Evaluation and management of chest pain from cardiovascular causes in female patients

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ABSTRACT

Chest pain is a common presenting complaint in clinical practice and a leading cause of emergency department visits. However, the assessment and management of cardiac causes of chest pain in female patients present unique challenges owing to sex related differences in symptom presentation, underlying pathophysiology, and risk factors. Female patients are often underdiagnosed and undertreated, contributing to poorer cardiovascular outcomes. This review explores the current approaches to acute and stable chest pain in female patients while highlighting sex specific considerations in diagnosis, treatment, and differentials. Given the scope of this topic, the review focuses largely on cardiovascular causes of chest pain. In the evaluation of female patients with chest pain, understanding the differences in presentation, interpretation of common diagnostic tests, and evidence behind treatment is important. As female patients are more likely than male patients to have a diagnosis of myocardial infarction with non-obstructive coronary arteries, spontaneous coronary artery disease, and Takotsubo syndrome, understanding the unique features of these diagnoses is also important. In addition, valvular disease has unique features in female patients. Other factors such as age, polycystic ovary syndrome, and pregnancy increase female patients' cardiovascular risk, yet little evidence is available on the optimal investigation and management of cardiac chest pain in these special populations. Focusing on the evaluation of female patients, the existing literature on the management of acute and stable chest pain is reviewed.

Introduction

Chest pain is one of the most common presenting complaints in emergency and outpatient settings, frequently prompting evaluation for acute coronary syndrome (ACS) and other cardiac and non-cardiac causes of chest pain.[1] However, despite advances in diagnostic tools and clinical awareness, significant sex based disparities persist in the recognition and management of chest pain in female patients.[2] For ACS, female patients are at a heightened risk of misdiagnosis or delayed diagnosis, often leading to worse outcomes than male patients.[3] Despite ongoing awareness of this disparity in outcomes, research has yet to correct the underdiagnosis paradigm. Although some emerging evidence has begun to shed light on potential physiological and clinical differences in the manifestations of cardiac chest pain in female patients, whether these insights will improve their outcomes if integrated into practice is still unclear.[3 4] This review explores the factors contributing to the underrecognition of cardiac causes of chest pain in female patients, examines current literature on sex specific pathophysiology and presentation, and highlights the need for more inclusive, nuanced diagnostic approaches in cardiovascular care.

Sources and selection criteria

We searched PubMed by using the following terms: "sex" AND "chest pain". Original search dates were between 1 January 2020 and 1 March 2025. We included the following filters: "full text", "clinical trial", "meta-analysis", "randomized control trial", and "systematic review". We limited our search to "English" and "humans". We reviewed references in articles and included those we deemed appropriate. We excluded articles on heart failure, cardiac arrest, arrhythmia, and gastrointestinal pain, as well as case reports and case series. We also did a separate review of guidelines.

Included studies differed on the use of terms "sex, female" and "gender, women". Recognizing that these terms have distinct meanings (for example, biological versus sociocultural), we are using "female patients" when citing studies in this paper. Detailed results of the randomized controlled trials (RCTs) included in this review can be found in the supplementary table.

Epidemiology

Cardiovascular disease is the leading cause of death among female patients worldwide, accounting for about one third of deaths in female individuals globally. ACS accounts for more than 7 million emergency department encounters annually in the US; up to 57% of those visits in one study were by female patients.[5] Approximately 30% of the total 81 765 myocardial infarctions registered in the UK between 2022 and 2023 occurred in female patients.[6] Additionally, normal coronaries or non-obstructive coronary artery disease (CAD) is more prevalent in female patients with suspected ischemic heart disease (up to 65%) than in male patients (up to 32%).[7]

Presentation

Symptoms

Historically, female patients were underrepresented in research defining the characteristics of myocardial infarction. As research aimed to close this gap, the nuances of presenting symptoms of chest pain in female patients have varied. Guidelines have emphasized that female patients present with "atypical" chest pain.[8] Poorer outcomes for ACS in female patients were believed to result from these atypical presentations leading to delayed diagnosis and treatment.[3 9] Recent prospective research has shown that typical symptoms are more common and have greater predictive value for female than male patients.[9]

A subset analysis of a prospective cohort study defined typical pain as chest, arm, or jaw pain with descriptors including dull, heavy, tight, pressure, ache, squeeze, crushing, or gripping. Atypical chest pain was characterized as epigastric or back pain or pain described as burning, stabbing, indigestion-like, or any other description.[9] This study included 1941 patients with suspected ACS and found that chest pain was the most common presenting symptom, reported by 92% of female and 91% of male patients. Pain with typical descriptors, the presence of radiation, and additional symptoms were all more common in female patients with suspected ACS.[9]

Similar findings were also noted in the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) trial, which reported that chest pain was the primary symptom in female patients with ACS. However, the authors also noted that female patients reported a higher percentage of nausea than male patients.[10] This trial of structured patient interviews of 2009 female and 976 male patients found that the vast majority of female patients (87%) presented with chest pain characterized by pain, pressure, tightness, or discomfort.[11] Additionally, female patients were found to be more likely to present with at least three associated symptoms, including epigastric pain, palpitations, and discomfort in the jaw, neck, or arms or between the shoulder blades.[2 11] Other associated symptoms reported more frequently by female patients included fatigue, anxiety, dyspnea, dyspepsia, and nausea.[2]

The VIRGO trial also indicated that among the subset of patients with ST elevation myocardial infarction (STEMI) presenting without chest pain, these patients were more likely to be female. The discrepancy between current literature and historical studies may stem from classifying chest discomfort the same as chest pain, which seems to have helped to capture at least some aspect of female patients' distinct presentation.[9 12] In summary, female patients are as likely as male patients to experience chest pain as their primary symptom of ACS, but they also represent a larger portion of patients presenting with ACS without chest pain. Early attempts to simplify the notion that female patients have atypical symptoms did not serve most patients, and clinicians should recognize atypical presentations in ACS for both female and male patients.

Advances have been made in removing the term "atypical" to describe chest pain in female patients. Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines no longer use this descriptor.[13] However, cognitive bias in the interpretation of symptoms in female patients may still exist. Implementing machine learning tools that incorporate symptoms has shown promise in the identification of female patients at low risk for ACS.[14] Use of artificial intelligence (AI) in assessing female patients with chest pain may help to eliminate disparities in diagnosis based on symptoms. Overall, ongoing education for healthcare providers and female patients alike, emphasizing the importance of evaluating chest pain and/or discomfort with or without associated symptoms for cardiac causes, should serve to mitigate this disparity.

Risk factors

Assessment of risk factors is essential for evaluating chest pain in female patients. Estrogen plays a dynamic role as a risk factor for ACS. More inclusive research indicates that certain risk factors for atherosclerotic heart disease are more present in female than male patients, including tobacco use, type 2 diabetes mellitus, and psychological risk factors such as anxiety and depression.[2 4 15] In addition, family history of diabetes has a stronger association with acute myocardial infarction (AMI) in young female than young male patients.[11] These data are crucial in acute settings when using risk stratification tools and in primary care for risk factor mitigation.

Delays to presentation

Compared with male patients, female patients have a delayed presentation for evaluation of their chest pain symptoms, which may contribute to worse outcomes.[16 17] Female patients are more likely to present later than three hours after chest pain onset. In a study of patients who had STEMI, female sex was independently predictive of presentation greater than 90 minutes from symptom onset (odds ratio 2.46, 95% confidence interval (CI) 1.10 to 5.60; P=0.03).[11] In a qualitative study of female patients

who had experienced ACS, thematic explanations for the delay in presentation included lack of recognition of symptoms, lack of acknowledgment of risk factors for ACS, and focus on treating symptoms instead of seeking care.[18 19] Even when presented with scenarios depicting common chest pain symptoms, female patients were less likely than male patients to intend to seek help even for typical pain, despite being more likely to identify these symptoms as cardiovascular.

