addition, in women treated with coronary artery bypass surgery, a higher mortality rate was attributed to the average diameter of the grafted vessel as demonstrated in the CASS registry [46].

CLINICAL PRESENTATION OF ACS IN WOMEN

Women presenting with ACS are usually older than men, and often have a greater burden of cardiovascular risk factors [47]. The "typical" symptoms of myocardial ischemia are well-known. These include precordial chest discomfort, pain, heaviness or fullness, dyspnea, and radiation to the left arm. For years, a misconception prevailed that women with ACS present often with "atypical" symptoms. Past data demonstrated that women were more likely to present with ACS without chest pain [48]. Furthermore, large cohorts showed that 37% of women eventually diagnosed with ACS, presented with atypical chest pain [48–51]. Nonetheless, more contemporary data suggest no differences regarding ACS symptoms between women and men. The VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) assessed sex differences in the presentation and perception of symptoms among young patients (<55 years old) with ACS. The results demonstrated that the majority of women, like men, present with a predominant complaint of chest pain (87.0% vs. 89.5%; $P = 0.19$) [50]. This was also confirmed in another study in 1941 patients (39% women). Chest pain was the most common presenting symptom, reported by 92% of women and 91% of men with suspected ACS.[51] Pain with typical characteristics, the presence of radiation, and additional symptoms were all more common in women with suspected ACS. Also, women are more likely to report >3 associated symptoms of ACS such as shortness of breath, discomfort in another body part, pain radiating to the jaw, vomiting, fatigue, and general weakness [50].

EVALUATION OF WOMEN WITH CHEST PAIN AND SUSPECTED ACS

According to the current chest pain evaluation guidelines, men and women with chest pain symptoms should not be assessed differently [52]. Initial assessment of patients presenting with acute chest pain is based on focused history that includes characteristics and duration of symptoms, as well as associated features and cardiovascular risk factors. The purpose of the assessment is first to identify patients with immediately life-threatening conditions such as STEMI and secondly to risk-stratify patients suspected of ACS into low versus intermediate- or high-risk groups. This is achieved by using clinical decision pathways (CDPs) to decide what is the best diagnostic test (functional tests, such as an exercise test, stress echocardiography, and myocardial perfusion imaging versus anatomical evaluation, such as cardiac computed tomography, angiography, and invasive coronary angiography) [52].

An initial ECG should be performed accompanied by serial ECGs to detect potential ischemic changes in addition to cardiac biomarker measurement. The preferred biomarker to detect or exclude myocardial injury is cardiac troponin I or T (cTn) because of its high sensitivity and specificity for myocardial tissue. Myocardial injury is defined as an increase in blood levels of cTn above the 99th percentile upper reference limit (URL) with no sex differences [52]. The High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients with Suspected ACS) was the first randomized controlled trial to evaluate the introduction of the high-sensitivity cardiac troponin I (hs-cTnI) assay with sex-specific thresholds into clinical practice [53]. Pre-specified secondary analysis of this study evaluated the impact of implementing sex-specific diagnostic thresholds on investigation and treatments for CHD and clinical outcomes in women and men separately. Myocardial injury was defined as high-sensitivity cardiac troponin I concentration >99th centile of 16 ng/l in women and 34 ng/l in men [54]. The primary outcome was recurrent myocardial infarction or cardiovascular death at 1 year. The study demonstrated that the use of a hs-cTnI assay with sex-specific thresholds

identified five times more women with myocardial injury compared with men [54]. This approach is still controversial, however, the fourth universal definition of myocardial infarction article recommends using sex-specific thresholds for the diagnosis of myocardial infarction [55].

