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MANAGEMENT OF ACUTE CORONARY SYNDROMES (H JNEID, SECTION EDITOR)

Diagnostic and Management Dilemmas in Women Presenting with Acute Coronary Syndromes

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Abstract

Purpose of Review To summarize gender- and sex-specific differences in the presentation, diagnosis, management, and pathophysiology of women presenting with acute coronary syndrome (ACS).

Recent Findings Sex differences exist in many aspects of ACS that impact the identification, treatment, and outcomes in women. There are delays in the initiation of care, under recognized diagnostic differences based on sex, and inconsistencies in the management of ACS in women compared with men, that ultimately impact outcomes. Additionally, women with ACS are more likely than men to present with non-obstructive coronary artery disease (CAD), which appears to be due to diverse underlying pathophysiology.

Summary Women with ACS face diagnostic and treatment dilemmas from time of symptom onset to hospital discharge. Under-recognition, under-diagnosis, and under-treatment ultimately result in poorer outcomes in women. Underlying pathophysiologic differences in women require additional testing to elucidate underlying etiologies.

Keywords Cardiovascular disease · Myocardial infarction · Acute coronary syndrome · Women · Sex differences · Myocardial infarction with non-obstructive coronaries (MINOCA)

Introduction

Cardiovascular disease (CVD) remains the leading cause of death for women in the USA, with over 418,000 deaths annually and affecting 44.7% of women in their lifetime [1]. Despite efforts to increase overall awareness and understand sex differences in CVD, there are still significant gaps in our knowledge related to differences in the presentation, pathophysiology, and treatment based on sex. Women continue to have poorer outcomes after presenting with ACS, particularly young women [2, 3]. In those presenting with ACS, it has been demonstrated that sex differences exist in the initial assessment, treatment, and interventions [4], as well as differences in long-term medical management and secondary prevention strategies [5]. In addition, the pathophysiology seen in women with ACS often differs from what is seen in men. The prevalence of myocardial infarction with non-obstructive coronary arteries (MINOCA) in women presenting with acute myocardial infarction (AMI) is 10.5% compared to 3.4% in men ($p < 0.0001$) [6]. The difference is even more pronounced in young patients where women are five times more likely than men to have MINOCA [7••]. This in itself poses distinct diagnostic and management considerations that affect overall morbidity and mortality [7••]. Despite these obstacles, the identification of these sex-related differences in care highlights areas of opportunity for systematic improvement.

This article is part of the Topical Collection on *Management of Acute Coronary Syndromes*

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Sex Differences in Presentation

Women with ACS remain under-recognized, resulting in delays in initiating care. The Victorian Cardiac Outcomes Registry which included 13,451 patients with ST segment

elevation myocardial infarction (STEMI) found that women waited on average 30 min longer to seek medical attention after symptom onset compared to men [2••]. A delay in seeking care was also seen in the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study, a prospective observational study of 2985 (2009 women) with AMI under the age of 55 [7••]. Women and men were equally inaccurate at self-identifying their symptoms as heart-related (54.7% vs. 52.3%), however, women were more likely to seek medical attention prior to their ACS event (29.5% vs. 22.1% $p < 0.001$) and be falsely reassured by their outpatient provider that indeed their symptoms were not cardiac in nature before subsequent AMI diagnosis (53.4% vs. 36.4% $p < 0.001$) [8].

Although older data suggested sex differences in symptoms of ACS, recent data of both younger and older women have shown that chest pain symptoms occur equally in men and women with AMI, with approximately 90% reporting chest pain [7–9]. Women do tend to report more additional symptoms with chest pain, which may be the reason that chest pain is under appreciated in clinical settings.

Despite a longer duration of symptoms before presentation, women do not receive expedited care upon arrival to the hospital, and instead face ongoing delays in assessment. The Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond—Premature Acute Coronary Syndrome (GENESIS-PRAXY) multicenter prospective study included 1123 patients under the age of 55 (32% women) admitted to the hospital for ACS, and demonstrated that women had a significant delay in initial electrocardiogram (ECG) assessment, compared with men (21 vs. 15 min, $p < 0.001$) [4].

Sex Differences on ECG

There are recognized sex differences in the diagnosis of ACS based on ECG interpretation. Women have higher rates of unstable angina and non-ST segment myocardial infarction (NSTEMI) than men [10]. Several large retrospective studies have found that this is especially true in younger women [4, 11–13]. In a study of 632,930 US patients 60 years of age or younger, women were less likely to present with STEMI compared with men (38.44 vs. 49.4% OR = 0.74, 95% CI 0.73–0.75) (12). The GENESIS-PRAXY study demonstrated that women were more likely to be diagnosed with NSTEMI compared to men (38% vs. 30%, $p < 0.003$) than STEMI (48% vs. 63%, $p < 0.001$) [4]. A retrospective study of 14,931 patients (4710 women) demonstrated that women over the age of 45 were more likely to present with NSTEMI compared to men of the same age (32.5% vs. 29.2, $p < 0.001$) [11]. Another large retrospective cohort study in Australia analyzed 28,985 adults with ACS from 2007 to 2009 and again women were more likely to have NSTEMI than men (86% vs. 80%, $p < 0.001$), but in contrast to other studies, the majority of NSTEMI diagnoses were in women > 75 years old [13].