Differences in pre-hospital treatment exacerbate this delay in presentation. A large registry study from China also found that female patients had longer times from symptom onset to arrival of emergency medical services (EMS).[19] Another study showed that female patients were less likely to receive guideline directed care across multiple measures including EMS transport, pre-hospital aspirin or analgesia, and electrocardiography.[20] In one EMS system, initiatives aimed at narrowing the gap in care for essential interventions, such as obtaining an electrocardiogram, showed improvement but did not entirely eliminate the gap.[21] Public service campaigns targeting female patients to call 911, such as "Make the Call, Don't Miss a Beat," have struggled to demonstrate efficacy.[22] Despite awareness of these problems regarding presentation of acute chest pain in female patients, sex differences persist (box 1).

Diagnosis

Accurate interpretation of diagnostic tests is essential when evaluating female patients with chest pain. However, sex based physiological differences may complicate the use of universal diagnostic algorithms. Understanding these differences in test interpretation and sex variations can enhance the assessment of acute and stable chest pain (box 2). Key areas of diagnostic testing include the electrocardiogram, cardiac biomarkers, and secondary anatomic or functional testing.

Electrocardiography

Differences in physiology for female patients lead to challenges to using the same diagnostic testing and algorithms as for male patients. Lower QRS voltage from smaller cardiac muscle, digoxin-like effects of endogenous estrogen, and even shifting estradiol concentrations during the menstrual cycle may affect the severity of electrocardiography based ischemia.[23 24] Population based studies have reported that after puberty, female patients have a longer QTc than male patients.[25] Recent studies have suggested that QTc may be reflective of microvascular disease, and understanding these differences may be clinically relevant.[23 26] In AMI, new ST elevations in V2-V3 have different cut-off points between sexes: ≥2 mm for male patients ≥40 years, ≥2.5 mm for male patients ≤40 years, and ≥1.5 mm in all female patients.[27] Data from a Swedish cohort of patients presenting with chest pain noted significant sex differences in the optimal point to measure ST depression and elevation; in female patients, the amplitude interpretation had the highest diagnostic accuracy at 20 ms after the J point, whereas male patients had the highest diagnostic accuracy for ST depression at 40 ms after the J point.[26] In a multivariate analysis adjusting for risk factors, female patients had more lateral ST depressions (odds ratio 2.43, 95% CI 1.56 to 3.56) and QTc interval prolongation (1.22, 1.15 to 1.31) than male patients.[28]

Troponin

High sensitivity cardiac troponins (hs-cTn) are increasingly standard of care for the diagnosis of AMI. When a sex specific value is used, female patients have significantly lower 99% centile cut-offs.[29 30] For example, the upper reference limit 99% centiles for 4590 samples in healthy individuals were 16 ng/L for female and 34 ng/L for male individuals, although these differences are not universal among assays.[30 31] The fourth universal definition of myocardial infarction supports using sex specific 99th centiles for diagnosis.[27 32] Despite this trend, extensive evidence for improved diagnosis of AMI with sex specific cut-off values for hs-cTn does not exist. An RCT that evaluated the use of sex specific thresholds for hs-cTnI reported that these thresholds increased the identification of myocardial injury by 42% in female patients and 6% in male patients.[33] However, other data suggest that sex specific thresholds in hs-TnT did not substantially affect the diagnostic accuracy for AMI. These variations in data may be related to differences in populations, the use of specific troponin assays, or the inclusion of serial testing. Despite the compounding evidence on different presenting symptoms, risk factors, electrocardiographic changes, and troponin concentrations, protocols for rule-out of ACS without sex specific pathways other than age modifiers continue to proliferate.[34-36] The Canadian Women's Heart Health Alliance is one group that has introduced a plan for the development of a chest pain protocol for female patients.[37]

The prognostic value of hs-cTn in patients with stable coronary disease is also important. Data in male patients show that a troponin value that is declining over a year is associated with a 1.4% lower risk of future coronary events over a five year period. However, these data are available only for male patients.[38]

Diagnostic testing

Diagnostic testing for female patients is further affected by physiologic differences. In a review of the sex related differences to consider when approaching diagnostic testing,[39] exercise stress testing, the most frequently used diagnostic test, has lower sensitivity and specificity for obstructive coronary disease.[39] This is further complicated because false positive testing was harder to predict in female patients than in male patients, in whom false positive stress testing can be predicted using age and demographics before testing.[40] For premenopausal female patients, endogenous estrogen can create a digoxin-like

effect and increase the rate of false positive stress testing. For postmenopausal female patients, the vasodilatory properties of hormone replacement therapy can cause false negative stress testing.[23]

Although exercise or dobutamine stress echocardiography is more accurate than exercise stress testing alone for female patients, evidence still suggests inferior performance in female patients for these studies.[39 41] Although limitations, such as breast attenuation and smaller cardiac size, exist for single photon emission computed tomography (SPECT) myocardial perfusion imaging, the overall diagnostic sensitivity is good.[23 39] Positron emission tomography is better than SPECT for evaluating myocardial function in both female and male patients, with specific data to characterize the potential benefit of revascularization.[39] Coronary computed tomography angiography (cCTA) has been shown to be equally sensitive and specific for male and female patients, although it does increase exposure of breast tissue to radiation.[39] In addition, the diagnostic accuracy of cCTA has been reported to be improved when combined with coronary artery calcification (CAC) quantification in female patients (area under the curve 0.76 for cCTA versus 0.84 for cCTA+CAC; P<0.001).[42]

Treatment

Treatment recommendations for obstructive CAD have remained relatively stable over the years. The foundation remains goal directed medical therapy, and acute medical management and revascularization guidelines depend on the presence of occlusive myocardial infarction, as well as acuity, presentation, and comorbidities. Although these recommendations have been extensively investigated, a dearth of research into the specific needs of female patients remains.

In most studies, female patients account for only 10-20% of participants, with little insight into dosing adjustments or sex specific guidelines. Notably, female patients have a higher bleeding risk with dual antiplatelet therapy (DAPT), anticoagulation, and glycoprotein IIb/IIIa inhibitors.[43-46] A reduction in bleeding in both female and male patients has been observed with an abbreviated treatment course of DAPT.[43 47] A small RCT in Bangladesh showed that bivalirudin had a more favorable risk profile in female patients than heparin with or without eptifibatide.[48] Regarding glycoprotein IIb/IIIa inhibitors, although female patients have shown higher bleeding risk, the mortality rate of those who bled with the use of eptifibatide was greater in male than female patients (13.5% *v* 6.4%).[46] Furthermore, in an analysis of sex differences in the effect of early administration of abciximab in patients with STEMI, female patients had a significant reduction in 30 day and one year mortality risk that was not seen in male patients.[49]

Regarding revascularization, female patients are generally less likely to undergo percutaneous coronary intervention (PCI); and when intervention is done, they are less likely to achieve optimal door-to-balloon time.[50-52] Female patients undergoing PCI have higher rates of periprocedural ischemic and bleeding complications, and they have significantly higher all cause mortality when undergoing PCI and coronary artery bypass grafting (CABG) than male patients. These sex differences diminish after five and 10 year follow-up.[53 54] Furthermore, in patients with chronic coronary artery disease, the COURAGE trial showed greater benefit in female than male patients who underwent PCI, with decreased hospital admissions and need for future revascularization (hazard ratio 0.59 (95% CI 0.40 to 0.84; P<0.001) for female patients; 0.86 (0.74 to 1.01; P=0.47) for male patients).[55] These data are limited by low female enrollment in trials and post hoc subgroup analyses. Although female patients have a different risk profile with goal directed treatments than male patients, female patients undoubtedly derive clinical benefit, and strategies to mitigate risks to female patients may benefit male patients as well. A more detailed list of sex specific considerations for treating obstructive coronary artery disease can be found in table 1.

