ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2024) **00**, 1–21
https://doi.org/10.1093/ehjci/jeae013

EACVI DOCUMENT

Cardiovascular multimodality imaging in women: a scientific statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology

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Reviewers: This document was reviewed by members of the 2022–2024 EACVI Scientific Documents Committee: Pal Maurovich-Horvat, Ivan Stankovic, Alexios Antonopoulos, Theodora Benedek, Philippe Bertrand, Yohann Bohbot, Maja Cikes, Marc Dweck, Pankaj Garg, Niall Keenan, Aniela Monica Petrescu, Fabrizio Ricci, Alexia Rossi, Liliana Szabo, and Valtteri Uusitalo.

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Received 28 December 2023; accepted 31 December 2023; online publish-ahead-of-print 10 January 2024

Cardiovascular diseases (CVD) represent an important cause of mortality and morbidity in women. It is now recognized that there are sex differences regarding the prevalence and the clinical significance of the traditional cardiovascular (CV) risk factors as well as the pathology underlying a range of CVDs. Unfortunately, women have been under-represented in most CVD imaging studies and trials regarding diagnosis, prognosis, and therapeutics. There is therefore a clear need for further investigation of how CVD affects women along their life span. Multimodality CV imaging plays a key role in the diagnosis of CVD in women as well as in prognosis, decision-making, and monitoring of therapeutics and interventions. However, multimodality imaging in women requires specific consideration given the differences in CVD between the sexes. These differences relate

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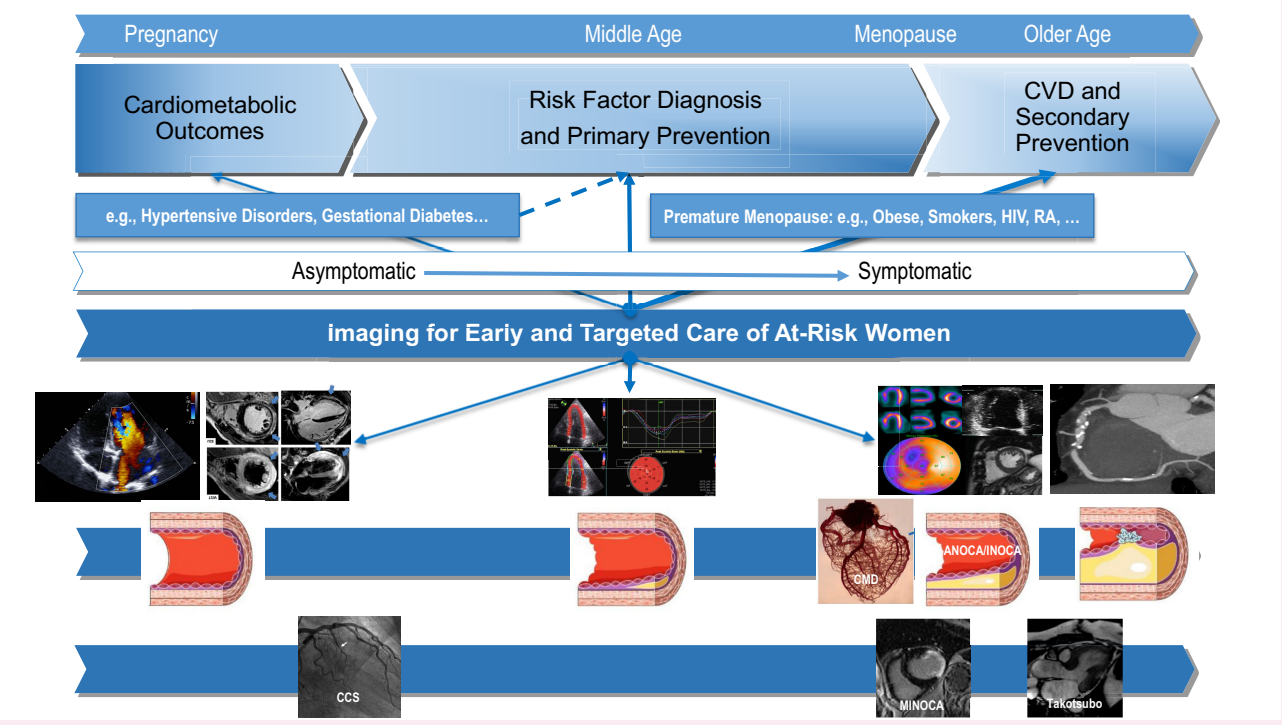
to physiological changes that only women experience (e.g. pregnancy and menopause) as well as variation in the underlying pathophysiology of CVD and also differences in the prevalence of certain conditions such as connective tissue disorders, Takotsubo, and spontaneous coronary artery dissection, which are all more common in women. This scientific statement on CV multimodality in women, an initiative of the European Association of Cardiovascular Imaging of the European Society of Cardiology, reviews the role of multimodality CV imaging in the diagnosis, management, and risk stratification of CVD, as well as highlights important gaps in our knowledge that require further investigation.

Graphical Abstract



Keywords cardiovascular diseases • women diseases • multimodality imaging • cardiovascular imaging

Introduction

Cardiovascular diseases (CVD) remain the number one cause of mortality globally both in males and females.[1] Across the European Union, CVD is the most common cause of death, exceeding the number of deaths from cancer, with ischaemic heart disease (IHD) accounting for 45% of these deaths in females and 39% in males.[2] At the same time, stroke and heart failure with preserved ejection fraction (EF) (HFpEF) are also both more prevalent in women than men as the first event.[3] Sex-related cardiovascular (CV) risk factors play a significant role in women, such as early menarche, early menopause, a history of miscarriage, stillbirth, or hysterectomy.[4] Myocardial angina (angina with non-obstructive coronary arteries, ANOCA) and ischaemia (ischaemia with no obstructive coronary arteries, INOCA) resulting from non-obstructive coronary artery disease (CAD) are more prevalent in women and are associated with adverse outcomes.[5] The same is true of myocardial infarction (MI) in the absence of obstructive CAD (MI with non-obstructed coronary arteries, MINOCA) or spontaneous dissection of the coronary arteries (SCAD), as well as non–ST-segment elevation MI (NSTEMI).[6]

There is also a higher prevalence of Takotsubo syndrome (TTS) in women, who have limited therapeutic options based on multicentre and randomized clinical trials.[7,8] Rheumatic heart disease and valvular sequelae also have a higher prevalence in women. Senile aortic stenosis (AS) is becoming more prevalent in both women and men, with particular considerations in women who have smaller valves and aortic roots, as well as a higher prevalence of low-flow states that require new strategies for diagnosis and therapy.[9] With respect to CVD management, women are subject to clear disadvantages compared with men, related not only to differences in disease presentation and female-specific characteristics but also to under-diagnosis and under-treatment. This treatment gap is probably due to a lack of awareness of sex-specific differences among both women patients and health professionals, as well as the lack of women representation in clinical trials.[10,11]

Appropriate multimodality imaging has a key role in the diagnosis and management of CVD in both sexes and the potential to have a clear impact on both clinical decision-making and long-term outcomes.[12,13] Of note, the use of CV imaging techniques in women has certain particularities that lead to differences in diagnostic performance compared with men. These relate to differences in pathophysiology and risk factors, smaller heart size and vessels, as well as different haemodynamic and remodelling responses to physiologic and pathological factors.[14–16]

Additionally, there are specific diseases and risk factors associated with pregnancy, breast feeding, and menopause, for example, peripartum cardiomyopathy (PPCM). These conditions occur specifically in women and often require specific multimodality imaging (MMI) approaches. In particular, they frequently raise specific issues related to the risk associated with radiation exposure and the administration of

radiotracers and contrast agents that influence which modality may be preferred.[17]

In this paper, we will review the role of MMI in the diagnosis of CVD in women, considering the diagnostic accuracy, limitations, advantages, and disadvantages of each of the CV imaging modalities, as well as, whenever possible, the optimal imaging algorithm for use in the types of CVD that most affect women. We will refer to sex differences as dictated by birth biology rather than gender and will use the terminology of men and women interchangeably with male and female.

Pathophysiological considerations of CV diseases in women

Risk factors

CAD and atherosclerosis starts later in women than men but has a more ominous prognosis. There are sex differences in both the prevalence and the impact of traditional CVD risk factors,[18,19] which account for 94% of the population-attributable risks of MI among women. Compared with men, women—especially younger (<55 years old) women—have a 25% increased risk for CAD due to cigarette smoking.[20] Hypertension is more predominant with age in women than in men with a greater prevalence in post-menopausal women than in men, yet it remains under-diagnosed and less well-controlled than in men.[21] This may be due to both sex effects, including genetic predisposition to medication side effects in women, and a sex bias in treatments. Women with diabetes have a two-to-four-fold excess risk of CAD and are an increased relative risk of heart failure compared with men.[22]

Dyslipidaemia contributes more strongly to the incidence of CVD in women than all other traditional risk factors for CVD[20] and is impacted by alterations in reproductive hormone levels during mid-life.[18] Of note, almost 50% of women have a clustering of ≥3 metabolic risk factors for IHD.