DELAY IN PRESENTATION AND TIME TO TREATMENT

Women compared with men tend to ignore or not recognize their CVD risk factors and are more likely to misattribute their pain to a non-cardiac cause [50]. A study investigating women who were admitted to the hospital after an AMI found that most women did not recognize their risk factors as possible contributors to cardiac disease, with hypertension being the least recognized risk factor for cardiac diseases [56]. Moreover, the VIRGO study demonstrated that even when women recognize the signs, they attribute their pain to stress/anxiety, a fact that probably explains the delay of women in seeking medical attention [50]. Also, among patients with AMI, 35% of women as opposed to 23% of men, present to the hospital with a delay of 6 hours or more [50]. Delay in seeking medical help in women has also been observed in other studies, suggesting a median delay in presentation between 2 to 5 hours [57, 58]. An additional delay occurs upon presentation, with numerous studies demonstrating a delay in the care of women presenting with signs of AMI. The VIRGO study demonstrated that 29.5% of women and 22.1% of men sought medical care for similar symptoms; however, 53% of women's symptoms as opposed to 37% in men were attributed to non-cardiac causes (P <0.001) [59]. A study investigating patients diagnosed with STEMI demonstrated a delay between first medical contact and hospital presentation in cases of female patients, which was primarily attributed to the lack of early diagnosis and/or lower priority for ambulance transport to a percutaneous coronary intervention (PCI)- capable hospital. Nevertheless, no significant difference was found in the usage rate of the emergency medical system (EMS) among women and men [60]. Moreover, women suffer from significantly delayed proper reperfusion therapies [61]. The median door-to-balloon time and door-to-needle time was longer for young women presenting with STEMI compared with men, exceeding the recommended time guidelines for PCI [61]. Additionally, women with >50% coronary occlusion documented on cardiac catheterization were less likely to receive reperfusion treatment than men [61].

TREATMENT GAPS IN WOMEN WITH ACS

According to the ACS international guidelines, treatment should not differ between men and women [58, 59]. However, women often receive less intensive therapy and much less secondary prevention treatment than men, thus leading to poorer prognosis and outcomes.

Reperfusion strategies

Several studies examining treatment with thrombolysis in women demonstrated a higher mortality rate than in men [64, 65]. In the GUSTO-1 trial (The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) women treated with thrombolysis had more complications such as shock, heart failure, reinfarction, recurrent ischemia, bleeding, and stroke compared with men [66]. The study also demonstrated that the risk of moderate to severe bleeding was increased 1.43-fold in women [66]. Moreover, female sex was found to be an independent predictor of bleeding after thrombolytic treatment [64].

Primary angioplasty is the main treatment in developed countries for AMI, yet studies show underutilization of PCI and a higher mortality rate in women [67, 68]. A recent meta-analysis of sex differences in presentation, treatment, and outcomes in ACS including 24 hospitals, demonstrated that women were less likely to undergo coronary angiography, regardless of the indication for PCI (STEMI, non-ST-segment elevation myocardial infarction [NSTEMI] and unstable angina) [69]. The study also investigated temporal trends between 2006–2010 and 2012–2016 and found a marked increase in the percentages of patients who underwent coronary angiography and PCI in both sexes across all ACS groups between the latter and the earlier period, but the change was less pronounced in women [69]. Studies investigating sex influences on safety and efficacy of drug-eluting stents (DES) compared with bare metal stents (BMS) demonstrated that DES use was associated with lower rates of clinically driven revascularization and low rates of in-hospital events, including MI, coronary artery bypass surgery (CABG), and death independent of sex [70]. A large meta-analysis of 26 randomized clinical trials (RCTs) investigated the long-term safety and efficacy of new-generation DES in women [71]. The trial confirmed the results of RCTs performed in predominantly male populations and consolidated new-generation DES as the standard of care for women with ACS [71]. However, studies still show underuse of stents in women who undergo PCI regardless of the indication [72, 73].

A systemic review of 23 studies found that women were referred less frequently to CABG, referred later in the course of the disease, and were more likely to undergo urgent surgery [74]. Women in these studies were older than men and more often had diabetes, hypertension, congestive heart failure, and severe noncardiac disease. Surgical technique was also different in women. Arterial grafts, especially internal mammary artery grafts, were less used although it is known that arterial grafting has higher potency and reduces CABG mortality [74]. The Society of Thoracic Surgeons Adult Cardiac Surgery Database studied patients who underwent first-time CABG in the United States (>1 000 000 patients, 25% female) [75]. The study demonstrated that female sex was associated with lower

unadjusted rates of revascularization with an internal mammary artery graft (93.9% vs. 95.9%; *P* <0.001), bilateral internal mammary artery graft (2.9% vs. 5.6%; *P* <0.001), or radial artery graft (3.2% vs. 5.6%; *P* <0.001) [75].