Secondary prevention

Female patients are less likely than male patients to have secondary prevention drugs prescribed, including established treatments such as β blockers and angiotensin converting enzyme inhibitors.[60-62] Female patients are also less likely to attend cardiac rehabilitation or adhere to prescribed drugs on follow-up.[63 64] A large prospective cohort study found that female patients had significantly higher rates of major adverse cardiovascular events (MACE) and stroke at 12 months post-PCI. On longer term follow-up (median 5 years), female patients had a 7% higher mortality rate; however, after adjustment for differences in medical therapy and risk factors, female patients had 22% lower mortality.[61] Another prospective study found that at six month follow-up, female patients had a 35% higher odds of MACE but without a significant difference of mortality, whereas at 12 month follow-up no significant difference in MACE and mortality was found between male and female patients.[63]

Box 1: Presentation of acute coronary syndrome in female patients

Symptoms
- Historically labeled "atypical," but recent data show that typical chest pain (chest, arm, jaw pain—dull, tight, pressure, ache) is common
- Female patients report more associated symptoms (nausea, dyspnea, fatigue, palpitations, neck/jaw/back pain)

Risk factors
- Higher prevalence of tobacco use, diabetes, anxiety, and depression
- Family history of diabetes carries stronger association with acute myocardial infarction in young female patients

Presentation delays
- Female patients often present >3 hours after onset
- Barriers include poor symptom recognition, underestimation of risk, focus on self-treatment, longer emergency medical services response, and lower pre-hospital care (aspirin, electrocardiography, transport)

Box 2: ACS diagnosis and management of acute coronary syndrome in female patients

Diagnosis
- Electrocardiogram—sex differences in voltage, QTc, ST segment changes
- High sensitivity troponin—female patients have lower normal cut-offs
- Stress tests—less sensitive/specific in female patients
- Imaging—positron emission tomography is better than single photon emission computed tomography; computed tomography with coronary artery calcification improves accuracy
- AI tools—show promise but often under-tested in female patients

Acute treatment
- Goal directed medical therapy (GDMT)—cornerstone of therapy
- Nitrates—underused pre-hospital
- Dual antiplatelet therapy (DAPT)—bleeding risk higher in female patients
- Anticoagulation—low molecular weight heparin, unfractionated heparin, bivalirudin; with bleeding risk considerations
- Fibrinolytics—similar outcomes by sex
- Percutaneous coronary intervention and coronary artery bypass grafting—female patients less likely to receive; more early complications

Chronic coronary artery disease and secondary prevention
- GDMT and symptom management—standard approach
- Secondary prevention—female patients less likely to get β blockers or angiotensin converting enzyme or to attend cardiac rehabilitation
- Novel agents—ezetimibe, PCSK9 inhibitors, bempedoic acid; show similar low density lipoprotein cholesterol reduction but sometimes lower target achievement in female patients
- DAPT—limited duration helps to reduce bleeding

Although DAPT is generally recommended post-PCI for 12 months unless contraindicated, the benefits of longer DAPT therapy are still being studied. A patient level meta-analysis including 5525 female patients compared DAPT with de-escalation to monotherapy with ticagrelor and reported a reduction in MACE in female patients who were on monotherapy (hazard ratio 0.67, 95% CI 0.49 to 0.93). This suggests that in female patients, de-escalation to monotherapy with ticagrelor after two weeks to three months may reduce mortality.[65]

Regarding cholesterol lowering agents, current guidelines support the addition of ezetimibe to statins for those patients whose low density lipoprotein (LDL) cholesterol is not at goal. The IMPROVE-IT trial found similar reductions in LDL cholesterol and in risk reduction, a 22% reduction in incidence of myocardial infarction in female patients, and no difference in significant adverse events with ezetimibe in female compared with male patients.[66] For patients who are still not at goal LDL cholesterol despite both statin and ezetimibe therapy, the European Society of Cardiology (ESC) recommends addition of a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor such as evolocumab or alirocumab.[67] The ODYSSEY trial studied patients treated with alirocumab. A cohort analysis of ODYSSEY found that 36.5% of female patients versus 58.7% of male patients reached target LDL cholesterol while on alirocumab, although no significant difference in MACE was seen.[68] Another agent that can be used is bempedoic acid, especially if the patient is intolerant of statin therapy or already on maximum dose statins. An RCT found that in patients on statins, female patients had a significantly lower reduction in LDL cholesterol than male patients (21% *v* 17%), whereas reductions were similar between male and female patients on low/no statins.[69] Finally, in patients on statin therapy whose triglycerides are not at goal, icosapent ethyl can be added. However, a RCT found that limited data are available on the performance of these agents in female patients.[70]

Specific diagnoses

Myocardial infarction with non-obstructive coronary arteries (MINOCA)

MINOCA is a subtype of myocardial infarction that is characterized by an absence of major obstructive CAD. It occurs in about 6-8% of patients with myocardial infarction and disproportionately affects female patients.[71] A systematic review of 28 studies of patients with myocardial infarction who underwent qualitative coronary angiography found that in patients with MINOCA, the proportion of female patients was 43%, but female patients constituted 23% of those with myocardial infarction with CAD.[72] Causes of MINOCA include coronary plaque disruption, coronary artery vasospasm, coronary artery dissection, coronary artery thromboembolism, type 2 myocardial infarctions, and microvascular disease.[73-75] In a prospective observational study of female patients with MINOCA, 75% were found to have an ischemic cause.[76] A meta-analysis of 112 studies including 5 908 768 patients with a myocardial infarction undergoing angiographyfound that, compared with female patients with obstructive coronary disease, those with MINOCA were younger and presented more frequently with atypical chest pain (8.45% *v* 8.18%; odds ratio 0.87) or dyspnea (7.76% *v* 5.47%; odds ratio 1.43).[77] Patients with MINOCA were more likely to have elevated C reactive protein, B-type natriuretic peptide, and high density lipoprotein than patients with myocardial infarction with obstructive coronary arteries.[77]

Guidelines from the AHA for diagnosis of MINOCA include three criteria—diagnosis of acute myocardial infarction per the fourth universal definition of myocardial infarction, non-obstructive coronary arteries on angiography (<50% stenosis), and no alternative cause such as pulmonary embolism, myocarditis, or sepsis.[27 73] Although myocardial injury is often seen on cardiac magnetic resonance imaging (MRI), a lack of ischemia may suggest an alternate cause of MINOCA in these patients such as brief vasospasm.[78] Another potential adjunct is coronary optical coherence tomography (OCT). Several studies of OCT in MINOCA identified the culprit lesion in 46-80% of patients.[71] For treatment, current AHA guidelines focus on supportive care, cardioprotective drugs and lifestyle adjustments like those for obstructive CAD, and targeted therapies for the cause of MINOCA.[73]

Table 1 | Sex specific considerations in treatment of obstructive coronary artery disease