Besides traditional risk factors, rheumatologic diseases and psychosocial factors including depression, anxiety, as well as professional and family stress are all highly prevalent in women and have a more significant impact on CV risk than in men.[7] Lipoprotein(a) [Lp(a)] has been identified as a genetic risk factor in the development of CVD in both men and women and is inversely associated with oestrogen levels.[18]

Myocardial remodelling

Important differences in cardiac remodelling exist in men and women. After puberty, women maintain the same heart mass and number of heart muscle cells. In contrast, men present a 15–30% increase in heart weight, suggesting that their myocytes must undergo a greater degree of hypertrophy than do women myocytes.[23] Before menopause, in response to pathological stimuli, women show a more favourable profile concerning hypertrophy compared with men, with less concentric hypertrophy, fibrosis, and apoptosis,[24] as well as less inflammation. These responses are modulated by oestrogens and also by genetic/epigenetic mechanisms that influence the expression of overall CVD.[24] Oestrogen protection comes from counteracting pro-hypertrophy signalling pathways and is partially restored after early oestrogen replacement therapy in menopause. However, when hypertrophy ensues, it is a stronger risk factor for heart failure than in men.[15] Sex differences have also been observed with exercise, with women predominantly using fatty acid oxidation for myocardial energetics and tending to develop eccentric hypertrophy more often than men.

Oestrogens

The role of endogenous oestrogens in CV physiology and pathology remains an open issue, with incomplete knowledge of its effects on the endothelium and cardiomyocytes. Oestrogens protect the heart from cytotoxic, ischaemic, and hypertrophic stresses and together with oestrogens' receptors have a key role in the regulation of cardiac metabolism, attenuation of apoptosis, promotion of cardiac regeneration, and modulation of physiological and pathological left ventricular (LV) hypertrophy.[25]

Heart–brain interaction

There are established physiological interactions between the two organs that play important roles in potentiating diseases.[26] Sex- and gender-related differences modify those interactions, and this should be taken into account. For instance, the brain's stress network is a promising signalling pathway underlying the predisposition of women to mental stress–induced ischaemia and sympathetic over-activity. Hormones, neurohumoral activity, and systemic inflammation are potential mechanisms mediating sex differences in heart–brain interactions that may be used for new therapeutic strategies.

MMI for specific conditions in women

Pregnancy and CV risk

Pregnancy is related to many vascular, metabolic, and physiological adaptations and can be considered as a form of CV stress test[27] that can help identify patients at risk of developing future CVD complications and metabolic diseases. Understanding the risks associated with CVDs during pregnancy and its related management[28] in pregnant women who suffer from serious pre-existing conditions (e.g. congenital heart disease or advanced heart valve disease) is of pivotal importance for advising patients before pregnancy.[29] With regard to patients with valvular heart disease (VHD), the increased cardiac output will increase gradient across stenotic valves, while the increased circulating volume may increase volume loading in regurgitant lesions. The management of these patients is therefore frequently challenging and requires a multidisciplinary heart team approach.[30]

Expected changes to cardiac structure and function in pregnancy include an up to 6% relative increase in LV end-diastolic diameter and up to 13% increase in left atrial diameters, a mean absolute increase of 25 g in LV mass (LVM) in normotensive pregnancy (with a mean increase of 92 g in hypertensive pregnancy), and an increase in right ventricular (RV) diameters.[31] In pregnancy, plasma volume and cardiac output increases by up to 40–50% above baseline at 32 weeks of gestation. Atrial and ventricular diameters increase, while ventricular function is preserved. Maternal cardiac dysfunction may lead to impaired uteroplacentar flow.[30] Furthermore, systemic and pulmonary vascular resistance both decrease during pregnancy.[32]

For the assessment of both previous and new CVD, echocardiography, and cardiovascular magnetic resonance (CMR) are safe in pregnancy and are not associated with any adverse foetal effects.

Echocardiography is the first-line imaging tool for the assessment of ventricular function and the detection and monitoring of CVD in pregnancy. Although there is still a need for further studies, in pregnant women with pre-existing CVD, current recommendations suggest cardiac imaging with echocardiography each trimester, with greater frequency in challenging clinical cases.[33] Cardiac imaging is also crucial for the appropriate diagnosis of CVD acquired during pregnancy. When echocardiography alone is insufficient, the use of CMR is a safe option.[34] However, the use of gadolinium-based contrast agents is controversial since these agents may cross the placenta and the risk to the foetus must be balanced against the benefit both to the mother and the foetus[35] (*Table 1*). Of note is the importance of the pregnant woman's position during image acquisition, since in the supine position, the gravid uterus can compress the inferior vena cava, which may affect cardiac output. The left lateral tilt position in the case of echocardiography should prevent this.

Table 1 MMI of coronary artery disease in pregnancy, pre-eclampsia, and menopause

	Pathophysiology	Echo	CMR	CCT	Nuclear
Pregnancy	PV/CO increase up to 40–50% at 32 weeks' gestation. Atrial/ventricular dimensions increase. LVEF is preserved.	**Advantages** Safe First-line method **Indications** Pre-eclampsia and novel and pre-existing CVD	**Advantages** Useful when echo inadequate Safe **Disadvantages** Gadolinium to be avoided	**Advantages** Alternative if echo/CMR cannot be employed **Disadvantages** Radiation exposure to be advised	**Advantages** Alternative if echo/CMR cannot be employed **Disadvantages** Radiation exposure to be advised
Pre-eclampsia		**Advantages** Detects LVH, LVEF, and LV diastolic dysfunction	**Advantages** Useful for detection of LV and calculation of LV volumes and EF		
Menopause	Vascular dysfunction Inflammation Up-regulation RAA	**Advantages** Stress echo (post-menopausal) for CAD exclusion	**Advantages** Stress CMR (post-menopausal) for CAD exclusion	**Advantages** Exclude CAD Coronary artery calcium score for risk stratification	**Advantages** Exclude CAD

Echo, echocardiography; CMR, cardiovascular magnetic resonance; CCT, cardiac computed tomography; nuclear, nuclear cardiology techniques; CO, cardiac output; LVH, left ventricular hypertrophy; LV, left ventricle; RAA, renin–angiotensin–aldosterone; CAD, coronary artery disease.

Different types of hypertensive disorder (HPD) may occur during pregnancy, namely chronic hypertension, gestational hypertension, and pre-eclampsia, that may each have an important clinical impact. Of note, treatment options are limited during pregnancy. Compared with normotensive pregnant women, women with HPD have up to eight-fold increased risk of future chronic hypertension,[28,36] especially within 1–5 years after pregnancy.[37–39] By the age of 50 years, this risk became similar. Echocardiography provides important information on LV wall thickness and diastolic function and will highlight the degree of any hypertension-induced cardiac systolic impairment.

Women with HPD also have an increased risk of insulin resistance and of developing diabetes later in life. A large Canadian study including 1 million women with a median follow-up of 8.5 years[39] found that women without gestational diabetes were more likely to develop diabetes after gestational hypertension (3.9%) or pre-eclampsia (6.6%) than after a normotensive pregnancy (2.5%). A register-based cohort study also demonstrated that the fully adjusted risk of type 2 diabetes 14.6 years after pregnancy was 3.1-fold for women with gestational hypertension and 3.7-fold after pre-eclampsia.[27]

The guidelines advise annual follow-up of blood pressure and metabolic factors in these patients.[28,39] At 50 years, all women, including those with HPD, qualify for regular CV risk assessment.[38,40]

Menopause and CVD

Despite recent improvements in mortality, CAD continues to be the leading cause of death and disability among elderly and middle-aged women, with a mortality rate that increases three- to five-fold times with each decade of life. It has been reported that women with intact ovarian hormonal function have a lower incidence of coronary disease up to 15 years after menopause.[41] A subanalysis of the multicentre study WISE study also showed that pre-menopausal women with hypo-oestrogenaemia had more angiographic coronary disease.[42] The life expectancy of a woman in Europe is currently around 80 years. Therefore, almost half of an average women's life is spent in menopause and without the potentially protective effects of oestrogen. Lower oestrogen levels after menopause are related to vascular dysfunction, inflammation, and up-regulation of both the renin–angiotensin–aldosterone and the sympathetic nervous systems all contributing to increased CV risk.[43] Early menopause has also been linked to increased heart failure risk.[44]

A recent meta-analysis from a Finnish register showed that initiating menopause hormone therapy within 10 years of the onset of menopause significantly reduces MI and death by around 50%, but this is still a controversial subject.[45]

Depending on symptoms, women will be risk stratified and follow the IHD diagnostic pathway, as it is described below regardless of their menopausal state. It has been advised to assess the coronary artery calcium score (CACS) in women at intermediate CV risk, since this technique has been found to have a higher prognostic value than in men[46] (*Table 1*).