The ability to recognize ACS in women requires an understanding of how sex-specific differences apply to our current diagnostic methodology. A prospective cohort study of 3501 individuals less than 55 years old hospitalized for AMI, including 2349 women (67%), found that women were less likely than men to have either ST elevation or left bundle branch block (47.9% vs. 59.5%, $p < 0.01$) or Q-waves on ECG (16.0% vs. 21.8%, $p < 0.01$) [14]. A retrospective cohort study in Finland between 1998 and 2017 looked at autopsy data of 1101 patients who experienced sudden cardiac death (SCD) [15]. Despite an overall higher proportion of SCD in women (69% vs. 57%, $p = 0.009$), only 20.2% of women were identified as having evidence of ischemia on ECG compared to 79.8% of men ($p = 0.005$). Women were less likely to have any identifiable ECG abnormality (73.1% vs. 85.2%, $p < 0.001$), including pathological Q-waves (9.4% vs. 19.3%, $p = 0.003$). Interestingly, in both the ischemic and non-ischemic groups, left ventricular hypertrophy was seen significantly more often in women than men (22.8% vs. 10.2%, $p < 0.001$ and 18.5% vs. 10.2%, $p = 0.025$ respectively).

Juvenile T-wave inversions(TWI) in leads V_1 to V_3 are commonly seen in adolescence and less frequently persist into adulthood [16]. Persistent juvenile T waves are usually asymmetric, seen in V_1–V_3, and not associated with ST segment changes [17]. Identifying juvenile TWI has important clinical implications in young women especially as it is considered a benign finding. Prevalence of juvenile TWI decreases with age and male sex. In children ages 5–11, an estimated 65% of females and 45% of males have TWI detected on EKG [18]. In contrast, prevalence in young women 19–45 years old is estimated at 13% compared to 0% in men. A large cohort study of individuals ages 16–35 years old (32% women) found anterior TWI more common in women than men (4.3% vs. 1.4%, $p < 0.0001$) [19]. Anterior TWI rarely extended beyond V_2 and no adverse events were reported at 2 years follow-up. In a retrospective study of 10,899 patients ages 30–59 (48% women), it was infrequent that women were more likely to have TWI in the right precordial leads than their male counterparts (0.9% vs. 0.1%, $p < 0.001$) [20]. These large differences in estimated prevalence are likely a reflection of the age groups included in the studies as TWI typically become upright post-puberty [18]. Identifying persistent juvenile TWI has important clinical implications in young women especially as it is generally considered a normal variant in healthy adults.

Sex-specific STEMI criteria for women include new ST elevation at J-points in two contiguous leads ≥ 1 mm, except for leads V2–V3, which requires ≥ 1.5 mm [21]. In comparison, V2–V3 ST elevation requirements for men ≥ 40 years is ≥ 2.0 mm and ≥ 2.5 mm for < 40 years old. Sex-specific cutoffs in V2–V3 are required due to overall lower J-point elevations in healthy women.

Sex Differences in Troponin

Introduction of the high sensitivity cardiac troponin (hs-cTn) has led to more rapid, early detection of AMI compared to the conventional cardiac troponin (cTn), allowing for quicker rule-out with a negative predictive value greater than 95% [22–24]. Assay thresholds for the upper limit of normal have been defined as the 99th percentile value in a healthy reference population. Studies validating hs-cTn assays found that these cutoffs were noticeably different between sexes. A multicenter study of 616 volunteers in Germany where half were women found the 99th percentile for hs-cTn was 13.5 ng/L overall, but differed between men and women (14.5 ng/L vs. 10.0 ng/L, $p < 0.01$) [25]. Another study of 348 subjects, of which the majority were women, reported the 99th percentile values as 16.58 ng/L and 9.36 ng/L for men and women, respectively [26]. It is important to note that there is significant variability in each hs-cTn assay characteristics, detection limits, and 99th percentile values depending on the manufacturer [27]. A large systematic review of 28 studies comparing two different hs-cTn assays between 2009 and 2017 found that 90% and 61% of studies for each assay reported lower female-specific hs-cTn cutoffs than the package insert directions provided by the manufacturer [28]. The decision to use overall rather than sex-specific cutoffs of hs-cTn will certainly contribute to the underdiagnosis of AMI in women. Therefore, taking into account the type of assay being used, individual validation at each medical center, and recognizing sex-specific thresholds of hs-cTn is imperative to accurately interpreting values.

The underutilization of sex-specific cutoffs can also lead to an underdiagnosis of AMI. A multicenter study of 48,282 patients (of which 47% were women) found that implementing sex-specific hs-cTn reclassified 1771 patients with AMI who were missed on cTn assays, of which 83% were women compared to only 17% of men [29]. A prospective cohort study of 1126 patients with suspected ACS, of which 504 were women, found that applying sex-specific hs-cTn thresholds drastically reclassified women with type I MI and to a lesser extent type II MI [30]. Using the standard hs-cTn cutoff in women increased type I MI diagnosis from 11 to 16% compared to cTn, whereas applying the sex-specific threshold hs-cTn increased detection from 11 to 22% ($p < 0.001$). In contrast, using sex-specific cutoffs in men only increased detection by 2%. Another multi-center study found that applying the overall cutoff value leads to a higher detection of NSTEMI patients specifically (45 vs. 20, $p = 0.0004$) [25]. Determination of the 99th percentile for the general population for these tests has not been universally agreed upon [30]. To achieve this would require increasing the number of women included in these studies as well as diversifying those included.