Treatment	Sex specific considerations	
Dual antiplatelet therapy (aspirin and $P2Y_{12}$ inhibitors)	Subgroup analysis of data from MASTER DAPT trial to evaluate association of sex with comparative effectiveness of abbreviated versus standard DAPT in patients with high bleeding risk[43]	Abbreviated DAPT associated with comparable net adverse clinical events in male (HR 0.97, 95% CI 0.75 to 1.24) and female patients (0.87, 0.60 to 1.26)
		Trend toward benefit with regard to major adverse cardiac or cerebral events in female (HR 0.68, 95% CI 0.44 to 1.05) but not male patients (1.17, 0.88 to 1.55)
		No significant interaction for major or clinically relevant bleeding across sex
	Systematic review of 15 RCTs examining clinical impact of abbreviated duration of DAPT in male and female patients[56]	No sex based differences in MACE; lower bleeding risk observed for both sexes with shorter duration of DAPT (1-3 months)
Anticoagulation (unfractionated heparin and low molecular weight heparin are primary recommendations in STEMI and NSTEMI; bivalirudin and fondaparinux are alternatives in selected populations)	Horizons AMI trial randomized 3602 patients (23.4% female and 76.6% male) with STEMI presenting within 12 h of onset of symptoms to bivalirudin or heparin plus glycoprotein IIb/IIIa inhibitors and to PCI with drug eluting or bare metal stents[44]	Female sex independent predictor of major bleeding (HR 1.81, 95% CI 1.41 to 2.33; P<0.001)
	RCT in Bangladesh evaluating safety and efficacy of bivalirudin in 100 female patients with ACS undergoing PCI[48]	Bivalirudin treatment associated with significantly lower incidences of 30 day net adverse clinical events (5.7% *v* 27.6%; P=0.009) and bleeding (2.8% *v* 16.9%; P=0.03) compared with heparin +/− eptifibatide
Fibrinolytics (tenecteplase, alteplase)	Cross sectional study of 150 patients with STEMI who were administered tenecteplase or alteplase and concomitantly given ticagrelor[45]	Bleeding rates higher in alteplase group regardless of sex (11.7 *v* 2.2%); no sex difference in major adverse cardiac events
Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban)	Analysis of interaction between sex and bleeding and 30 day mortality outcomes among 2975 female and 6431 male patients with high risk non-ST elevation acute coronary syndrome enrolled in EARLY ACS trial (early versus provisional/ delayed administration of eptifibatide in patients undergoing PCI)[46]	Higher overall bleeding rate in female than male patients. Rates of excess eptifibatide dosing and access site bleeding higher among female than male patients. However, among those who bled, male patients had higher 30 day mortality than female ones (13.5% *v* 6.4%)
	Analysis of impact of early administration of abciximab in female and male patients with STEMI transferred for primary angioplasty; data derived from EUROTRANSFER registry[49]	Early abciximab in female patients led to decrease in ischemic events, including 30 day (adjusted OR 0.26, 95% CI 0.10 to 0.69; P=0.007) and 1 year (0.37, 0.16 to 0.84; P=0.017) mortality reduction; similar reduction in 30 day and 1 year mortality was not found to be statistically significant in male patients
Percutaneous coronary intervention	Analysis of data for patients with STEMI aged 18-59 from Nationwide Inpatient Sample; examined temporal trends and sex differences in revascularization strategies, in-hospital mortality, and length of sta[y5]0	Female patients less likely to undergo PCI (OR 0.74, 95% CI 0.73 to 0.75)
	Analysis of clinical characteristics, management strategies, and outcomes of 11 536 male and female patients ≤55 years of age enrolled in biennial Acute Coronary Syndrome Israeli Surveys between 2000 and 2013[51]	Female patients less likely to undergo coronary angiography during hospital admission for acute coronary syndrome (OR 0.6; P=0.007)
	Study of 104 817 patients with ACS enrolled in AHA Get With the Guidelines Coronary Artery Disease registry from 2003 to 2008.[52] Female sex associated with higher rate of 30 day readmission post-PCI[57]	Target door-to-balloon time of 90 min achieved less often in female than male patients (<55 years: 54.1% of female *v* 58.7% of male patients; P=0.003; 55-64.9 years: 52.1% *v* 58.6%; P=0.002)
	Evaluation of sex differences in mortality among patients in SYNTAX trial with three vessel and left main coronary artery disease who were randomized to PCI versus CABG[53]	Higher 5 year mortality rate with PCI than CABG among female patients (19.3% female *v* 10.3% male patients; P=0.01); sex difference not present at 10 year follow-up
	Analysis of sex differences in outcomes among patients in EXCEL trial with unprotected left main disease undergoing PCI versus CABG[54]	Female patients undergoing PCI had higher rates of both periprocedural ischemic and bleeding complications than male patients
		Significantly higher all cause mortality in female patients undergoing PCI than in those undergoing CABG and male patients treated with either PCI or CABG, but effect less evident at 5 year follow-up
Coronary artery bypass grafting	Pooled analysis of RCTs evaluating outcomes of female patients after CABG[58]	Graft failure more frequent in female than male patients (37.3% *v* 32.9%; P=0.02); female sex independently associated with risk of death (HR 1.84, 95% CI 7.35 to 2.50)
Chronic coronary artery disease	COURAGE trial (15% female, 85% male patients) investigated sex based differences in effectiveness of PCI in stable coronary disease[55]	Higher benefit in female patients who underwent PCI, with decreased hospital admissions and need for future revascularization (HR 0.59, 95% CI 0.40 to 0.84; P<0.001 for female patients versus 0.86, 0.74 to 1.01; P=0.47 for male patients)
	ISCHEMIA trial randomized patients with chronic CAD and ischemia to invasive management + GDMT or GDMT alone[59]	Female patients had less extensive coronary disease than male patients and had lower PCI rate in invasive management arm; GDMT use also lower in female patients, but overall no sex difference in primary and secondary outcomes

ACS=acute coronary syndrome; AMI=acute myocardial infarction; CABG=coronary artery bypass graft; CAD=coronary artery disease; CI=confidence interval; DAPT=dual antiplatelet therapy; GDMT=goal directed medical therapy; HR=hazard ratio; MACE=major adverse cardiovascular event; NSTEMI=non-ST segment myocardial infarction; OR=odds ratio; PCI=percutaneous coronary intervention; RCT= randomized controlled trial: STEMI=ST segment myocardial infarction.

Spontaneous coronary artery dissection (SCAD)

SCAD occurs when tearing of the arterial wall creates a false lumen and hematoma leading to potential obstruction of blood flow. Whereas 2-4% of patients with ACS have SCAD,[79 80] female patients comprise approximately 80-90% of SCAD cases.[81] SCAD tends to affect younger female individuals, causing up to 45% of ACS in female patients under 50 years of age.[82] It is the most common cause of myocardial infarction in pregnancy and the postpartum state and occurs more frequently during the last trimester and within the first week of delivery.[83] Traditional risk factors for ACS are less prevalent in patients with SCAD, whereas fibromuscular dysplasia, connective tissue disorders, and stress predispose to SCAD.[79 81 82 84] The diagnosis of SCAD is made with coronary angiography, and further testing with OCT or intravascular ultrasonography can be considered if the diagnosis is unclear.[85] A retrospective study using cCTA identified only 78% of lesions in patients with confirmed SCAD on coronary angiography and may miss smaller distal lesions.[86]

Management of SCAD is primarily conservative and supportive care, as follow-up of SCAD lesions has shown that most will spontaneously heal within 30 days [87] A meta-analysis of 24 observational studies with 1720 patients with SCAD comparing conservative versus invasive management found no difference in mortality, myocardial infarction, or recurrence.[88] Guidelines recommend reserving PCI or CABG for patients with hemodynamic instability, ongoing ischemia, or left main dissection.[79 82 85] Medical management of SCAD involves the use of β blockers (thought to reduce shear force on coronary arteries) and aspirin.[89] The role of DAPT in patients managed conservatively is unclear.[84 90] Patients with SCAD who have undergone PCI should be started on DAPT.[82 91]

Takotsubo syndrome

Takotsubo syndrome is a condition that mimics AMI, characterized by transient left ventricular regional dysfunction, ischemic electrocardiographic changes, and elevated cardiac biomarkers in the absence of significant CAD. It is often triggered by emotional or physical stress.[92-94] A marked age and sex discrepancy remains in the prevalence of this disorder,[95] with the vast majority of cases occurring among postmenopausal female patients.[93 94] Takotsubo syndrome accounts for 1.7-2.5% of patients with ACS and 5-6% of female patients presenting with suspected STEMI.[93 95]