Radiotherapy and chemotherapy for cancer

Beyond traditional risk factors for CVD, chemotherapy (CHT) and radiotherapy (RT) for cancer are specific risk factors in women, as well as men, due to their cardiotoxicity. An increased risk of developing cardiac dysfunction has been most closely evaluated in patients with breast cancer undergoing treatment with anthracycline-based chemotherapy, targeted trastuzumab therapy, and left-sided breast cancer RT. Breast cancer survivors are more likely to die due to CVD. Thus, detailed evaluation of CHT- and RT-related side effects is particularly important in breast cancer and other gynaecological cancers typical for women.

The cardiotoxicity of cancer therapy in women is defined as any reduction of left ventricular ejection fraction (LVEF) by echocardiography to below 50% or as a >10% reduction from baseline falling below the lower limit of normal values (54%) for women.[47,48] An early sign of cardiotoxicity assessed by LV global longitudinal strain (GLS) is defined as a relative reduction in GLS by >15% from baseline.[24,25,40,41] GLS has become an accurate echocardiographic marker for the prediction and early detection of cardiotoxicity and a guide for the initiation of cardioprotective therapies in women with breast cancer.[47,49,50]

Table 2 MMI in women with cancer undergoing chemo- and radiotherapy

Pathophysiology	Echo	CMR	CCT	Nuclear
Cardiac dysfunction (cardiotoxicity)	TTE: method of choice before, during, and after cancer therapy LVEF, LV GLS, masses, pericardium 3D echo: LV GLS Stress echo: LV contractile reserve and exclusion of CAD	Echo inadequate or inconsistent High reproducibility Myocardial perfusion and exclusion of CAD Myocardial fibrosis/scar for suspected myocarditis/MI Tissue viability Pericardial diseases Cardiac masses	Risk stratification CAD exclusion	Generally not advised due to radiation exposure

Echo, echocardiography; TTE, transthoracic echocardiography; CMR, cardiovascular magnetic resonance; CCT, cardiac computed tomography; nuclear, nuclear cardiology techniques; MI, myocardial infarction; see abbreviations of *Table 1*.

The European Association of Cardiovascular Imaging (EACVI) has proposed that cancer patients should be assessed before receiving particular potentially cardiotoxic therapies in order to stratify their risk of cardiotoxicity based on both therapy- and patient-related factors.[47,51] Cardiotoxicity may be studied with various imaging techniques. Two- and three-dimensional transthoracic echocardiography (TTE) is the method of choice for the evaluation of cardiotoxicity in cancer patients before, during, and after cancer therapy. LVEF and LV GLS are the best-established echocardiographic parameters of systolic function.

Important sex-related differences are worth considering in these studies, in particular that women are more likely to have smaller remodelled hypertrophic ventricles with perceived increased contractility, higher heart rates, supraventricular arrhythmias, and presence of the HFpEF. These may all influence the echocardiographic examination, most notably in regard to LVEF measurements which may overestimate cardiac systolic function and miss the early stages of cardiotoxicity particularly in the setting of regional wall motion abnormalities.[52] It has therefore been proposed that GLS measured by 2D speckle tracking and the wall motion score index (WMSI) are used as additional, more sensitive indicators of systolic function alongside LVEF to detect therapy-related changes in cardiac function.[53,54] Of note, GLS values have been found to be slightly higher in women than men for the same equipment vendor.[48,55] GLS reduction together with increases in WMSI and LV dimensions has demonstrated strong prediction for the development of cardiotoxicity in women with breast cancer receiving CHT.[55] The role of left atrial strain remains unclear. While left atrial strain has been found to be predictive of events in populations of healthy women, no data are available with respect to cardiotoxicity.[56] There have been no significant sex-related differences involving the valves on preventing and monitoring cancer cardiotoxicity. 3D echocardiography has a better accuracy for the detection of minor LVEF changes and a higher reproducibility compared with 2D.[57] 3D speckle tracking imaging (3D STI) may be useful for the evaluation of LV systolic function, in particular, in detecting early changes in LV systolic function.[58] Further studies with these 3D techniques are required in cardiotoxicity. Similarly, the role of left atrial strain remains unclear. While it has been found to predict events in healthy women, no data are available with respect to cardiotoxicity.[56]

TTE image quality may be inadequate due to the effects of RT, left-sided mastectomy, or a left breast prosthesis. Therefore, contrast echocardiography or CMR, according to guidelines, should be considered for the quantification of LVEF and ventricular volumes, given their better test–retest variability. CMR is also a useful diagnostic tool in cancer patients for the assessment of myocardial perfusion, suspected myocarditis (e.g. in patients on checkpoint inhibitors), myocardial perfusion, fibrosis, tissue viability, pericardial diseases, and cardiac masses.[47,51] Increases in myocardial T1 and T2 relaxation times at follow-up after epirubicin-based chemotherapy may indicate myocardial injury.[59] Circumferential strain can also be assessed by CMR, showing reductions during trastuzumab treatment in breast cancer.[60] Regardless of the imaging modality, the recommendation is to use the same technique for baseline and all follow-up exams for consistency and accurate comparisons.[61] Nuclear imaging is no longer recommended for cardiotoxicity detection as a first-line cardiac imaging modality in women with cancer due to the high associated radiation exposure.[47,62]

Transoesophageal echocardiography (TOE) and 2D and real-time 3D echocardiography are excellent imaging modalities for the diagnosis of non-bacterial thrombotic endocarditis or infective endocarditis which can also be complications of CHT in oncologic patients, frequently found in ovary adenocarcinoma.[47]

Moreover, both CHT and RT are considered risk factors for CAD in women. Due to the lack of radiation combined with high negative predictive value and safety, functional imaging with stress echocardiography, using either exercise, dobutamine, or pacing, is useful for the evaluation of ischaemia without radiation exposure in female patients with cancer.[18,63] A higher rate of positive stress test results was found in women irradiated for left breast cancer compared with those with right-sided disease.[48] Stress echocardiography may also be used to evaluate the contractile reserve to predict outcomes in women with cardiac dysfunction related to cancer therapy.[64,65] Stress perfusion CMR is an alternative functional imaging test of particular use when further information on myocardial characterization is needed (e.g. when myocarditis is suspected) or when precise functional assessment and follow-up are required.[51] Cardiac CT may be useful for diagnosis and risk stratification using CT CACS and coronary CT angiography (CCTA) which allows direct visualization of coronary atherosclerosis.[66] The diagnostic information provided by imaging modalities is presented in *Tables 2* and *3*. A representative case is presented in *Figure 1*.

In conclusion, echocardiography, with the benefit of new techniques, is the first choice method for the evaluation and surveillance of female cancer patients treated with cardiotoxic therapies. As an alternative to echocardiography, CMR is considered a gold standard method for evaluating ventricular volume, mass, and function, also providing additional data on tissue viability, fibrosis, inflammation, and ischaemia. Patients should be followed with the same echocardiography machine for baseline assessment and all follow-up exams.

Autoimmune rheumatologic diseases

Autoimmune rheumatologic diseases (ARD) predominantly affect women. Differences in sex hormones, genetics, and environmental factors

(including oestrogens) between men and women have been proposed as underlying mechanisms for this observation.[67] The European Society of Cardiology (ESC) 2021 primary prevention guidelines highlight a disproportionately increased risk of CVD in the setting of ARD.[68] Notably, CV involvement in ARDs may affect the valves, microvasculature, pericardium, myocardium, and large vessels. Accelerated atherosclerosis triggered by inflammation is associated with excess mortality in rheumatoid arthritis (RA)[69] and premature MI and stroke in systemic lupus erythematosus (SLE).[70] Significant under-estimation of CV event risk by classical risk scoring systems,[71] atypical presentations, resting electrocardiogram (ECG) abnormalities, limited exercise capacity, silent episodes, and sudden cardiac death[67,72] justifies the diagnostic role of MMI and suggests that screening with imaging may also be helpful. In particular, among patients with ARD, those having SLE or RA are considered in a high-risk category for CAD akin to diabetic patients.[4,73]

The American College of Cardiology (ACC)/American Heart Association (AHA) primary prevention guidelines recommend considering carotid ultrasound and CACS, respectively, as additional tools to re-classify risk estimate among individuals at borderline and intermediate risk.[74] The use of carotid ultrasound in ARD helped to re-classify RA patients into more appropriate CV risk groups and also revealed rapid disease progression and the association of atherosclerotic plaques with high levels of systemic inflammation.[75,76]

CCTA has demonstrated an increased incidence of silent coronary atherosclerosis in patients with RA, SLE, and psoriatic arthritis,[77] although the associated radiation exposure in young women with no CV symptoms should be advised. Stress echocardiography and stress CMR are sensitive to detect ischaemia in women with ARD, while single-photon emission computed tomography (SPECT) scintigraphy is less so because of small ventricles and breast tissue attenuation. Positron emission tomography (PET) with rest–stress quantification of myocardial blood flow (MBF) is the most accurate technique to quantify regional MBF and coronary flow reserve (CFR) but is again associated with radiation exposure. Coronary flow reserve assessment by transthoracic Doppler echocardiography seems promising in detecting non-atherosclerotic vascular involvement.