Sex Differences in Treatment

There are persistent sex differences in the management of ACS, contributing to poorer outcomes in women. From the VIRGO study, younger women with AMI experienced longer door-to-needle times (exceeding 30 min, 55% women vs. 41% men) and longer door-to-balloon (DTB) times (exceeding the 90-min window, 41% women vs. 19% men) [14]. In the Victorian Outcome Registry of 13,451 patients, mean DTB time for women was significantly longer by 7 min (88.4 min vs. 81.3 min, $p = 0.01$) [2••] which is substantial considering each 10-min reduction in DTB time reduces in-hospital mortality by 12.7% [31]. Procedure modality differs as well. Despite robust evidence that transradial artery access is superior to transfemoral access with regard to stroke risk, vascular complications, and death, women with NSTEMI and STEMI are less likely to undergo revascularization using a radial approach (41.0% vs. 50.2%, $p < 0.001$; 44.4% vs. 53.4%, $p < 0.001$) [1, 2, 32].

Despite increasing awareness of sex-specific differences in care of these patients, women continue to receive less revascularization and reperfusion therapies compared to men. A large retrospective study from 2010 to 2016 looked at 1,260,200 hospitalizations in the US for STEMI (32% women) and subsequent therapies received stratified by sex [33]. After multivariable adjustment, women were less likely to receive fibrinolytic therapy (OR = 0.924, 95% CI 0.860–0.994, $p = 0.033$), PCI (OR = 0.739, 95% CI 0.723–0.756, $p < 0.001$), or CABG (OR = 0.540, 95% CI 0.540–0.590, $p < 0.001$). When stratified by age, the sex disparities in treatment remained significant for PCI and CABG as well as fibrinolytic therapy for the age groups 70–79 years and ≥ 80 years old ($p < 0.001$ for each age group). A national cohort study involving 691,290 patients in England and Wales with AMI from 2003 to 2013 (34.5% women), women with NSTEMI were less likely to undergo an early invasive strategy with left heart catheterization (LHC) within 72 h (24.2% vs. 36.7%, $p < 0.001$), yet still received antithrombotic therapy less than men (24.2% vs. 24.6%, $p = 0.028$) [34].

Guideline-directed medical therapy is also underutilized in women. Younger women from VIRGO were less likely to receive statins and angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) at time of discharge ($p = 0.01$), despite no difference in guideline-directed medical therapies at time of diagnosis of AMI [14]. In a study from China including 82,186 ACS patients from 2014 to 2018, women were less likely to receive dual-antiplatelet therapy (DAPT), statins, ACE-I, or ARBs at discharge compared to men [35]. In the England and Wales cohort, these same discrepancies were seen, but extended to decreased beta-blocker prescriptions and cardiac rehabilitation referrals for women at discharge (all $p < 0.001$) [34].

Sex Differences in Pathophysiology

Some of the dichotomy in clinical presentation can be explained by underlying pathological sex-specific differences. Plaque rupture is responsible for the majority of STEMI cases, while NSTEMIs are often associated with plaque erosion, which is characterized by a superficial thrombus attached to underlying intact plaque or a luminal irregularity in the absence of thrombus [36–38]. A multi-center retrospective study looking at 1241 patients with ACS found plaque erosion more prevalent in NSTEMI than STEMI cases (47.9% vs. 29.8%, $p < 0.0002$) [37]. The idea that there are sex differences in the underlying pathophysiology of ACS gained recognition over 25 years ago. A study in 1996 comparing the coronary arteries of patients with recent SCD found that an overwhelming majority of women had plaque erosion rather than plaque rupture [39]. Since then, numerous studies have discovered a higher preponderance of plaque erosion in women that is even more pronounced in younger age groups [36, 40]. This is likely one of the underlying explanations for a disproportionate number of NSTEMI cases in women.

Diagnostic and treatment dilemmas for women presenting with AMI is further complicated by the higher incidence of MINOCA. MINOCA is defined as clinical myocardial infarction (MI) with coronary stenosis < 50%, in the absence of another inciting clinical condition [41]. VIRGO demonstrated that 11% of young AMI patients who underwent angiography had non-obstructive coronary arteries, with a predominance in women compared with men (14.9% vs. 3.5%, OR 4.84, CI 3.29–7.13) [7]. Importantly, 1-month and 12-month mortalities were similar in MINOCA compared to AMI patients with obstructive lesions. Of the 299 MINOCA patients in VIRGO, 224 (75%) had unidentified etiology for MI. It has previously been emphasized that MINOCA is a working diagnosis, with prognosis and treatment reliant on the underlying cause [41, 42]. These causes can be atherosclerotic- or non-atherosclerotic-related, with extra-cardiac causes such as pulmonary embolism and stroke excluded. The American Heart Association scientific statement on MINOCA considers Takotsubo cardiomyopathy and myocarditis as separate entities, not as a form of MI, and these patients were excluded in the VIRGO study [7, 41, 42]. Coronary-related causes include spontaneous coronary artery dissection (SCAD), plaque disruption, coronary spasm, coronary microvascular disorders, spontaneous coronary thrombosis secondary to thrombophilia, and coronary emboli. As each of these etiologies requires different treatment modalities, further diagnostic studies should be pursued based on patient presentation and clinical suspicion [5, 42, 43] (Table 1).