Pharmacological strategies

Post-ACS treatment includes antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and statins. The guidelines recommend that women with ACS be treated with the same pharmacological agents as those used in men for both acute care and secondary prevention of AMI [62, 63].

The NCVD-ACS registry and ACC-NCDR demonstrated that women diagnosed with ACS were less likely to be treated with aspirin (ASA) [69, 76]. In the CCC-ACS project (Improving Care for CVD in China–ACS) which included 82196 patients with ACS (25.6% women), women were less likely to be treated with dual antiplatelet therapy during hospitalization and at discharge compared to men (89% vs. 93.5%; *P* <0.001, 82.2% vs. 90.1%; *P* <0.001 respectively) [77]. The START-ANTIPLATELET investigated whether sex influences the choice of antiplatelet treatment upon admission for ACS and its impact on 1-year clinical outcomes [73]. The study showed that a significantly higher proportion of female patients diagnosed with NSTEMI were treated without dual antiplatelet therapy (DAPT) compared to men. When DAPT was prescribed regardless of the indication, the combination of ASA plus ticagrelor was the preferred one, regardless of patients' sex. Prasugrel prescription was significantly lower in women compared to men, while clopidogrel was more often used for DAPT in women. Nevertheless, the study showed that the $P2Y_{12}$ inhibitor choice did not affect the 1-year clinical outcome [73]. Several studies investigated the optimal duration of DAPT in women. A meta-analysis of 11 473 patients comparing clinical outcomes of short (6-month) with prolonged (12-months) DAPT after DES implantation in women versus men demonstrated that short-term DAPT was associated with similar rates of major adverse cardiac events (MACE), including the composite of cardiac death, AMI, or definite/probable stent thrombosis, but lower rates of bleeding as compared with prolonged DAPT in both men and women [78]. In the GLOBAL LEADERS trial, after one year of follow-up, women were at greater risk of bleeding than men, however, after two years of follow-up, the risk of bleeding was similar in both sexes [79]. A sex-based analysis of the TWILIGHT study demonstrated similar ischemic events between sexes and higher bleeding events, however, after adjustment for baseline characteristics, the incremental bleeding risk associated with female sex was no longer significant [80]. Nonetheless, the female subgroup in these trials was modest in size, yet those studies emphasize the need for careful examination of the patient's profile and not just his/her sex to tailor the right treatment [80].

Regarding beta-blockers and ACE-I, only 64.8% of women were treated with beta-blockers as a secondary prevention [76]. In the NCVD-ACS registry, the Malaysian National CVD Database, women presented with STEMI and NSTEMI were less likely to be treated with ACE-I during hospitalization than men (43.8% vs. 40.5%; *P* = 0.003) [69].

Statin therapy is another mainstay of post-MI pharmacotherapy. The long-term intervention with pravastatin in ischemic disease (LIPID study) demonstrated a reduction in the mortality rate in both sexes [81]. In the Pravastatin or PROVE IT-TIMI 22 trial, which included 21.9% women, intensive therapy in women was associated with a significant 25% relative reduction in the primary composite endpoint compared with a 14% reduction in men [82]. Nevertheless, target cholesterol levels are less often achieved in women, partially due to a lower likelihood of receiving lipid-lowering therapy prescriptions. A study investigating the usage of high-intensity statin therapy following an MI among women and men demonstrated that women were less likely than men to have filled a prescription for high-intensity statin dosages (50% vs. 60%) [83]. Sex differences in the use of high-intensity statins following AMI were present in all subgroups but more pronounced among those without prior statin use or with prior low/moderate intensity statins, the youngest and oldest individuals, and those without prevalent comorbid conditions [83]. The study also examined the sex-specific temporal trends in the intensity of dosages of statin therapy from 2007 to 2015 and found no change by sex in the use of high-intensity statins post-MI between 2007 and 2015 [83]. As for PCSK9 inhibitors, data from the FOURIER trial demonstrated that inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL-C levels in all subgroups with no sex differences [84]. However, only one multicenter registry investigated sex-related differences in PCSK9 inhibitors' efficacy [85]. The study demonstrated that women had substantially higher LDL-C levels and a lower LDL-C reduction compared with men (47.4% vs. 56.9%; *P* = 0.0002) [85].