ARD can lead to myocardial damage including inflammation, microvascular dysfunction, and fibrosis. These can lead to CV complications and symptoms in women with ARD including the development of heart failure.[78,79] Echocardiography with strain is very sensitive for detecting

Table 3 Cardiotoxicity diagnosis using MMI

	Echo	CMR	CCT	Nuclear
Ventricular volumes and function	+++[a]	++++	+	++
Ventricular deformation/strain	++++	+++/++++	–	–
Tissue characterization	++	++++	+	++
Myocarditis	–	++++	–	+++/++++
Pericardial disease	+++	++	+++	–
Valve disease	++++	++/+++	+	–
Coronary artery disease	+++	+++	+++	+++

Echo, echocardiography; CMR, cardiovascular magnetic resonance; CCT, cardiac computed tomography; nuclear, nuclear cardiology techniques.
[a]3D more reproducible than 2D.

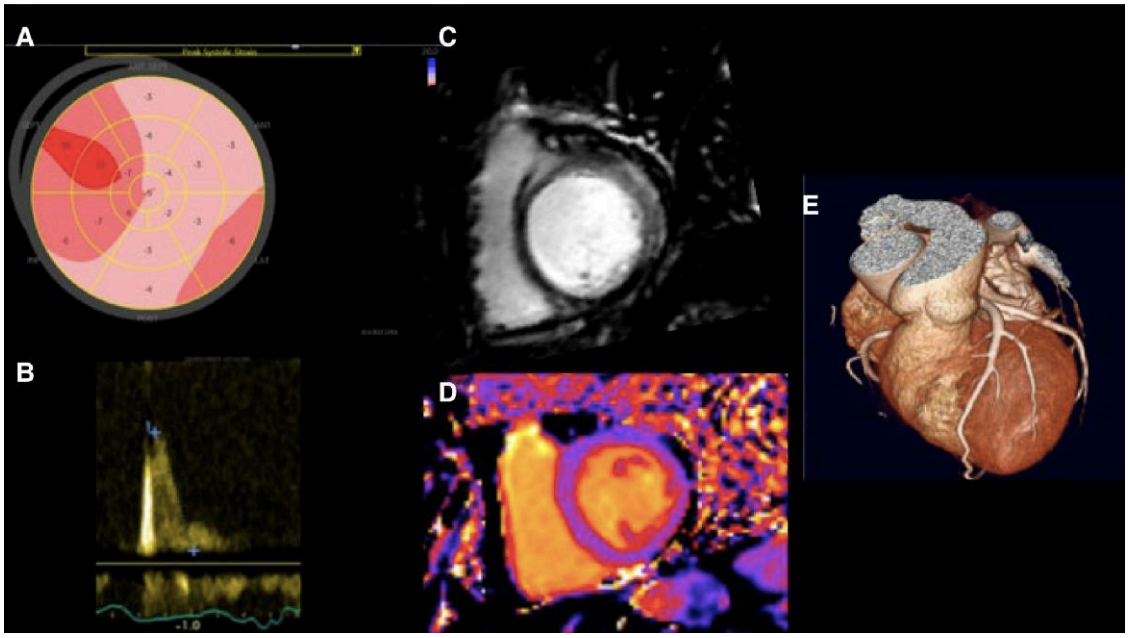


Figure 1 A case of cardiotoxicity. A 45-year-old woman presented with heart failure 1 year after chemo- and radiotherapy following a breast cancer diagnosis. Echocardiography showed LVEF mildly depressed (51%), GLS severely depressed (−7%) (*A*), and restrictive pattern mitral inflow (*B*). CMR depicted midwall/subepicardial LGE at the anterior, lateral, and inferolateral walls (*C*), increased native T1 values (*D*), and ECV (34%) representing focal and interstitial fibrosis. A CCTA (*E*) excluded coronary artery disease. LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; T1, myocardial relaxation constant T1; ECV, myocardial extracellular volume; CCTA, cardiac computed tomography angiography.

Table 4 MMI of cardiovascular involvement in autoimmune rheumatologic diseases

Pathophysiology	Echo	CMR	CCTA	Nuclear
Inflammation Fibrosis CMD CAD CMP Valvulopathy Pericarditis	TTE Strain patterns for CMP Stress echo for CAD Doppler/CFR for CMD	Perfusion for patchy defects LGE and mapping for fibrosis patterns T2/mapping for inflammation Stress CMR for ischaemia (CAD/CMD) Pericardial disease and arterial inflammation	Coronary calcium score: risk re-classification, more predictive in women Obstructive and non-obstructive CAD, more frequent in women vs. men	PET for myocardial flow reserve (CMD, more frequent in women vs. men) PET for myocardial inflammation (e.g. sarcoidosis) SPECT for ischaemia (CAD), radiation Vascular inflammation

Echo, echocardiography; CMR, cardiovascular magnetic resonance; CCT, cardiac computed tomography; nuclear, nuclear cardiology techniques; CAD, coronary artery disease; CMD, coronary microvascular disease; CRF, coronary reserve flow; SPECT, single-photon emission computed tomography; PET, positron emission tomography.

subclinical myocardial dysfunction and monitoring anti-inflammatory treatment effects in ARD.[80] CMR allows detection of patchy perfusion defects as well as differentiation of ischaemic and non-ischaemic patterns of myocardial fibrosis. CMR, PET, and PET/CMR can add information about ongoing inflammatory activity in the heart muscle as well as the vasculature in cases of suspected vasculitis or myocarditis.[81]

Acute valvular pathology is sometimes the initial presentation in ARD, particularly in SLE and ankylosing spondylitis.[82] Patients also carry a high risk of infective endocarditis because of immunosuppressive therapy. As well as being an independent cause of stroke and mortality, antiphospholipid antibody positivity increases the risk of VHD and non-bacterial vegetations, often requiring the use of TOE to confirm the diagnosis in suspected cases. Pulmonary arterial hypertension (PAH) is also an important cause of mortality in women with ARD, particularly in systemic sclerosis where yearly screening is recommended by the 2022 ESC/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension.[83]

Pericardial effusions and pericarditis are common in ARD, although usually without causing significant haemodynamic compromise. Echocardiography, CMR, or CCTA are appropriate to assess symptomatic patients. *Table 4* summarizes the role of MMI in women with ARD.

Ischemic heart disease and chronic coronary syndromes

Coronary atherosclerotic disease: obstructive and non-obstructive

Invasive coronary angiography (CA) is used as a first-line diagnostic procedure for high-risk women presenting with chronic chest pain. For the lower/intermediate risk woman, non-invasive CCTA and a functional diagnostic test by echocardiography, nuclear imaging, or CMR are recommended procedures in the evaluation of suspected CAD, similar for both sexes.[84]

Both CCTA and invasive angiography allow assessment of obstructive and non-obstructive coronary plaque. With respect to obstructive plaque, consistent data demonstrate a graded relationship between outcomes and the burden of coronary atherosclerosis as assessed by the number of vessels with an obstructive stenosis. Indeed, women, similar to men, have an elevated hazard for CAD events in the setting of more extensive, obstructive multivessel CAD.[46,85]

However, non-obstructive CAD appears to be of particular importance in women. Indeed, for women undergoing invasive or non-invasive CA, the frequency of non-obstructive CAD is decidedly higher than in men.[86] For women referred to invasive CA, about half have non-obstructive CAD; this rate is much higher for lower risk women undergoing CCTA and is generally in the range of 80–90%.[87] Importantly, the burden of non-obstructive plaque is also associated with risk of future CV events.

Several studies have compared prognosis among women with non-obstructive CAD (coronary stenosis from 1% to 49%) with those without any plaque or stenosis.[88] From the CONFIRM registry, non-obstructive CAD on CCTA worsens mortality and CAD event risk,[80] namely with non-obstructive left main stenosis[89] and among women who are more than 60 years old.[90] The higher the number of segments with non-obstructive plaque, the higher the CAD event risk both in women and men.[85]

Suspected CAD in women may be assessed both by anatomic and functional testing. There have been several studies comparing risk associated with anatomic tests as compared with ischaemic tests. In the PROMISE trial ($n = 8966$), 92% of women in the CCTA arm of the trial had non-obstructive CAD, while 88% of women in the functional testing arm had an abnormal stress test ($P < 0.001$).[91] Additionally, the relative hazard for risk for outcomes was 10-fold increased in the presence of obstructive CAD as compared with normal coronaries on CCTA ($P < 0.001$), whereas the hazard ratio for an abnormal vs. normal stress test was only 5 ($P = 0.002$). When examining an interaction, event risk was significantly elevated with CCTA as compared with stress testing for women ($P = 0.043$). These findings suggest that CCTA provides better prognostic information than functional testing in women. In the CE-MARC trial, in patients with suspected angina and with a prevalence of obstructive CAD of 23% in women vs. 50% in men, sensitivity and specificity of CMR was similar in women and men. In contrast, sensitivity was significantly lower for SPECT in women than in men, with similar specificity.[92] Interestingly, in CT fractional flow reserve (FFR_{CT})-positive CAD, women have less obstructive CAD at CA and less revascularization showing the need for different interpretations in both sexes.[93]

Also, there is increasing evidence with regard to sex differences in atherosclerotic plaque, namely a different aetiology for acute coronary syndromes (ACS) with plaque erosion vs. rupture occurring more in women vs. men.[94,95] A smaller plaque burden with less calcification and less positive remodelling[96,97] occurs in women in comparison with men.