Sex Differences in Outcomes

Culmination of diagnostic issues and treatment differences portends sex-related differences in morbidity and mortality. Women who experience STEMI experience higher in-hospital events, heart failure, cardiogenic shock, stroke, and cardiac arrest ($p < 0.001$) [44]. Overall in-hospital mortality for STEMI and NSTEMI is higher in females, and of those that survive their first MI, 47% of women compared to 36% of men will die within the next 5 years [1]. Recurrent MI, heart failure, and stroke occur more frequently in women during this same time period [1]. In a study by Liu et al., in-hospital mortality rates were higher for women increasing across age groups ranging from 3.9% in the youngest group (19–49 years old) to 20.5% in the oldest (> 80 years old) [33], but after multivariant adjustment, the increased mortality in women compared with men was only significant in those aged 19–49 years (OR = 1.259, 95% CI 1.083–1.464, $p = 0.003$).

In order to address these discrepancies in mortality, potential sex-specific factors must be taken into account such as the difference in the impact and management of traditional risk factors, sex-specific risk factors, and the impact of hormonal replacement therapy (HRT). The Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II) examined the impact of HRT on postmenopausal women with coronary disease and found a pattern of early increased risk of coronary events. The greatest risk with HRT use was in the first year of starting HRT (1.52, 95% CI 1.01–2.29) compared to the subsequent combined 7 years (0.92; 95% CI 0.77–1.09; interaction $p = 0.03$) [45]. As such, the use of HRT in women with established coronary disease is not recommended.

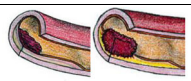
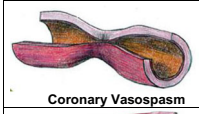
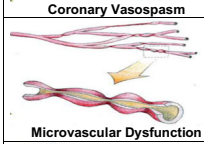
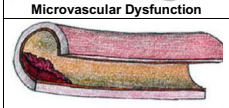
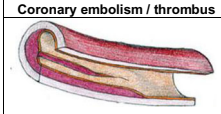
Case Examples

The opportunity for morbidity and mortality improvement in women with ACS relies on recognition of sex-related differences in presentation, diagnosis, and treatment, as well as timeliness of the aforementioned factors. Improvement in ACS management among women should involve a broad differential to include not only obstructive CAD but also the possibility of MINOCA and other non-ischemic conditions that can mimic MINOCA, as illustrated in the following cases.

Case #1: Coronary Vasospasm (Prinzmetal's Angina)

A 60-year-old female with past medical history of hypertension, hyperlipidemia, and migraines was brought in by ambulance for sudden onset chest pain. ECG prior to arrival showed alternating periods of both significant ST elevations and ST depressions in the inferior leads (Fig. 1A, B). She was taken emergently for LHC. Her coronary angiogram was significant for 90% proximal to mid-left circumflex (LCx) artery stenosis

Table 1 Clinical presentations with a working diagnosis of MINOCA

	Underlying Mechanism / Clinical Disorder	Diagnostic Investigations	Targeted / Empirical Therapies
Non-coronary etiologies mimicking MINOCA	Supply-demand mismatch	History, identification of potential stressors	Treatment of underlying condition
	Takotsubo Cardiomyopathy	Left Ventricular Angiogram, contrast MRI	GDMT for HF, ACE-I, beta blocker, mechanical circulatory support as needed
	Cardiomyopathies	Contrast CMRI	GDMT for HF, treatment of underlying etiology
	Myocarditis	Contrast CMRI	GDMT for HF / myocarditis
Coronary Etiologies of MINOCA	 Plaque erosion / rupture	Angiogram review, consider IVUS/OCT	Aspirin, high intensity statin, beta blocker, ACE-I, consider P2Y12 inhibitor
	 Coronary Vasospasm	Resolution with vasodilators, provocation testing, history of migraine medications or cocaine use	CCB, nitrates, cilostazol, consider statins
	 Microvascular Dysfunction	Invasive or noninvasive (PET) coronary blood flow and coronary flow reserve, cMRI	Lifestyle modification especially exercise, consider statin, ACE-I, beta blockers, L-arginine supplementation
	 Coronary embolism / thrombus	Angiogram review, consider IVUS/OCT, thrombophilia screen / workup	Consider anticoagulation, treatment of underlying thrombotic condition
	 SCAD	Angiogram review, consider IVUS/OCT	Aspirin, beta-blocker, consider P2Y12 inhibitor

Clinical presentations and management for myocardial infarction with non-obstructive coronary arteries.