A study that assessed the level of adherence to the guidelines for secondary prevention of cardiovascular disease in everyday clinical practice showed that even though women were better responders than men, women achieved worse glycemic control than men and worse control of total cholesterol and HDL fraction cholesterol levels [86].

BLEEDING COMPLICATIONS

Bleeding during the course of elective or urgent PCI is one of the factors contributing to higher mortality rates in women. Increased bleeding risk in women is attributed to vascular access and at least in part to inappropriate dosing of thrombotic treatment [87]. Women treated with antithrombotic therapy have a higher risk of bleeding independently of age, weight, baseline blood pressure, renal function, baseline hematocrit, and other potential confounders [88, 89]. The SAFE-PCI study investigated PCI

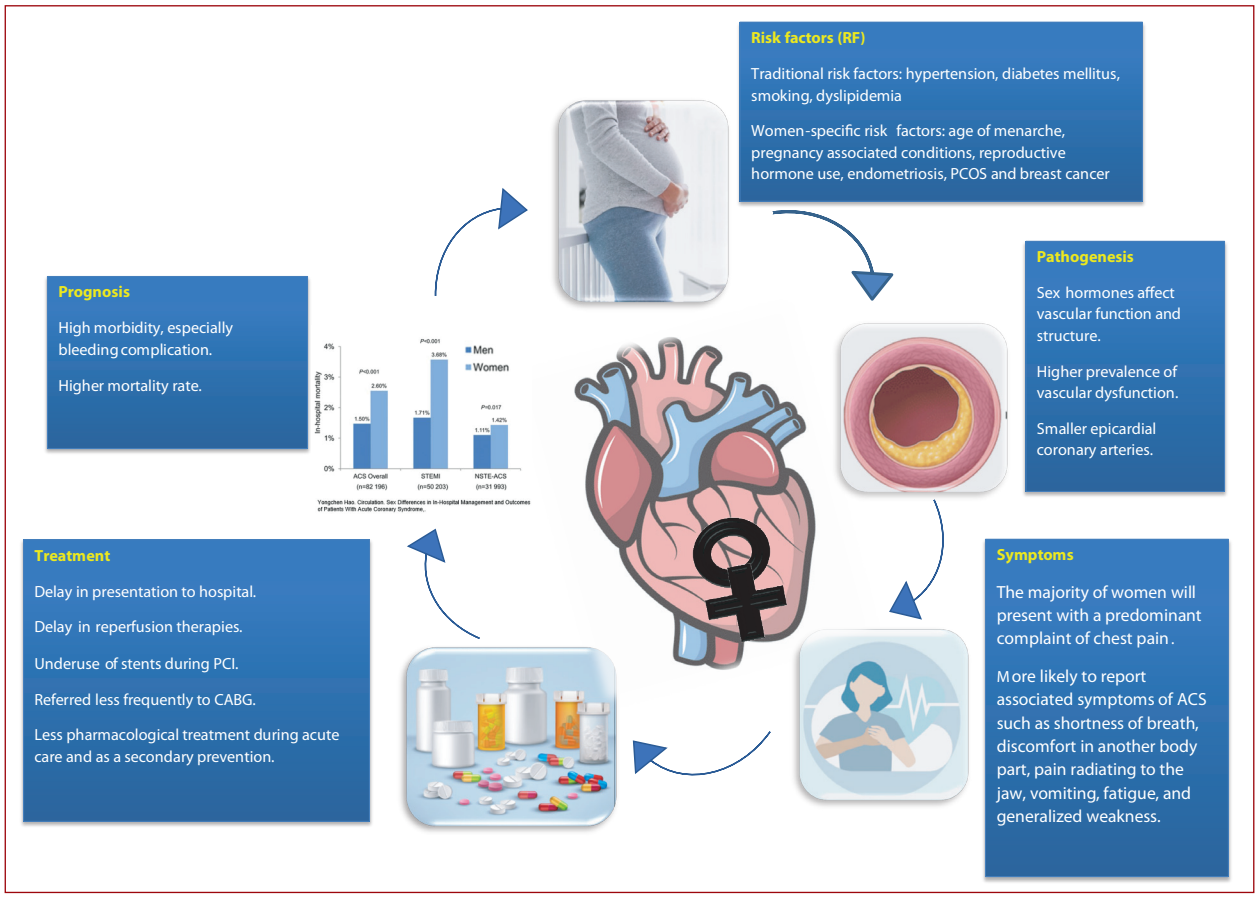

Figure 1. Central illustration

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention; PCOS, polycystic ovary syndrome

access strategies in women undergoing elective or urgent cardiac catheterization and demonstrated reductions in bleeding and vascular complications with the radial access approach [90]. The CathPCI registry also studied the effectiveness of various bleeding avoidance strategies (vascular closure devices, bivalirudin treatment, radial access, and a combined approach) and found that women had significantly higher rates of bleeding than men (12.5% vs. 6.2%; P <0.01) when avoidance strategies were not used [91].

PROGNOSIS

Several factors, including older age, multiple comorbidities, and delay in diagnosis and treatment, contribute to higher mortality rates observed in women diagnosed with ACS. Delays in presentation to the hospital and providing proper care for women are one of the reasons for the higher mortality rate among women [60]. A study investigating sex-related differences in timely access to care among STEMI patients demonstrated higher 30-day mortality in women (10.8% vs. 5.3%) [60].

Studies have also examined variability in mortality stratified by sex after PCI. Results from a large registry identified 13 752 patients (4761 female, 34.6%). Unadjusted post-PCI mortality rates were higher in females versus males; however, multivariable regression analyses failed to identify female sex as an independent predictor of mortality [92]. Similar results were shown in a meta-analysis of observational studies that examined differences in mortality by sex in patients with STEMI treated with primary PCI; in the adjusted analysis, the association between women and a higher risk of all-cause mortality was attenuated [93].