Using non-invasive CCTA for anatomic assessment, data are available with regard to the prognostic value of high-risk atherosclerotic

plaque features (e.g. low attenuation plaque, positive remodelling, or a napkin ring sign) in women and men, particularly those with non-obstructive CAD, as precursor features of an ACS.[95,98,99] From the PROMISE trial, these high-risk plaque features were significantly predictive in women but not men. In a report from the SCOT-HEART trial, the risk of incident MI was elevated 6.6-fold among patients who had a high burden of low attenuation plaque (a marker of necrotic core).[100,101] While women overall had a lower plaque burden than men, a threshold of low attenuation plaque > 4% was as strong a predictor of subsequent MI in women as in men.

In summary, in women undergoing invasive or non-invasive CA, the frequency of non-obstructive CAD is higher than in men; moreover, in FFR_{CT}-positive CAD, women have less obstructive CAD at CA and less revascularization referral. Women have a lower plaque burden than men, but where present, the burden of low attenuation plaque appears of similar prognostic value in women as men.

From the presented data, the need for further studies to establish the optimal insights for the appropriate diagnostic and risk stratification strategy in women with suspected CAD is clear.

Ischaemia from non-obstructive coronary artery disease: ANOCA/INOCA

Despite signs and symptoms suggestive of myocardial ischaemia, women have at least twice higher prevalence of ischaemia and angina with non-obstructive CAD (ANOCA/INOCA) as confirmed from CCTA than men.[102] In a study of stable angina and ANOCA/INOCA, 70.2% of female vs.[103] 43.1% of male patients had coronary microvascular dysfunction (CMD) or epicardial artery vasospasm,[104] the two main endotypes of ANOCA/INOCA, according to the current concepts as proposed by the COVADIS group.[105] INOCA is associated with a significant risk of major adverse CV events[86,103] with an annual major adverse CV event rate of 2.5% present in women with CMD.[106] Of note, CMD is a strong determinant of prognosis, even in patients with coronary stenosis of intermediate severity.

Patients with coronary vasospasm are frequently younger and have fewer CV risk factors than patients with effort angina.[4,64] Diagnosis is based on ST-segment elevation on the ECG (or Holter monitoring) during the chest pain episode, but confirmation needs angiographic documentation of coronary spasm upon a provocation test with intracoronary administration of acetylcholine or ergonovine.[107]

The WISE study, among others, showed that CMD plays an important role in INOCA in women, suggesting the need for a different diagnostic and therapeutic strategy in females.[106] CMD is defined as limited CFR and/or coronary endothelial dysfunction at microvascular level, underlying myocardial ischaemia in the absence of significant obstructive epicardial CAD. Microvascular remodelling, microembolization, as well as the smaller calibre of coronaries and lower vascular density are proposed as the main mechanisms associated to CMD in women.[108]

For the diagnosis of CMD, general recommendations propose the following criteria:[109] (i) presence of symptoms and objective evidence of ischaemia, (ii) absence of obstructive coronary disease, and (iii) evidence of impaired coronary microvascular function: impaired CFR, abnormal coronary resistance indices, coronary microvascular spasm, and coronary slow flow phenomena. So far, the reference method is the invasive testing of CFR and the index of microvascular resistance (IMR) using acetylcholine and adenosine to assess for endothelial-dependent and endothelial-independent dysfunction.[108] Thresholds for an abnormal CFR cut-off have been defined as <2.0 and >5 units for microvascular resistance > 25 units. This assessment is, however not routinely used in the clinical setting in most centres with non-invasive testing often preferred.

Among the non-invasive techniques, PET with vasodilator stress is considered the gold standard non-invasive method to diagnose CMD, although it uses radiation, has limited availability, and is costly. Myocardial flow reserve (MFR) by PET has been validated against both invasive assessments[110] and against outcomes. Indeed, PET assessments of MFR are independently associated with increased CV risk in women.[111]

An alternative non-invasive modality for assessing CFR is CMR, which allows the qualitative diagnosis and quantitative assessment by measuring the CFR, microcirculatory perfusion index (MPI), and perfusion resistance index (MPRI) all of which correlate well with invasive measurements and provide important prognostic information.[112,113]

CFR may also be assessed by stress Doppler echocardiography, which can measure the maximal diastolic flow in the left anterior descending coronary artery at rest and during adenosine or dipyridamole stress. This technique has been validated against intracoronary Doppler measurements and outcomes, with cut-offs similar to invasive testing; however, it can be challenging to perform and is not widely used.[114] Myocardial contrast echocardiography also shows a particular value for CMD evaluation, delivering MBF velocity and CFR, but the lack of widespread experience and absence of approval from the regulatory agencies for this purpose has presented a limitation for its universal use.

Cut-offs for diagnosis of CMD using the available non-invasive techniques are currently being reviewed, and consideration is being given to the possible differences between women and men,[115] with smaller vascular diameter in women and suggested higher resting coronary blood flow than in men. This will likely influence the values of CRF in women, but there is a need for further studies for cut-off establishment in women.

In the last years, elevated pro-inflammatory mediators were found to be associated with lower CFR.[108] However, evidence on their association to CMD severity and prognosis is still lacking and does not include a comparison between sexes.

In summary, given the high prevalence of ANOCA/INOCA in women, the absence of obstructive coronary lesions by CA or CCTA in cases of suspected ischaemia from clinical and ischaemia tests should lead to consideration of further functional testing for assessing the possibility of coronary microvascular disease or vasospasm.

Ischaemic heart disease and acute coronary syndromes

Acute coronary syndromes: conventional presentations

ACS present significant disparities between men and women. These differences refer to anatomical, physiological, biological, and psychosocial factors which affect each other. As mentioned above, there is increasing evidence regarding sex differences in atherosclerotic plaque. In fact, the pathologic and invasive angiographic literature suggests varied aetiology for ACS, with plaque erosion occurring more in women vs. plaque rupture in men.[94,95,116]

Consistent with the anatomic data among women, plaque erosion occurs more often with a smaller plaque burden, which is often not calcified and which demonstrates less positive remodelling.[95,96] In a subanalysis from the PROSPECT study, plaque rupture occurred less often in women ($P = 0.002$).[89,116] Additional contributors to the unique risk profile in women include smaller vessel size as well as the role of microvascular disease.

Women present with a similar constellation of symptoms as men even though women more frequently present with alternative underlying aetiologies such as SCAD. However, in spite of a considerable overlap of symptoms at presentation, women do have different symptoms than men, considered 'atypical' (like back pain, nausea and vomiting, or shortness of breath), that can delay the suspicion of ACS.[117] No differences in the accuracy of the diagnostic tools between sexes have yet been described.

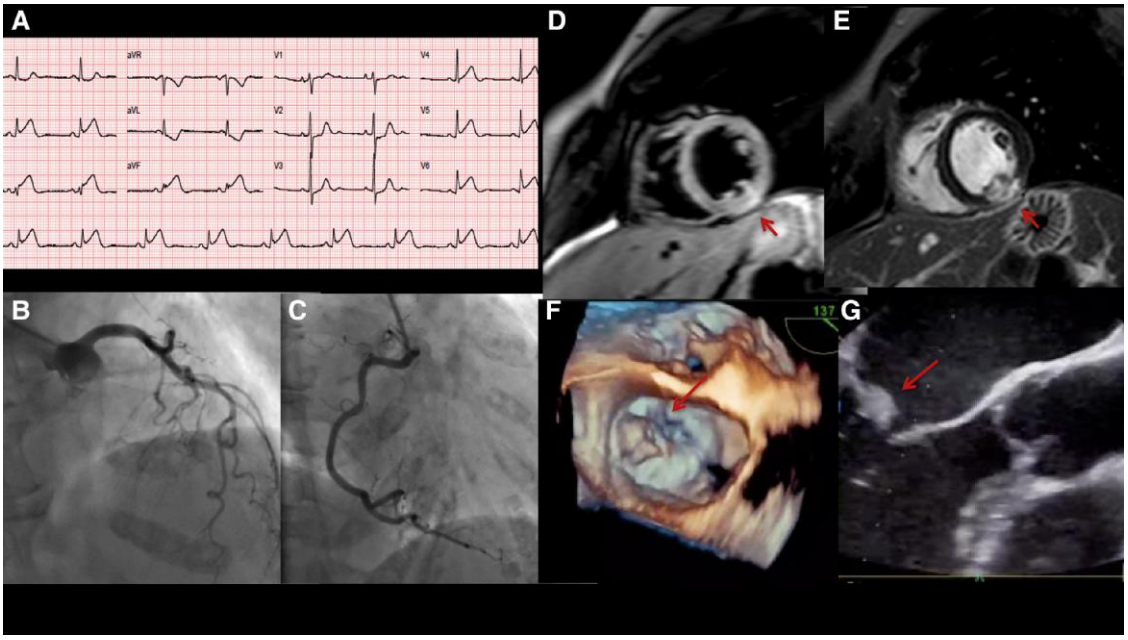


Figure 2 A representative case of MINOCA. A 45-year-old woman with systemic lupus erythematous under treatment with corticosteroids, presented at the emergency with acute chest pain and raised troponin. (*A*) ECG at admission, with ST elevation at inferior leads. (*B* and *C*) Coronary angiography with no coronary lesions. (*D* and *E*). CMR short-axis images on T2-weighted depicting oedema and subendocardial LGE depicting necrosis at inferior wall. (*F* and *G*) 3D and 2D TOE showing a marantic vegetation likely cause of coronary embolism. CMR, cardiac magnetic resonance; T2, myocardial relaxation constant T2; LGE, late gadolinium enhancement; TOE, transoesophageal echocardiography.