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *cMRI* cardiac magnetic resonance imaging, *IVUS* intravascular ultrasound, *MINOCA* myocardial infarction in the absence of obstructive coronary artery disease, *OCT* optical coherence tomography, *PET* Positron Emission Tomography, *SCAD*, spontaneous coronary artery dissection

Adapted/Modified from Tamis-Holland et al. Circulation. 2019;139(18):e891-e908 [35]

and total occlusion of the proximal second diagonal artery. She received percutaneous coronary intervention (PCI) to both arteries with drug-eluting stents, as well as aspirin and ticagrelor loading doses. The right coronary artery (RCA) was also noted to have severe mid and distal stenosis, however, staged PCI was planned due to high-contrast administration. The patient was discharged to the coronary care unit, but upon arrival, she reported left arm pain with simultaneous ST elevations on telemetry, confirmed on ECG (Fig. 2). An emergent repeat LHC demonstrated vasospasm in the proximal LCx and proximal left anterior descending (LAD) arteries (Fig. 3) with widely patent mid-LCx and diagonal artery stents. Intracoronary nitroglycerin 400 mcg was administered, resulting in normalization of the vasospasm (Fig. 3B). Angiography of the RCA was then performed, and in contrast to the initial LHC that demonstrated RCA stenosis (Fig. 4), stenosis was no longer visualized (Fig. 4B). She remained chest pain–free and was discharged on a beta blocker, high-intensity statin, DAPT, and a long-acting nitrate.

Coronary vasospasm, also known as Prinzmetal's angina, is defined as transient vasospasm of an epicardial artery causing chest pain with ST elevations on ECG. The myocardial ischemia can result in AMI, ventricular arrhythmias, and SCD. Vasospasm can occur in both the presence and absence of CAD.

Prevalence Vasospasm prevalence varies geographically; from 4% in the USA, 12% in France [46], and 30% in Japan, and also dependent on the use of provocative testing with ergonovine [47, 48].

Impact on Women Coronary vasospasm occurs more frequently in women. Women more commonly present at a younger age compared to men who tend to present later in life [49].

Risk Factors Smoking is the strongest risk factor seen in vasospasm, but physiological triggers also include exercise, stress, hyperventilation, and cold temperatures [50, 51]. There is also an association of coronary vasospasm with methamphetamine and cocaine use [52, 53].

Diagnosis Diagnostic criteria include nitrate-responsive angina during a spontaneous episode and either transient ischemic

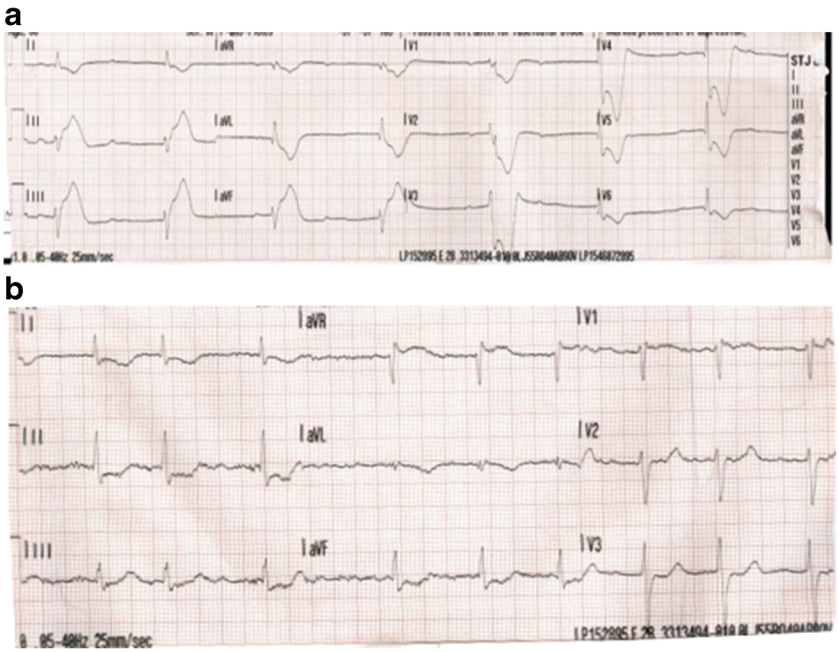


Fig. 1 Telemetry strips recorded during ambulance transport showing ST elevation in the inferior leads (**A**), and 45 min later ST depression in the same leads (**B**)

ECG changes or coronary artery spasm on provocative testing [54]. The first diagnostic step typically involves assessment for significant obstructive CAD. The gold standard for provocative vasospasm testing is with either intracoronary acetylcholine or ergonovine. The test is considered positive when all three components are present during provocation: chest pain, ischemic ECG changes, and > 90% vasoconstriction.

Management Oral calcium channel blockers (CCBs) are the cornerstones of treatment [55]. Long-acting nitrates can also be added in conjunction with CCBs if symptoms do not improve. Current recommendations also include emphasis of tobacco cessation and atherosclerotic cardiovascular disease (ASCVD) risk assessment and treatment. A rare but often life-threatening complication of coronary vasospasm is SCD from fatal ventricular arrhythmias. For these patients, ICD implantation should be considered.

Outcomes Coronary vasospasm was thought to be benign, but the prognosis varies greatly depending on vasospasm patterns. Those with positive provocation tests for vasospasm compared to those without negative tests had a higher all-cause mortality (32% vs. 5%, $p = 0.002$) and cardiac mortality (18.9% vs. 0%, $p = 0.005$) [56]. Higher mortality rates are reported with multivessel involvement and presence of CAD. AMI and fatal arrhythmias occur in 6.5% and 7.5% of cases, respectively [57, 58]. Coronary vasospasm recurrence occurs in 13% of patients despite medical management, and those with refractory vasospasm have an increased risk of SCD [59]. These patients have a relatively poor prognosis