A triggering event is identified in 76% of female and 86% of male patients with Takotsubo syndrome.[96] The potential triggers of Takotsubo syndrome include physical and emotional stressors.[96] Female patients often have either an emotional stressor or no identifiable stressor.[93 96] The predominance of this syndrome in postmenopausal female patients suggests that declining estrogen concentrations may increase susceptibility, although a specific pathophysiologic mechanism is still unknown.[97]

The most common symptoms of Takotsubo syndrome are chest pain, dyspnea, and syncope, which are usually indistinguishable from AMI.[96] Given the variety of potential physical triggers, symptoms related to the trigger may dominate the initial presentation.[97] Some patients present with symptoms related to complications of cardiomyopathy.[96 97]

ST elevation on the electrocardiogram occurs in 85% of patients on admission, with later findings including T wave inversion and QTc prolongation.[96] ST elevations usually involve the precordial, lateral, and apical leads.[97] Cardiac troponin is elevated in 92% of patients, with higher elevations observed in male patients.[96] For patients who do not undergo coronary angiography, transthoracic echocardiography may be used as a diagnostic tool to demonstrate characteristic regional wall motion abnormalities.[97] Coronary computed tomography angiography can provide information on coronary artery anatomy and regional left ventricular contraction and has also been proposed as a diagnostic tool.[97]

Given that Takotsubo syndrome may initially resemble ACS, the initial management should focus on excluding and treating possible ACS with antiplatelet agents, anticoagulation, vasodilators, continuous electrocardiographic monitoring, and urgent coronary angiography.[97] For patients who develop cardiogenic shock, left ventricular outflow obstruction contraindicates the use of inotropes, diuretics, and nitroglycerin, instead necessitating administration of intravenous fluids and short acting β blocker therapy.[97]

Aortic dissection

Table 2 lists sex differences in patients with a diagnosis of aortic dissection. Approximately 20% of thoracic aortic aneurysms and dissections (TAADs) are associated with a family history of dissection. X linked inheritance patterns have been observed, predominantly consistent with X linked dominance.[99] The lower incidence in female individuals may be due to the protective effects of female sex hormones, which up regulate the estrogen receptor α, providing vasoprotection and reducing vessel inflammation. Older female patients have stiffer aortas with exaggerated systolic pulse amplification, potentially contributing to the development of TAAD.[98]

Female patients often present with type A dissections, whereas male patients present with both type A and type B dissections.[98] A systematic review and meta-analysis of type A acute aortic dissection identified sex specific risk factors (table 2).[24] The meta-analysis reported no consistent differences by sex in presenting symptoms. A scoping review noted that female patients often experience delayed diagnoses, attributed to older age at presentation and atypical symptoms,[101] such as altered levels of consciousness. Studies using the aortic dissection risk score and D dimer have limited data on diagnostic accuracy in female patients. A case-control study

Table 2 | Sex specific differences in cardiovascular disease states

Disease state	Sex specific risk factors	Sex specific outcomes
Aortic dissection	Female patients have lower incidence (owing to protective estrogen effects), more type A presentations, older age at diagnosis, stiffer aortas, and lower BMIs[98]; X linked inheritance implicated; male-to-female ratio ~2.5-3.0 in sporadic cases[99]	Female patients are more likely to have diabetes (RR 1.41) and less likely to smoke (RR 0.47) or have bicuspid aortic valves (RR 0.51).[100] Delayed diagnoses more common in female patients[101]; female patients >55 have higher operative mortality.[102] No difference in in-hospital outcomes post-TEVAR.[103] Female patients more often treated conservatively (OR 0.65 *v* male patients)[104]
Myocarditis/pericarditis	Female sex linked to ICI related myocarditis (OR 3.34)[105] and readmission after pericarditis (aHR 1.33).[106] Female patients present older, with fewer ST elevations and lower troponins.[107] Risk from covid-19 vaccine higher in male patients, but relative risk same[108]	Female patients more likely to have severe SOB, higher hospital admission rates,[109] poor NSAID response (OR 3.57), and higher recurrence risk with corticosteroids (HR 2.06).[110] No sex difference in short term mortality
Mitral valve disease	More common in female patients, especially with rheumatic disease. Sex differences in extracellular remodeling and calcification patterns	Female patients are less likely to receive surgery and have worse outcomes after repair[111] and higher rates of pulmonary hypertension. Higher stroke and bleeding risk with MitraClip but better adjusted long term survival[112]
Tricuspid regurgitation	More prevalent in female patients; underdiagnosed and undertreated.	Female patients benefit more from early surgery. No sex difference in surgical mortality (RR 1.19; P=0.29) or post-TTVR outcomes[113]
Aortic stenosis	Female patients have smaller annulus, more concentric LV remodeling, more diastolic dysfunction,[114] and less calcific load.[115] Pregnancy exacerbates stenotic lesions such as aortic stenosis	More symptoms at presentation, delayed diagnosis, better post-TAVR survival, but higher procedural complications (eg, pericardial bleeding: 17% *v* 6.6%)[114]
Hypertrophic cardiomyopathy	Female patients are older and have worsening left ventricular diastolic function and obstruction and increase in morbidity ≥60 years[33]; female patients have LP/P sarcomere variant, whereas male patients are more likely to be sarcomere negative [116]	Sarcomere positive status increased with risk of death in male but not female patients (HR 0.86, 95%CI 0.71 to 1.21)[116]; female patients have lower incidence of outflow obstruction but have reduced exercise capacity[117]

aHR=adjusted hazard ratio; BMI=body mass index; ICI=immune checkpoint inhibitor; LV=left ventricular; NSAID=non-steroidal anti-inflammatory drug; OR=odds ratio; RR=risk ratio; SOB=shortness of breath; TAVR=transcatheter aortic valve replacement; TEVAR=thoracic endovascular aortic repair; TTVR=transcatheter tricuspid valve replacement.

using AI to predict the risk of acute aortic dissection rupture within 72 hours of imaging identified female sex as a predictor in the multivariable model.[118] However, other observational studies and meta-analyses note differences in in-hospital outcomes, with female patients tending to have poorer long term outcomes. One observational study found that female patients aged over 55 had higher odds of operative mortality than male patients.[102] Studies evaluating type B dissection showed that male patients were less likely to be treated conservatively than female patients (odds ratio 0.65, 95% CI 0.58 to 0.72) and had similar outcome differences to type A dissection.[104] These studies showed no differences in in-hospital outcomes after thoracic endovascular aortic repair.[103]

Myocarditis/pericarditis

Myocarditis and pericarditis can present with acute and recurrent chest pain syndromes. They share overlapping causes and may represent a continuum of disease. Female sex has been identified as a possible risk factor for cardiovascular immune related adverse events with an odds ratio of 3.34 (95% CI 1.42 to 7.85; P=0.006). This has been attributed to down regulation of mesencephalic astrocyte derived neurotrophic factor owing to reduced β-estradiol concentrations for treatment.[105] Recently, the risk of myocarditis and pericarditis following covid-19 vaccination in a meta-analysis of 17 studies including patients who had a covid-19 vaccine and myocarditis and pericarditis was reported. Although the relative risk of myocarditis after covid-19 vaccination does not differ by sex, the attributable risk is much higher in male patients.[108]

A systematic review and meta-analysis of 11 studies including 34 791 patients with myocarditis reported that most present with chest pain and normal ejection fraction, whereas 25% can present with heart failure or arrhythmias.[119] Table 2 lists differences in presentation by sex. Despite this, no differences were seen in risk of stroke, atrial fibrillation, or left ventricular ejection fraction.[107] For pericarditis, one observational study found that female sex was associated with readmission to hospital (adjusted hazard ratio 1.33, 95% CI 1.18 to 1.49).[106]