Regarding risk factors, according to the EPIHeart cohort study,[118] women more frequently had hypertension (81.5% vs. 62.7%, $P < 0.001$) and diabetes (38.8% vs. 29.9%, $P = 0.014$) and were more frequently obese (25.5% vs. 18.5%, $P = 0.020$) and never-smokers compared with men ($P < 0.001$). Despite their presentation, women were generally referred later for CA and received less invasive and aggressive pharmacological treatment when compared with men.[118] Over the last decade, there has been an increasing interest in ACS and women. There is now a need for larger studies, and therefore, greater representation of women in clinical trials is imperative, and larger studies will highlight the importance of early identification of IHD in women.

MINOCA

MINOCA is present in up to 6–15% of patients with ACS and non-obstructive coronary arteries on invasive CA and has a non-negligible 12-month all-cause mortality rate of 4.7%.[113,119] It disproportionally affects women, with women having five times higher odds of having MINOCA than men, according to the VIRGO study.[120]

Suspected MINOCA is a working diagnosis with multiple potential causes requiring further evaluation and often reflects the group of patients with a suspected ACS diagnosis who are then found to have non-obstructive plaque on invasive angiography. The differential diagnoses is wide and includes patients who have a true final diagnosis of MINOCA (type 1 MI, plaque rupture/erosion; type 2 MI, coronary spasm, SCAD, and coronary emboli) and those with non-ischaemic aetiologies [myocarditis, TTS, and non-ischaemic cardiomyopathies (CMP)].

The management and prognosis differ significantly depending on the underlying aetiology of the final diagnosis of ischaemic and non-ischaemic aetiologies and are independent from sex.[121] Establishing an accurate final diagnosis is therefore crucial for both sexes and differ significantly with the worse prognosis seen in patients presenting with ST elevation on ECG coupled and those with a CMR diagnosis of CMP.[121] The 2017 ESC ST-segment elevation MI (STEMI) guidelines presented two diagnostic pathways for MINOCA: a non-invasive approach using echocardiography and CMR or an invasive approach using intravascular ultrasound (IVUS) and/or optical coherence tomography (OCT).[122] The 2018 fourth definition of MI[123] further emphasized the crucial role of imaging (particularly CMR) in identifying the correct underlying condition. Finally, the 2020 ESC NSTEMI guidelines[65] now recommend CMR in all MINOCA cases without an obvious underlying cause.

Data on comparative imaging approaches and sex differences in suspected MINOCA are limited, but while echocardiography and CMR are most used in clinical practice, the nuclear cardiology techniques and CCTA also can also prove helpful with a distinctive role. Echocardiography can assess the presence and extent of global and regional wall motion abnormalities and the presence of pericardial effusion and other forms of CMP, as well as the characteristic appearances of TTS. CMR is a critical diagnostic imaging tool in the assessment of patients with a working diagnosis of MINOCA, due to the unique myocardial tissue characterization (myocardial inflammation/oedema, scarring/fibrosis) and the ability to discriminate between each of the possible underlying ischaemic and non-ischaemic aetiologies. CMR can identify the underlying aetiology in up to 87% of patients with MINOCA,[124] demonstrating a clinical impact (change in diagnosis and/or change in management) in ~70% of patients.[125] The CMR diagnosis of myocarditis is based on the updated 'Lake Louise criteria' of myocardial oedema, hyperaemia, and fibrosis using a combination of traditional and parametric mapping techniques.[126] Although there are no differences in the CMR diagnostic criteria for myocarditis in women vs. men, sex differences are noted, in particular related to the subsequent risk of chronic dilated cardiomyopathy (DCM). Myocarditis is

more common in men than in women, but there are other differences such as the older age of women with myocarditis.[127]

Takotsubo syndrome is an increasingly recognized differential diagnosis in patients presenting with a working diagnosis of MINOCA. As detailed below, it may present as MINOCA whenever troponins are raised, leading to suspected MI. TTS is more prevalent in women and is often precipitated by an emotional or physical stress with a characteristic akinesia/ballooning of the mid-apical cavity, although sometimes other regional wall motion abnormalities in the basal or mid-cavity segments can be observed. Echocardiography can detect additional specific findings such as LV outflow tract obstruction, mitral regurgitation (MR), and RV involvement,[128] while serial speckle echocardiography can document the progressive functional LV recovery in LV function and resolution of the wall motion abnormalities which serves to confirm the diagnosis from baseline to Week 5 after discharge.[129] CMR has added diagnostic value in TTS, detecting myocardial oedema (typically a transmural pattern) in regions with wall motion abnormalities, in the absence of myocardial scarring.[130] Of note, MINOCA characterization is time-sensitive so that prompt appropriate imaging, ideally while the patient is an inpatient, should be performed.[125]

The role of CCTA in MINOCA is limited to ruling out obstructive CAD in patients presenting with ACS not requiring an urgent invasive angiography. However, Gaibazzi *et al.*[131] recently showed evidence of altered pericoronary fat attenuation detected by CCTA in patients with TTS, a finding typically associated with coronary artery inflammation. Although the role of nuclear imaging in TTS has not yet been well established, the combination of perfusion and metabolic imaging can provide useful information on sympathetic activity and myocardial function in both the acute and post-acute phases.[132] A case of MINOCA is presented in *Figure 2*.

Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) can be defined as an epicardial coronary artery wall disruption unrelated to atherosclerotic plaques, iatrogenic, or traumatic lesions.[133] The prevalence of the disease is still poorly known, mostly due to its under-diagnosis. However, the rate derived from recent registries and case series seems higher than previously estimated. Although SCAD can affect both sexes, more than 90% of patients are women, with a mean age of 40–50 years. In fact, while being responsible for 1–4% of ACS in the overall population,[134] SCAD reaches a prevalence of 35% in women < 50 years with suspected ACS. Moreover, SCAD can be responsible for about 25% of ACS during pregnancy and in the peripartum period, mostly in the first 2–3 weeks after delivery.[135]

The pathophysiology of SCAD is characterized by an intramural haematoma, consequent to *vasa vasorum* damage or *tunica media* dissection, which provokes separation of the coronary artery wall layers. An intimal flap can divide the true and the false lumen, with or without a connecting tear between the two. The left anterior descending artery, and its septal and diagonal branches are the most common sites for SCAD accounting for up to 60% of cases.[133,136] Four different SCAD types are described according to their angiographic appearance.

The aetiology of SCAD can be considered as multifactorial. Considering the strong sex-association and the association with pregnancy,[137] hormonal factors seem to have a role.[138] The high incidence of either a stressful event or intense physical activity in the 24 h before presentation supports the hypothesis of a catecholaminergic surge similar to TTS.[139] Fibromuscular dysplasia in non-coronary arteries is commonly observed in patients with SCAD, which also demonstrates a strong predilection for females (>90% of cases).[140] Uncommon genetic predispositions for SCAD have also been described, including genes for inherited connective diseases[141] and systemic inflammatory diseases but not with autoimmune diseases.[142]

Acute MI (AMI) in female patients with SCAD has a seven-fold higher rate of adverse CV events compared with atherosclerotic AMI (44% vs. 6%, $P < 0.001$). Pregnancy-associated SCAD carries a poorer prognosis than with SCAD unrelated to pregnancy[135,143] probably related to hormonal effects on the arterial vasculature and the haemodynamic stress associated with pregnancy.