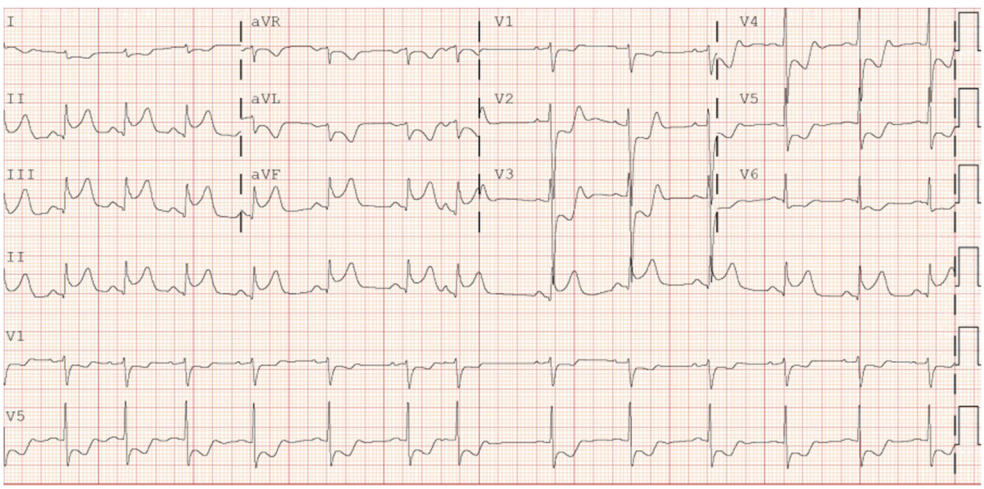


Fig. 2 Repeat ECG after PCI to LCx artery and second diagonal artery showing new ST elevations in inferior leads

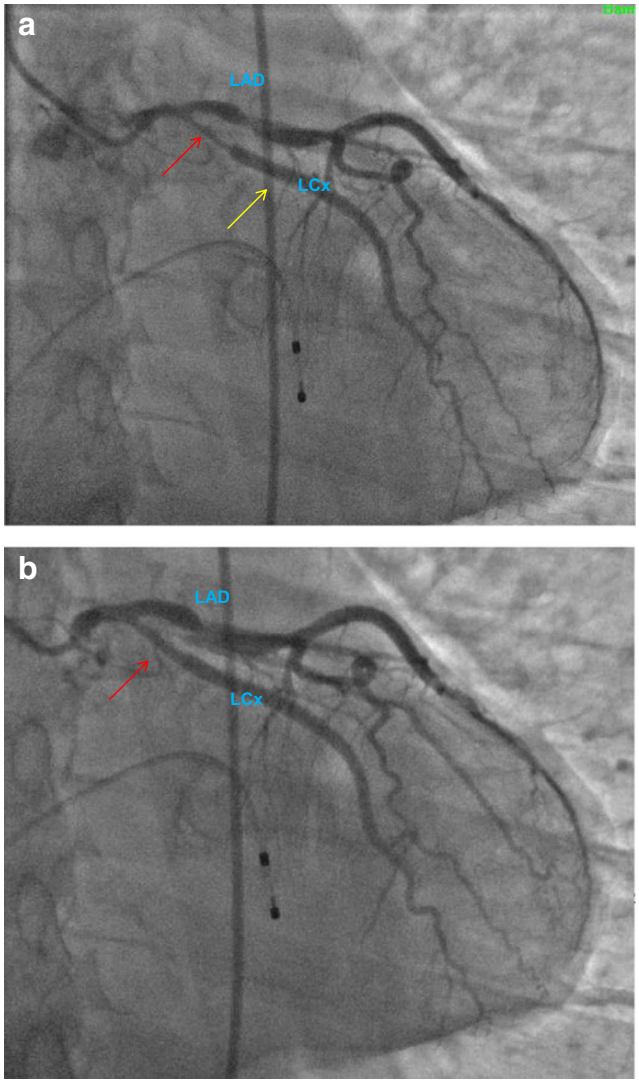


Fig. 3 **A**. Coronary angiogram demonstrating LCx coronary spasm (red arrow) proximal to the recently placed stent (yellow arrow). **B**. LCx coronary artery after administration of intracoronary nitroglycerin (red arrow)