Nevertheless, data from large registries from the United Kingdom and Sweden found that female sex was an independent predictor of all-cause mortality at 30 days and 1 year [94]. A large cohort of 6.5 million PCI discharges across the United States from 2004 to 2014, demonstrated higher in-hospital mortality rate that also persisted over time with women consistently at 20% greater risk compared to men, even after adjustment [95]. Moreover, several studies showed that sex-based differences in survival varied according to age, with younger women, below the age of 55 years old, having a higher mortality rate than men [96, 97]. Long-term follow-up data from a large Polish acute myocardial infarction demonstrated lower mortality risk at 5-year follow-up in women compared with men. The study also shows a decline in relative survival with increasing age in both sexes with a stronger impact in women compared with men. However, in-hospital survival was lower in women, especially in women below the age of 55 [98].

The operative mortality rate is also higher in women. A study that analyzed data from 121 hospitals with a total of 10 708 women and 29 669 men who underwent CABG between 2003 and 2004 found a higher mortality rate among women (4.6% vs. 2.5%; *P* <000.1), with the highest likelihood of death in younger women, under the age of 65 years (odds ratio [OR], 2.13; *P* <0.001) [99]. The specific reasons for the higher mortality rate in women undergoing CABG are not well elucidated, yet it is probably related to female risk factors, delay in referral to CABG treatment, and the underuse of internal mammary grafting [99].

In summary, cardiovascular disease and CAD are among the leading causes of morbidity and mortality in women. Thus, it is of utmost importance to understand the major gaps in diagnosis treatments and outcomes in women with ACS. Even in the contemporary era, issues such as women-specific risk factors, hormonal influences, and different pathophysiological mechanisms are under-researched and under-recognized. There is an unmet need for improving our understanding, diagnosis, and treatment of women with ischemic heart disease, specifically with ACS. Raising public awareness, educating medical teams, involving more women in research trials, and women-specific guidelines can narrow existing disparities.

Article information

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