CA using intravascular imaging (i.e. OCT and IVUS)[121] remains the gold standard for SCAD diagnosis. Most SCAD cases can be diagnosed on angiography alone, with intracoronary imaging reserved for cases where diagnostic uncertainty exists. CCTA is possible alternative imaging technique with the advantage that instrumentation of the coronary arteries and potential extension of the dissection is not required. However, CCTA still requires contrast and radiation and is less sensitive in the detection of SCAD than CA. Possible pitfalls and artefacts can misinterpret normal coronary arteries in acute SCAD. Indeed, a negative CCTA cannot exclude SCAD, when there is a strong clinical suspicion.[144] CMR may describe patterns of late gadolinium enhancement (LGE) similar to type 1 MI, including oedema, abnormal LV wall motion, and ischaemic pattern of LGE. Echocardiography, although unable to visualize the coronary arteries, is helpful in the acute setting to detect the resultant wall motion abnormalities and assess their impact on systolic function.[144]

Takotsubo syndrome

Takotsubo syndrome (TTS) is an acute heart failure syndrome that predominantly affects post-menopausal women and is characterized by substantial morbidity and mortality.[144,145] Patients with TTS show typical regional wall motion abnormalities that reflect impairment of myocardial contractility in the absence of culprit epicardial CAD. The clinical presentation of TTS is generally similar to AMI, with chest pain, transient ECG changes, and elevation of serum cardiac troponin.[146] Acute complications are not infrequent and can be severe, including a 4–5% in-hospital mortality related to cardiogenic shock, cardiac rupture, and cardiac arrest.[146,147]

MMI plays an important role in the evaluation of TTS.[132] Echocardiography can be used as first technique, particularly in the acute care setting, allowing for the assessment of LV systolic and diastolic function and the identification of the typical apical–mid-ventricular ballooning pattern, as well as the circumferential pattern of wall motion abnormalities.[148,149] It is also useful in the early detection of complications and monitoring of systolic function recovery. However, CMR provides a more comprehensive depiction of cardiac morphology and function alongside tissue characterization (oedema and myocardial lesion) and offers additional value to other imaging modalities for differential diagnosis (MI and myocarditis).[148,149] CCTA has a substantial role in the diagnostic work-up of patients with acute chest pain and a doubtful TTS diagnosis to rule out other medical conditions, and it can be considered as a non-invasive appropriate alternative to CA in several clinical scenarios.[150]

Finally, nuclear cardiology can play a very important role by adding different information, not available from other techniques. Quite recently, an association between dysfunctional sympathetic nervous system and TTS has been suggested, with initial reports showing relevant alterations of myocardial sympathetic firing activity in this patients' cohort.[145,151] Specifically, studies in patients with TTS showed that regional myocardial uptake of 123I-metaiodobenzylguanidine (MIBG)—a non-metabolized norepinephrine (NE) analogue that undergoes reuptake by the uptake 1 mechanism labelling sympathetic neurons—was markedly decreased in the apical akinetic regions of the LV, suggesting disturbances in pre-synaptic NE uptake and an increased pre-synaptic catecholamine discharge.[152] These abnormalities may persist long after recovery of contractile function, providing some insight in the time course of functional myocardial changes in TTS.[146]

Interestingly, a dysfunctional sympathetic nervous system plays a pivotal role in cardiac re-adaptation during major pathologic conditions and measures of sympathetic dysfunction have already been associated with adverse cardiac prognosis.[148,153]

Table 5 Chronic coronary syndromes

Stress echo	Stress CMR	CACS and CCTA	Nuclear	Invasive coronary angiography
Dobutamine/ dipyridamole/ exercise	**Stress perfusion CMR**	**CACS**	**SPECT**	**Coronary angiography**
Lack of studies on diagnostic performance for ischaemia in men vs. women	Similar accuracy between sexes for CAD diagnosis	Higher predictive value for women vs. men	Lower sensitivity with similar specificity in women vs. men for CAD diagnosis	No differences in accuracy for CAD in both sexes, but women with limitations for smaller calibre of coronaries
No radiation, advantageous for young women	Lack of controlled studies for CMD between sexes	**CCTA**	Lack of controlled studies for CMD	**Functional reactivity testes**
May assess diastology in women with shortness of breath	No radiation, advantageous for young women	Non-obstructive coronary lesions in low-risk women, higher than men	Breast attenuation is a common pitfall in SPECT perfusion. Women are more symptomatic in vasodilator stress due to differences in pharmacokinetics	Invasive gold standard for CMD
	Limitations of gadolinium use in renal dysfunction	Event risk for obstructive coronary disease higher than positive stress test	**PET**	Radiation issues
		Women with lower plaque burden than men	Non-invasive gold standard method for CMD, lack of comparison of both sexes	
		Radiation issues	Radiation issues	

Echo, echocardiography; CMR, cardiovascular magnetic resonance; CCT, cardiac computed tomography; nuclear, nuclear cardiology techniques; CMD, coronary microvascular dysfunction; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CAD, coronary artery disease; PET, positron emission tomography.
Comparison of women vs. men. Women have lower pre-test probability (2019 ESC guideline) which impacts the accuracies of some functional modalities for CAD.

Imaging IHD in women: challenges and prospects

Women with IHD are more likely to present with atypical symptoms of angina, such as nausea, dyspnoea, and fatigue, and non-obstructive CAD on CA.[154,155] Other aetiologies, including coronary vasospasm and CMD, might also coexist, making the differential diagnosis more difficult. Furthermore, given the higher prevalence of atypical symptoms, determining the pre-test probability of CAD in women is more challenging, often resulting in risk under-estimation, missed diagnosis, and treatment. All these factors can contribute to the higher morbidity and mortality due to IHD in women compared with men.[20,156]

A diagnostic work-up based on a stepwise approach to non-invasive testing to investigate a broader spectrum of IHD aetiologies can provide increasingly accurate diagnoses and risk stratifications of future adverse cardiac events, potentially improving women's clinical outcomes.[157]

In the clinical scenario of acute chest pain syndromes and unobstructed coronaries, which represents a genuine clinical dilemma, CMR can have a prominent role in establishing an accurate diagnosis that can guide a timely and more appropriate treatment in women.[124,158,159] This modality allows the detection of small MIs, differentiation of MI from myocarditis, and exclusion of other causes of acute myocardial injury that cannot be captured with traditional tests. Furthermore, recent advances in tissue characterization and parametric mapping techniques, including the assessment of the extracellular volume (ECV) and myocardial interstitium, can provide new insights into the differences in the pathophysiology of ACS between men and women.[160]

In the diagnostic work-up of women with stable chest pain and low-to-intermediate risk of IHD, CCTA can be used as a first-line test to assess the coronary anatomy and to detect the presence of atherosclerotic plaque and flow-limiting stenoses.[161] However, the higher prevalence of CMD and the poor correlation between symptoms and ischaemic burden means that functional imaging tests are also often useful to guide clinical decision-making in women.[21] Stress echocardiography and SPECT myocardial perfusion imaging (MPI) are widely used to diagnose obstructive CAD. However, their ability to exclude CMD is limited, often resulting in a missed opportunity for treatment in women.[89,162] More advanced quantitative modalities, such as CMR and PET, can be used when conventional imaging tests fail to provide answers in women with persistent angina and significant risk factors for IHD. Stress CMR combined with contrast-enhanced imaging and tissue mapping can provide information on both macrovascular and microvascular CAD with no sex differences in performance and without any radiation exposure.[163,164] This makes this technique particularly useful in the assessment of young women with suspected coronary microvascular angina. PET MPI allows the measurement of CFR and MBF, potentially representing the gold standard non-invasive test in the assessment of CMD.[162] Furthermore, myocardial perfusion PET-CT has high sensitivity (92%) for detecting single-vessel CAD in women.[165] In comparison with SPECT, this technique offers lower radiation exposure and higher diagnostic accuracy making it particularly suitable for women with dense breast and high body mass index.[166] However, the high costs of the equipment and its relatively limited accessibility remain issues. CFR assessed at the left anterior descending artery by stress echocardiography is a promising tool, although it requires a high level of technical expertise for the proper acquisition and only assesses one region of the myocardium.

Finally, it is worth mentioning the emerging role of CCTA in evaluating plaque characteristics to identify individuals most vulnerable to future events and disease progression of atherosclerotic disease. Positive results from the PROMISE and SCOT-HEART trials suggest this technique might significantly improve diagnosis and risk stratification in young women with angina and non-obstructive disease.[98] A summary of MMI use in chronic chest pain syndromes in women is presented in *Table 5*.

Heart failure and cardiomyopathy

Heart failure with preserved ejection fraction

In contrast to heart failure with reduced EF, which is more widespread in males, lifetime incidence of HFpEF is similar in males and females.[167] Yet, because of higher life expectancy, HFpEF is more prevalent in

women.[168] Also, HFpEF phenotypes differ among sexes.[169,170] In contrast to males, where HFpEF presents at a younger age and is often associated with obesity and CAD, female HFpEF patients are older and have higher comorbidity load, in particular, hypertension, anaemia, diabetes, renal disease,[171] and atrial fibrillation.[172] Higher age likely predisposes women to this higher prevalence of HFpEF, as cardiac ageing leads to LV concentric remodelling, diastolic dysfunction, and atrial fibrillation. Finally, and importantly, despite its high prevalence, the female HFpEF phenotype has been consistently under-represented in HFpEF trials.[171]

MMI is key in the investigation of patients with suspected HFpEF. Echocardiography is the principal imaging modality for the diagnosis of diastolic dysfunction through measurement of mitral inflow and tissue Doppler velocities, tricuspid velocity, and left atrial size. New methods of diastolic function assessment include measurement of LV diastolic strain, left atrial stiffness, and diastolic stress test.[173] CMR also plays an important role in the assessment of HFpEF. It allows precise estimation of LV mass and volumes, systolic function by LVEF and feature tracking or tagging strain imaging, and evaluation of diastolic function by LV time–volume filling curves and phase contrast assessment. Recently, a physiological CMR model was validated invasively for estimating the LV filling pressure in patients with HFpEF.[174,175] CMR's principal advantage is its ability to provide tissue characterization and direct assessment of replacement and interstitial fibrosis by T1 mapping and ECV fraction computation. It can help exclude important differential diagnoses (e.g. myocardial disease and pericardial constriction) and elucidate conditions that underlie the development of HFpEF (e.g. cardiac amyloid). Further, CMR allows precise estimation of left atrial volume and RV function in HFpEF patients. Elevated T1 and ECV expansion indicating myocardial fibrosis have been demonstrated in patients with HFpEF,[176] correlate with histologically detected fibrosis,[176,177] and are directly associated with LV stiffness and impaired diastolic function.[177,178] ECV expansion also correlates with other markers of disease severity such as N-terminal pro B-type natriuretic peptide (NT-proBNP), 6 min walk test distance, New York Heart Association (NYHA) class, and right atrial pressure. Importantly, ECV expansion is also an important predictor of outcome in patients with HFpEF.[179] Of note, ECV expansion can be observed prior to the development of overt heart failure in patients with predisposing conditions and risk factors for HFpEF such as hypertension[180] and diabetes.[181] Bone scintigraphy can be used in HFpEF to detect ATTR amyloidosis, and nuclear cardiology can contribute in the diagnosis of inflammatory CMP.