Given the low incidence of disease, data on sex differences in treatment effects of drugs for acute symptoms are limited. In a study of patients with acute pericarditis, female sex was associated with a poor response to non-steroidal anti-inflammatory drugs, leading to a switch to corticosteroid treatment (odds ratio 3.57, 95% CI 1.0 to 12.5).[110]

Current AHA guidelines recommend that investigation of patients with acute chest pain and myocardial injury includes cardiac MRI, transthoracic echocardiography to identify signs of myopericarditis, and contrast cardiac computed tomography to assess pericardial thickening,[120] as well as C reactive protein; recent published guidelines for the management of pericarditis do not provide any sex specific recommendations or discussion.[121]

Valvular disease

Differences also exist in valvular heart disease between female and male patients (table 2). Mitral valve disease is more prevalent in female patients, especially in those with rheumatic disease, with mitral valve stenosis and mitral valve prolapse being

more common in female patients. These findings may relate to sex based differences in extracellular matrix remodeling and calcification patterns.[122] At presentation, female patients may have symptoms, and, like female patients with aortic stenosis, they seem to have a higher rate of pulmonary hypertension than male patients.[122] Female patients with mitral valve prolapse are less likely to undergo surgical repair than male patients, and female sex has been associated with worse outcomes in mitral valve surgery.[111] This may partly result from delays in surgery, influenced by surgical criteria largely based on male cohorts. Female patients with moderate to severe mitral regurgitation undergoing transcatheter edge-to-edge repair with MitraClip have higher unadjusted rates of periprocedural stroke and bleeding than male patients. However, female patients have lower adjusted mortality in long term follow-up.[112]

Tricuspid regurgitation is more prevalent in female patients; however, it can be underdiagnosed and undertreated. Prognosis is poor in both sexes, but female patients have shown increased benefit from early surgery. A meta-analysis of tricuspid regurgitation treatment outcomes showed no significant difference between male and female patients in both in-hospital mortality (risk ratio 1.19, 95% CI 0.86 to 1.64; P=0.29; I^2=45%) and late mortality (risk ratio 0.99, 0.17 to 5.65; P=0.99) among patients who underwent open heart surgery. No difference in mortality post-transthoracic valve replacement was reported.[113]

Female patients with aortic stenosis tend to have smaller aortic valve area, more concentric left ventricular remodeling, and greater diastolic dysfunction, even with similar transvalvular gradients.[114] Cardiac symptoms at presentation are present in both sexes but are often more pronounced in female patients.[123] This may be due to age at presentation or the presence of concentric left ventricular hypertrophy. Smaller aortic annulus and root dimensions may lead to higher rates of inaccurate measurements, resulting in delayed diagnosis.[115] Differences in aortic valve calcification exist, with female patients having less calcific load after adjustment for body surface area.[115] Young female patients with bicuspid aortic valves may experience severe aortic stenosis without significant valvular calcium. Despite presenting with more symptoms, female patients have better survival after transcatheter aortic valve replacement but also higher rates of procedural complications.[114] An observational study showed sex differences primarily in pericardial bleeding (17.0% in female versus 6.6% in male patients; P=0.025) and urogenital bleeding (3.8% *v* 19.0%; P=0.001).[124]

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a genetic disorder characterized by thickening of the heart muscle, which can lead to symptoms such as chest pain, shortness of breath, or sudden cardiac death. Biological reasons for sex differences (table 2) include increased fibrosis, increased tubulin and heat shock proteins in female patients with hypertrophic cardiomyopathy, greater rate of transcriptional and proteomic dysregulation, and a greater counter-regulatory down regulation of hypertrophy pathways than in male patients with hypertrophic cardiomyopathy.[125] Female patients with hypertrophic cardiomyopathy are also reported to have an LP/P sarcomere variant whereas male patients are more likely to be sarcomere negative. This difference has been associated with outcomes, as sarcomere positive status increased with risk of death in male patients but was not associated with death in female patients (hazard ratio 0.86, 95% CI 0.71 to 1.21).[116] An observational study of 292 patients with hypertrophic cardiomyopathy reported phenotypic differences in female patients with hypertrophic cardiomyopathy, including smaller left ventricles, higher left sided filling pressures, and lower incidence of outflow obstruction. Additionally, this study reported that female sex was an independent predictor of reduced exercise capacity.[117]

Recent guidelines on the treatment of hypertrophic cardiomyopathy include specific recommendations by sex. These recommendations advocate for the use of age and sex adjusted exercise capacity measurements to prompt consideration of advanced therapies for left ventricular outflow tract obstruction. Although no sex specific treatment recommendations were provided, the guideline recommended that algorithms use the presence of obstruction and symptoms as guides for treatment. However, it does provide specific recommendations for management of hypertrophic cardiomyopathy in pregnant patients; specifically, shared decision making should convey that maternal mortality with pregnancy is low and cardiac events usually occur in those with pre-existing conditions.[126]

Special patient populations

Box 3 summarizes the key features and clinical considerations in special female populations.

Box 3: Features and considerations in special female populations

Older people
- Older age at myocardial infarction presentation
- More atypical symptoms
- Greater cognitive/functional impairment
- Less likely to undergo invasive management despite similar or higher risk

Polycystic ovary syndrome
- High prevalence of metabolic syndrome and insulin resistance
- Higher risk of cardiovascular disease events even independent of body mass index
- Long term risk monitoring needed

Peripartum
- Pregnancy/postpartum shifts increase risk of myocardial infarction
- Spontaneous coronary artery dissection is a major cause of myocardial infarction
- Drug/radiation safety concerns limit treatment options
- Adverse pregnancy outcomes (eg, pre-eclampsia, gestational diabetes mellitus) indicate long-term cardiovascular disease risk

Older people

Although estrogen mitigates cardiovascular risk in the younger female population, this protective effect diminishes at the onset of menopause. Reproductive and ovarian age, determined using age at menopause as a proxy for cumulative ovarian aging,seem to play an important role in the increased risk of cardiovascular disease as female individuals age.[8 127-129] Development of metabolic syndrome, hypertension, and insulin resistance seem to be more closely linked to chronologic age.[128]

When presenting with AMI, age >65 years and female sex are associated with delays to presentation.[130-133] A multicenter cross sectional study of 619 patients with STEMI in Munich found that female patients ≥65 years had a 2.39-fold (95% CI 1.39 to 4.10) higher odds of a delay longer than two hours compared with all other patient groups, and this was especially marked in comparison with younger female patients (excess odds ratio 3.33, 95% CI 1.62 to 6.87).[130] Although the absence of typical chest pain has been identified as a contributor to delay in presentation,[134] it does not account for the significant age and sex difference noted.[130]

Absence of chest pain in AMI, as well as atypical symptoms, does increase with age.[134] Patients in the Worcester Heart Attack Study were stratified into five age groups (<55 years, 55-64 years, 65-74 years, 75-84 years, and >85 years); although chest pain remained the most common complaint among patients of all age groups, the proportion of atypical symptoms, including shortness of breath, weakness/fatigue, abdominal pain, and syncope, increased linearly with age.[134] In one analysis of data from the SILVER-AMI Study, a prospective cohort study of 3041 patients aged ≥75 years with AMI, the average number of symptoms per patient was greater in female than male patients (4.2 *v* 2.5; P<0.001).[135] In a retrospective study of symptom presentation in 172 981 cases of AMI registered in the SWEDEHEART registry, the proportion of patients presenting without chest pain was significantly higher in female than male patients (16.2% *v* 11.0%; P<0.001), and this proportion increased with age (5.5% *v* 4.7% of female compared with male patients aged 18-44 years; 20% *v* 16.8% of female compared with male patients aged 75-84 years); however, the impact of absent chest pain on mortality was more pronounced in younger than older patients.[136]