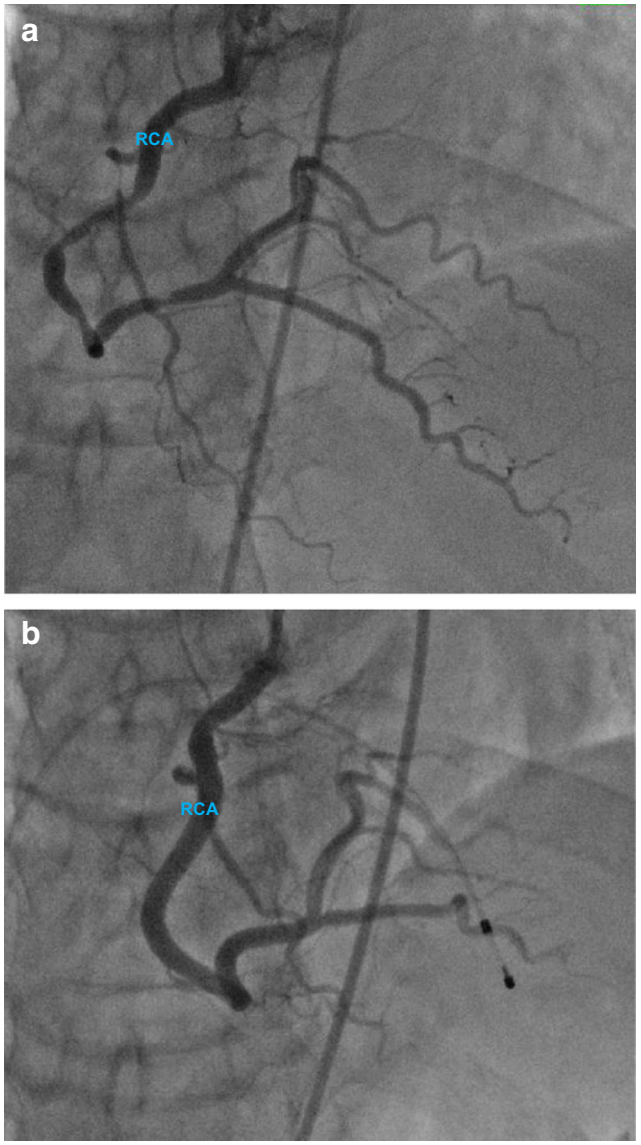


Fig. 4 **A**. RCA on initial coronary angiogram with noted significant mid and distal stenosis. **B**. Repeat angiogram of RCA after administration of nitroglycerin 400 mcg to left coronary system

compared to other vasospasm patients, with a 10-year mortality rate of 18.4% vs 2.9%, $p < 0.001$ [60]. It should be noted that much of the current literature lacks sex-specific comparisons.

Case #2: Spontaneous Coronary Artery Dissection (SCAD)

A 38-year-old female with a history of hypertension and tobacco use presented to the emergency room with sudden onset of sharp, central chest pain, 10 out of 10 in severity, associated with shortness of breath and diaphoresis. Her vital signs and physical exam showed an increased respiratory rate and an uncomfortable-appearing woman. Her ECG was significant for ST elevations in leads V2–V6, and hs-cTn rose from 221 to 3855 ng/L over 3 h. She was started on a heparin drip and taken emergently to the catheterization laboratory, revealing a Type 2 SCAD in the mid to distal LAD (Fig. 5). No intervention was performed and she was treated with DAPT, atorvastatin, and metoprolol. She was discharged in 24 h, chest pain–free.

SCAD is defined as an epicardial coronary artery dissection that is the result of an intramural hematoma or internal disruption rather than atherosclerotic plaque rupture or thrombus [61, 62]. The most common presenting symptom is chest pain with STEMI, although ventricular arrhythmias and cardiogenic shock can also be seen on presentation [63–65].

Prevalence The true prevalence remains uncertain as SCAD is often misdiagnosed and treated as CAD [62, 66]. Studies show that SCAD may be a cause of up to 1 to 4% of ACS cases overall [63].

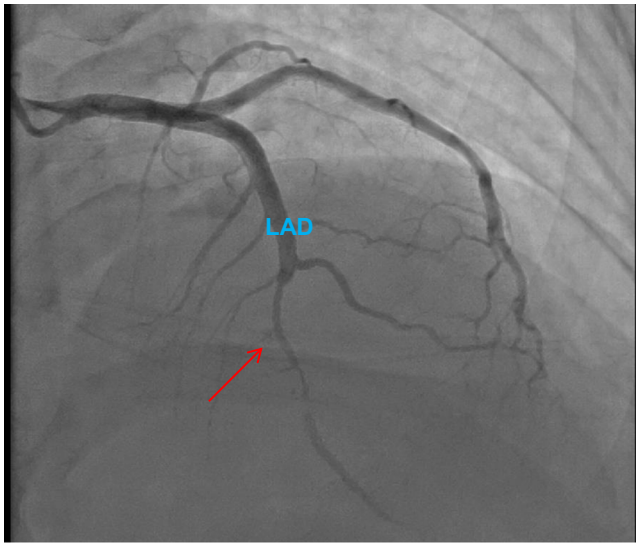


Fig. 5 Type 2 SCAD involving the mid to distal LAD artery (red arrow)

Impact on Women SCAD occurs predominantly in women and may be the cause of AMI in up to 35% of women under the age of 50. It is also the most common cause of pregnancy-associated MI, accounting for 43% of cases [63, 65]. Men can also have SCAD, although less frequently (accounting for 10–15% of all cases) and are more often atherosclerotic in origin [63, 65].

Risk Factors Predisposing factors for SCAD include female sex, fibromuscular dysplasia (FMD), postpartum status, multiparity (≥4 births), connective tissue disorders, systemic inflammatory conditions, and hormonal therapy [66, 67]. Extreme exertion preceded SCAD in over half of men but was rare in women [61, 63, 65]. 40% of women reported preceding emotional stress [63, 65, 68]. Postpartum status was reported in 18% of women [63–65].

Diagnosis The diagnosis of SCAD is made by coronary angiography and is classified by three types. Type 1 shows contrast dye staining of the arterial wall with a radiolucent lumen. Type 2 demonstrates a long, smooth diffuse stenosis. Type 3 shows focal or tubular stenosis resembling atherosclerosis that necessitates optical coherence tomography or intravascular ultrasound to differentiate the cause [61, 64, 68]. In both men and women, SCAD has been shown to favor the LAD in 50% of cases [64, 68].