Polycystic ovary syndrome (PCOS)

PCOS is one of the most common endocrine disorders in female patients, with a worldwide prevalence of 5-13%.[137] It is characterized by menstrual irregularity, hyperandrogenism, and polycystic ovaries.[138 139] The prevalence of metabolic syndrome in PCOS is 43-47%, twice that of the general population.[139] PCOS is also associated with cardiovascular disease markers such as increased endothelial dysfunction, arterial stiffness, and carotid intima media thickness.[140] Although the consensus is that PCOS is associated with an increased prevalence of these traditional cardiovascular risk factors, some disagreement exists in the literature as to whether PCOS itself carries with it increased risk of cardiovascular disease, rather than obesity and insulin mediated mechanisms.[141 142] Recent large population studies indicate that young female patients with PCOS have an increased incidence of major cardiovascular events, myocardial infarction, angina, and revascularization.[140] This risk of cardiovascular disease starts to increase by age 35 in female patients with PCOS and is independent of body mass index.[143] The 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome states that female patients with PCOS should be considered to be at increased risk of cardiovascular disease and potentially of cardiovascular mortality, acknowledging that the overall risk of cardiovascular disease in the premenopausal female population is low.[138]

Peripartum

Pregnancy causes significant shifts in maternal physiology affecting systemic vascular resistance, cardiac output, blood pressure, blood volume, cholesterol concentrations, and insulin sensitivity.[144 145] ACS is three to four times more likely to occur in pregnant female patients than in similarly aged non-pregnant female patients.[146] ST elevations, persistent ST depressions in the setting of chest pain, or T wave inversions that are deep and/or present in leads other than V1-V3 should prompt consideration of AMI.[147] A rise in serum troponin should suggest myocardial ischemia.[147 148]

Guidelines for drug therapy for AMI in pregnancy are primarily based on professional consensus owing to limited information on fetal safety of several drugs, including P2Y12 inhibitors and glycoprotein IIb/IIIa inhibitors.[149] Low dose aspirin seems to be safe, and β blockade may be beneficial in reducing shear stress in SCAD.[149] Thrombolytic agents may induce bleeding complications, but no complications related to drug therapy were reported in a review of 150 cases of pregnancy associated myocardial infarction between 2006 and 2011.[150] Generally, statins are considered category X in pregnancy owing to their inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and subsequent decrease in cholesterol, which is essential for fetal development of cell membranes and steroid hormones.

Emerging literature focuses on the future cardiovascular risk posed by adverse pregnancy outcomes (such as gestational hypertension, pre-eclampsia, gestational diabetes, preterm birth, and small for gestational age infants), which affect up to 20% of pregnancies.[151] Adverse pregnancy outcomes have been shown to be associated with higher prevalence of traditional cardiovascular risk factors such as chronic hypertension, type 2 diabetes mellitus, hypercholesterolemia, and changes in body mass index.[152-156] For instance, by age 50-59, female patients with a history of pre-eclampsia have an absolute risk of a cardiovascular

event of 17.8%, compared with 8.3% risk in those without a history of pre-eclampsia.[157] Ultimately, pregnancies complicated by an adverse outcome can be thought of as a "failed stress test," identifying a population of female patients at high risk for future vascular disease, and have been proposed as a target for cardiovascular risk reduction strategies.[145 158]

Emerging treatments

Treatment options are being studied that may affect the care of female patients with angina with non-obstructive coronary artery disease (ANOCA). An RCT of a sodium-glucose cotransporter 2 inhibitor is being conducted as preclinical data have suggested a variety of mechanisms by which these drugs can potentially attenuate microvascular and endothelial dysfunction, including nitric oxide production, oxidative stress, and inflammation, among others (Clinicaltrials.org, NCT06600178). Another single site randomized trial will evaluate inorganic nitrate supplementation with beetroot juice in female patients with ANOCA. Inorganic nitrate decreases blood pressure, arterial stiffness, oxidative stress, and inflammation (NCT06948201). N-acetylcysteine will also be studied to see if it reduces anginal frequency in female patients with ANOCA (NCT06890507).

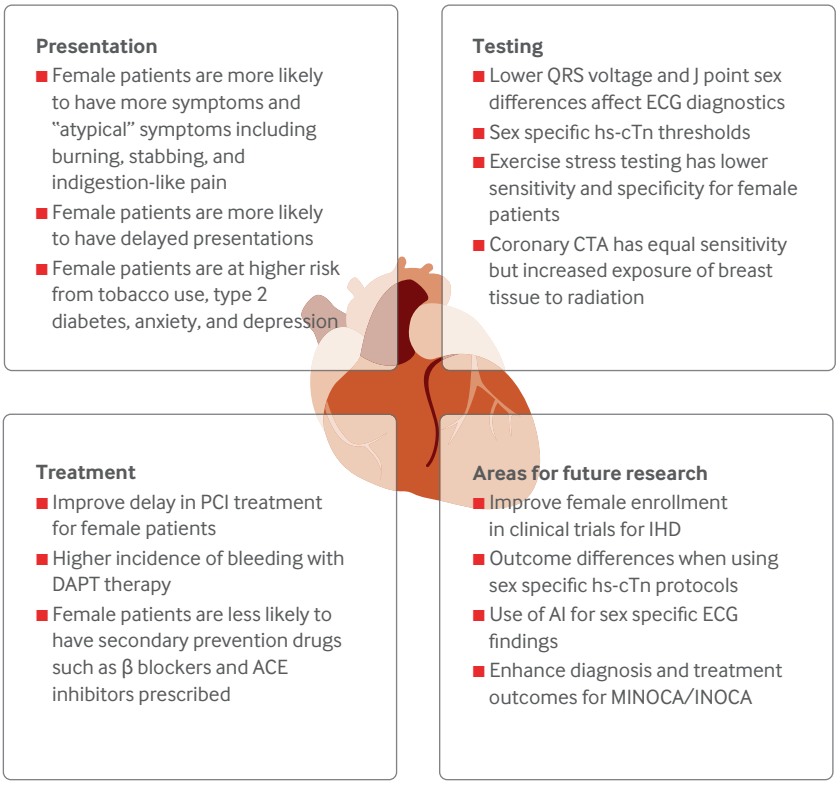

Fig 1 | Summary of chest pain from cardiovascular causes in female patients. ACE=angiotensin converting enzyme; AI=artificial intelligence; CTA=computed tomography angiography; DAPT=dual antiplatelet therapy; ECG=electrocardiography; hs-cTn=high sensitivity cardiac troponins; IHD=ischemic heart disease; INOCA=ischemic non-obstructive coronary artery disease; MINOCA=myocardial infarction with non-obstructive coronary arteries; PCI=percutaneous coronary intervention

A pilot study has been registered to evaluate the use of transcutaneous electrical nerve stimulation in patients with refractory angina and ANOCA (NCT06401291).

Many studies are enrolling participants to enhance the diagnosis of myocardial infarction or ischemia with non-obstructive coronary disease. These include one trial of stratified medicine for guidewire based interventional diagnostic procedures during coronary angiography (NCT04674449). A single center study aims to look at the value of measuring retinal vascular density by OCT angiography as a non-invasive way to diagnose ischemia with non-obstructive coronary disease (NCT06692751).

Clinical trials are enrolling participants to evaluate the use of methylprednisolone (NCT05150704), colchicine (NCT05855746), and abatacept in immune checkpoint inhibitor associated myocarditis (NCT05335928); an analysis of efficacy by sex is anticipated.

Technology

The focus on enhanced technologies, such as AI, has the potential to improve the evaluation of female patients with chest pain. Current AI developments include better risk stratification, the use of imaging for disease prediction, and early detection of injury based on the electrocardiogram. This technology may reduce cognitive burden and the potential bias that may exist in the evaluation of female patients with chest pain. However, as AI models are created using existing data, biases may exist owing to cohort selection and verification bias.

The incorporation of AI in evaluating female patients with chest pain can begin at triage in acute care settings. An AI guided triage program has been shown to reduce time to cardiac intervention by 300.0 (95% CI 119.3 to 480.0) minutes in an emergency department in the US.[159] AI interpretations of electrocardiograms have been shown to predict troponin biomarker elevation and identify biomarker defined myocardial injury.[160 161] Another study found that a machine learning model using only the electrocardiogram outperformed the HEART score in predicting mortality among patients with suspected ACS.[162] Additionally, an AI algorithm using a single point-of-care hs-cTnI measurement reported a negative predictive value of 100% (95% CI 99.9% to 100%) in female patients.[163]

AI can also guide management decisions in patients with stable chest pain. In a recent cohort study of an algorithmic machine learning testing strategy, deviations from the AI approach were associated with a 19-26% increased risk of death or AMI.[164] The researchers noted that black people, people with diabetes, younger patients, and female patients were less likely to have testing that aligned with the AI driven recommendations.[164] Therefore, AI will probably see increased utilization in managing patients with chest pain. Pre-specified analyses evaluating the diagnostic accuracy by sex are needed to understand performance in female patients.

GLOSSARY OF ABBREVIATIONS

- ACC—American College of Cardiology
- ACS—acute coronary syndrome
- AHA—American Heart Association
- AI—artificial intelligence
- AMI—acute myocardial infarction
- ANOCA—angina with non-obstructive coronary artery disease
- CABG—coronary artery bypass grafting
- CAD—coronary artery disease
- cCTA—coronary computed tomography angiography
- CI—confidence interval
- DAPT—dual antiplatelet therapy
- EMS—emergency medical services
- ESC—European Society of Cardiology
- hs-cTn—high sensitivity cardiac troponins
- LDL—low density lipoprotein
- MRI—magnetic resonance imaging
- OCT—optical coherence tomography
- PCI—percutaneous coronary intervention
- PCOS—polycystic ovary syndrome
- RCT—randomized controlled trial
- SCAD—spontaneous coronary artery dissection
- SPECT—single photon emission computed tomography
- STEMI—ST elevation myocardial infarction
- TAADs—thoracic aortic aneurysms and dissections

Guidelines

Several guidelines and risk stratification tools exist for the diagnosis, treatment, and prognosis of cardiac chest pain, some of which include female focused recommendations.

The 2025 ACC/AHA/American College of Emergency Physicians/National Association of Emergency Medical Services Physicians/Society for Cardiovascular Angiography and Interventions guidelines for ACS acknowledge that differences may exist in hs-cTn cut-off values between male and female patients; however, no recommendations are made regarding the use of sex specific hs-cTn.[13] These guidelines recommend increased use of cardiac rehabilitation, especially for female patients, who have been shown to have lower referral rates for this intervention. Guidelines from 2021 by this group discuss differences in symptomatology as well as preferred cardiac testing methods for pregnant women.[165]

The 2023 ESC guidelines on the assessment and management of patients with ACS state that no current recommendations are available for differences in treatment based on sex.[67] However, they do include sections on SCAD and MINOCA, which disproportionately affect women. The guidelines also highlight the differences in treatment for pregnant women with ACS. The ESC calls for increased representation of female participants in RCTs and increased use of cardiac rehabilitation for female patients, and urges people to be wary of bias.

Conclusions

Figure 1 summarizes the main messages of this review. The assessment and management of chest pain in female patients are clinically important owing to ongoing sex related disparities in diagnosis, treatment, and outcomes. Established diagnostic algorithms, risk stratification tools, and biomarker thresholds may not adequately reflect the unique pathophysiological and clinical features seen in female patients, leading to delayed recognition of serious cardiac events and suboptimal care. In acute settings, timely identification and appropriate

PATIENT PERSPECTIVES

- A 40 year old woman presented to the emergency department with epigastric pain radiating into her chest. She waited 24 hours after the onset of her symptoms to seek care and was ultimately given a diagnosis of acute myocardial infarction
  1. Her delay to presentation was influenced by an initial misattribution of her symptoms to gastroesophageal reflux, as she found it difficult to believe that she could be having a heart attack. Furthermore, she considered her husband and daughter's respective schedules, believing that it would be less disruptive to present on a Saturday morning instead of a Friday afternoon
  2. Following discharge from the hospital, she was referred to cardiac rehabilitation but was hesitant to attend. Scheduling appointments would be difficult owing to her personal work schedule. In addition, she feared that she would be the only younger woman among a group of older men undergoing cardiac rehabilitation
  3. She was concerned about her future health, worried that she may have another myocardial infarction or misattribute symptoms that may lead to another delay in presentation
- A 35 year old woman experienced a spontaneous coronary artery dissection during her third trimester of pregnancy
  1. She felt a sense of betrayal by her own body and mourned the loss of a "normal" postpartum experience
  2. She feared that the stress and sleeplessness of caring for a newborn may trigger another cardiac event
  3. She wished a medical provider would have spoken with her at length about the risks and benefits of breastfeeding her newborn, having assumed that breastfeeding was absolutely contraindicated
- A 72 year old woman presented to the emergency department with three days of fatigue and nausea that began after she planted flowers in her garden. She was found to have non-ST segment elevation myocardial infarction
  1. Despite the fact that she typically had good exercise tolerance and had never before experienced these symptoms while gardening, she initially attributed her symptoms to her advancing age and presumed she was simply becoming frail
  2. Once given a diagnosis of a myocardial infarction, she feared a potential loss of her independence, having lived alone up until that point. If she decided to live with one of her adult children after this event, she could lose her much valued autonomy
  3. For several months following her discharge, she became anxious and hypervigilant, concerned that any vague symptom could be a harbinger of much more serious pathology. As a result, she limited many of the outdoor activities (including gardening) that she had previously enjoyed

QUESTIONS FOR FUTURE RESEARCH

- How will the use of AI driven diagnostic algorithms mitigate misinterpretation of multiple symptom complaints or atypical symptom phenotypes?
- How will sex specific high sensitivity troponin thresholds affect the sensitivity and specificity of diagnosis of acute coronary syndrome in female versus male patients?
- Given that female patients have a higher risk of bleeding, what are the optimal dual antiplatelet therapy and anticoagulation therapy?
- How can the factors that influence female patients receiving less optimal cardiovascular interventions and long term preventive therapies be altered to minimize the care gap?
- What are optimal risk mitigation strategies for populations of younger female patients with increased atherosclerotic cardiovascular disease risk, such as those with polycystic ovary syndrome or adverse pregnancy outcomes?
- What is the optimal management strategy for secondary prevention of myocardial infarction with non-obstructive coronary arteries in female patients?
- What are the effects of long term hormonal therapy on cardiovascular risk and diseases in patients undergoing gender affirming care?

management of ACS and underlying causes, such as Takotsubo syndrome or SCAD, are essential to improving outcomes. Management strategies must consider biological differences as well as social and systemic factors that affect access to care for female patients. Further research on chest pain in female patients, such as the use of sex specific hs-cTn thresholds and the management of non-obstructive causes of CAD such as MINOCA, is needed to help to close the gap in cardiovascular care. Although AI has the potential to advance research on special populations, a risk exists that it will "learn" existing biases in research and continue sex related discrepancies in outcomes.

In taking into account patients' lived experiences with chest pain, we share the perspectives of three women, particularly highlighting what they would like their doctor to know.

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Web appendix: Supplementary table