Management In most SCAD patients, treatment is conservative in the absence of ongoing ischemia or hemodynamic compromise. Revascularization with PCI or coronary artery bypass grafting is challenging due to vessel wall fragility and is associated with higher failure rates and complications, including propagation of intramural hematoma [64, 65, 68]. There are no randomized controlled trials of optimal medical management in SCAD, but current medical recommendations include lifelong aspirin, beta-blocker, clopidogrel for 1 year, and initiation of a statin in those with hyperlipidemia [69].

Outcomes Prognosis is better in those managed conservatively, however, several patient series have shown repeat coronary dissection rates of 10–17% with long-term follow-up [64, 65, 68]. Coronary tortuosity and patients with FMD have a poor prognosis [61, 67].

Case #3: Takotsubo Cardiomyopathy

A 58-year old female with a past medical history of breast cancer presented to the emergency room with substernal chest pressure and shortness of breath. Her vital signs and physical exam were normal. ECG showed sinus tachycardia with no acute ischemic changes. Initial hs-cTn was 389 ng/L, with brain natriuretic peptide (BNP) elevated at 1211 ng/L. Subsequent hs-cTn increased to 451 ng/L (1 h) and 500 ng/L (2 h). She was treated with aspirin, heparin drip, metoprolol, and nitrates. Echocardiogram demonstrated an ejection fraction of 35% with apical hypokinesis and ballooning. Angiography revealed normal coronary arteries; and left ventriculogram confirmed apical ballooning (Fig. 6). A diagnosis of Takotsubo cardiomyopathy was made. Lisinopril was started and she was discharged home 2 days later. At 6-month follow-up, BNP levels had normalized and repeat echocardiogram revealed normal left ventricular systolic function.

Takotsubo cardiomyopathy is also known as stress cardiomyopathy, broken heart syndrome, and apical ballooning syndrome [70, 71]. The typical presentation includes chest pain in the setting of intense emotional or physical stress, presenting as MINOCA [21, 72]. The pathogenesis most widely accepted for Takotsubo cardiomyopathy is a direct and indirect catecholamine surge [73, 74], leading to myocardial dysfunction, however, endothelial dysfunction [75, 76], epicardial

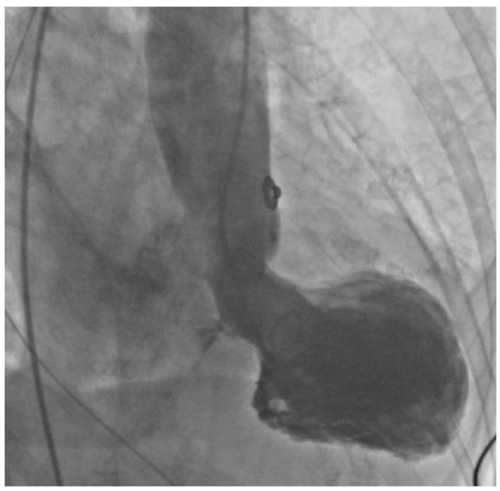


Fig. 6 Left ventriculogram showing apical ballooning

vasospasm [77–79], and both age- and estrogen-related coronary vasomotor abnormalities [80–82] may contribute to the disease process. The Fourth Universal Definition of MI does not consider Takotsubo cardiomyopathy an AMI and is recognized as a separate syndrome [21].

Prevalence Takotsubo cardiomyopathy accounts for 2% of those presenting with presumed ACS [83, 84], although the prevalence is higher in women (5.9–7.5%) [85, 86].

Impact on Women Takotsubo cardiomyopathy primarily affects post-menopausal women (89.9%) [87].

Risk Factors Female sex and intense physical or emotional stress can be identified in some but not all cases [72, 87, 88].

Diagnosis Troponin, creatinine kinase, and BNP levels are all elevated in Takotsubo cardiomyopathy. Notably, BNP levels are higher, peak around 48 h, and remain elevated for 3 months, which differs from ACS [72, 73, 89, 90] and may be due to myocyte stretching. Transient wall motion abnormalities not explained by one vascular territory seen on ventriculography, echocardiography, or cMRI provide the diagnosis, after coronary angiography reveals no obstructive lesions [83, 91, 92].

Management To date, there are no randomized control trials on the treatment of Takotsubo cardiomyopathy. Beta blockers appear to provide no benefit for the index event or prevention of subsequent episodes [87, 93, 94]. There is some observational benefit using ACE-I with improved 1-year survival [95]. Due to paucity of data and without randomized control trials, treatment efficacy and duration cannot be determined. Currently, treatment for the syndrome remains entirely empirical [72].

Outcomes Initially thought to be a reversible benign disease process, acute morbidity and mortality is ~ 4–5% [95], which is comparable to STEMI. Major cardiac and cerebrovascular event rates were reported to be 10% in the InterTAK Registry [96]. The cumulative risk of recurrence of Takotsubo cardiomyopathy is 6% in 6 years [97].

Conclusion

Women presenting with ACS are at higher risk of in-hospital mortality despite lower rates of STEMI. Women more frequently have non-obstructive coronary arteries in the setting of ACS, however, the lack of obstructive lesions does not convey a benign prognosis. Understanding the sex differences in the diagnosis, treatment, and pathophysiology of ACS can improve the management and outcomes of women.

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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- • Of importance
- •• Of major importance

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