Overall, there are significant sex differences in myocardial imaging parameters at baseline with women having lower LV mass and volumes and higher RV function parameters,[182] such as RVEF and RV-GLS. They also present with higher native T1 and ECV values,[183] suggesting differences in interstitial matrix. Importantly, the phenotypic expression of HFpEF also differs between sexes. Whereas male HFpEF patients present with predominantly concentric hypertrophy, increased filling pressures, and increased LV volumes, elderly females principally present with isolated left atrial enlargement and RV dysfunction.[169] Also, women present with both higher LV diastolic and systolic stiffness even after adjusting for LV concentricity and clinical covariates.[184] These differences need to be accounted for when interpreting imaging in women with HFpEF (*Figure 3*). However, a clearer understanding of sex differences in physiological and imaging parameters with normal ageing compared with HFpEF is also warranted, so that effective sex-specific diagnostic algorithms and more distinct diagnostic strategies in men and women can be developed.[185]

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) presents with heart failure secondary to LV systolic dysfunction towards the end of pregnancy and in the months following delivery, with the majority of patients diagnosed post-partum.[33] Predisposing factors include, but are not restricted to, multiparity, African ethnicity, smoking, diabetes, and pre-eclampsia.[186] The exact mechanisms for PPCM are unknown and potentially include inflammation and vascular damage. Approximately 15% of PPCM patients screened for CMP genes have an identified pathogenic mutation, with TTN truncations most commonly implicated.[187] Symptoms and signs are typical for heart failure but are also non-specific with shortness of breath and cough predominating. Therefore, diagnosis can initially be missed when occurring in the last trimester of pregnancy. Patients frequently present with acute heart failure but also with ventricular arrhythmias and/or cardiac arrest.

Echocardiography is the first-line diagnostic tool. The LV may be non-dilated due to the short duration of pathology, but LVEF is usually <45%. Initial LVEF < 30%, marked LV dilatation (LV end-diastolic diameter ≥ 6.0 cm), and RV involvement are associated with adverse outcomes.[188] Whether strain echocardiography can identify early PPCM, before overt reductions in LVEF, remains to be explored.[189] A representative case of PPCM with a benign evolution is presented in *Figure 4*. CMR is recommended to confirm the diagnosis and severity of this CMP. Tissue characterization by CMR may be helpful to clarify the pathogenesis and disease processes of PPCM, although it cannot distinguish it from related phenocopies such as DCM or myocarditis.[160,190] The pattern of LGE in PPCM is non-specific and often similar to other idiopathic non-ischaemic CMP. When present, the pattern of LGE shows has a focal and linear distribution, involving the mid-myocardial wall and subepicardium.[190] The presence of LGE is associated with adverse outcome, namely subsequent heart failure exacerbations.[191]

Pre-existing CMP, like hypertrophic or dilated CMP, or conditions occurring during pregnancy like TTS are possible differential diagnoses for post-partum CMP. Echocardiography is the first-line method and CMR the next one for identifying other pre-existing CMP without ionizing radiation.[160] Other potential differential diagnoses can include pulmonary embolism, CAD, and pregnancy-related SCAD.[185] Imaging work-up in pregnant patients presenting with breathlessness requires careful planning. The use of radiation, radiopharmaceuticals, and contrast agents should be minimized. Both pulmonary and CCTA are associated with minimal foetal radiation, and ventilation–perfusion scintigraphy offers relatively low foetal irradiation, which may minimized further if the ventilation part is omitted. Cardiac catheterization and CA also cause relatively low foetal exposure. Even nuclear cardiology procedures are unlikely to exceed negligible risk (50 mGy cut-off) in foetal radiation doses.[192]

After a diagnosis of PPM is established, echocardiography follow-up should be performed every 6 months until LVEF recovery. When the LVEF has not recovered to >50–55% at 6 months after delivery, subsequent pregnancy should be discouraged. Even with normalized LVEF, counselling is required due to potential recurrence.[193,194]

Other cardiomyopathies

In the broad spectrum of CMP, there are only limited data focussing on sex differences. The diagnosis of CMP depends on the accurate detection of specific phenotypes such as LV hypertrophy in hypertrophic cardiomyopathy (HCM). But the relation between body height and/or surface and the size of all cardiac chambers may influence the diagnosis.[182,195] For example, the diagnosis of HCM is often based on an LV wall thickness (larger than >15 mm) that may lead to the underestimation of HCM in females who start off with a thinner myocardium. Potential solutions include providing indexed values after correction for body surface area (BSA)/height or the introduction of sex-specific cut-off values. Further research in this important area is required. Moreover, specific CMP types, e.g. wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM), are observed more frequently in men vs. women (~9:1), helping in the diagnosis.[196]

	Male HFpEF	Female HFpEF
		
Clinical characteristics	Younger Age	Older Age
Principal mechanism	Hypertension Endothelial dysfunction	Atrial Fibrillation
Comorbidities	Obesity Coronary artery disease	Hypertension Anaemia Renal failure
Cardiac structure and function	Concentric hypertrophy Filling pressures	Left atrial dilatation
Outcomes	Cardiovascular Death Sudden Cardiac Death	Higher overall mortality Non cardiovascular death More readmission

Figure 3 Comparison of characteristics of women vs. men in patients with heart failure with preserved ejection fraction (HFpEF).

Echocardiography is the first-line imaging method in all CMP. CMR provides added value, contributing to risk stratification, providing precise functional assessments (e.g. EF assessments), and also can guide therapy by identifying the underlying pattern of myocardial injury. Most CMP have a genetic component that should encourage a careful diagnostic work-up including imaging as part of a family screening.[33]

Here, we can only highlight some aspects within the broad range of CMP. We will focus on HCM and DCM in their primary and secondary forms. In cases of unexplained left ventricular hypertrophy (LVH), HCM should be ruled out as sudden cardiac death (SCD) may occur at young age. In case of clinically unexplained LVH, CMR should be applied to identify the aetiology. The application of parametric mapping techniques can be helpful to identify underlying storage diseases like amyloidosis (high native T1) and Fabry CMP (low native T1).[196] T1 mapping by CMR can also help identify diffuse fibrosis as a contributor to the development of heart failure. Interestingly, women with HCM have higher T1 values as well as ECV values than men. That is in line with higher BNP and troponin values, supporting the hypothesis that women develop heart failure more often or earlier heart failure than men in HCM.[197] The application of LGE to detect a high burden of focal fibrosis is an accepted modifier to help borderline decisions regarding implantable cardioverter defibrillator (ICD) implantation, with a high scar burden indicating an increased risk of death in both men and women.[197]

DCM may be caused by a variety of underlying diseases. LGE imaging is crucial in the diagnostic work-up of DCM patients as it can differentiate between ischaemic and non-ischaemic causes.[198] One important cause of DCM in females are systemic inflammatory disorders, such as rheumatic disease and SLE, both of which are more common in women than men, as detailed in a previous chapter. One well-studied example is SLE, with the disease affecting women more often than men. While echocardiography nicely identifies cardiac structure and function as well as pericardial effusions, CMR provides more detail with the application of LGE and parametric mapping, which allows identification of even subclinical cardiac involvement. The assessment of myocardial oedema[122,126] as well as fibrosis is crucial for further guidance of therapy, allowing further differentiation of inflammation, fibrosis, and oedema from ischaemic and inflammatory lesions. Sarcoidosis, more frequent in women than in men, is another condition that may affect the heart, and when present, cardiac involvement should be searched for. CMR and nuclear cardiology may provide important information for its diagnosis. Moreover, vasculitis can present with inflammation of the aorta and coronary arteries as well as the pericardium and myocardium.[199] A careful stepwise approach using ultrasound, CCTA as well as CMR allows the identification of aortic and coronary wall

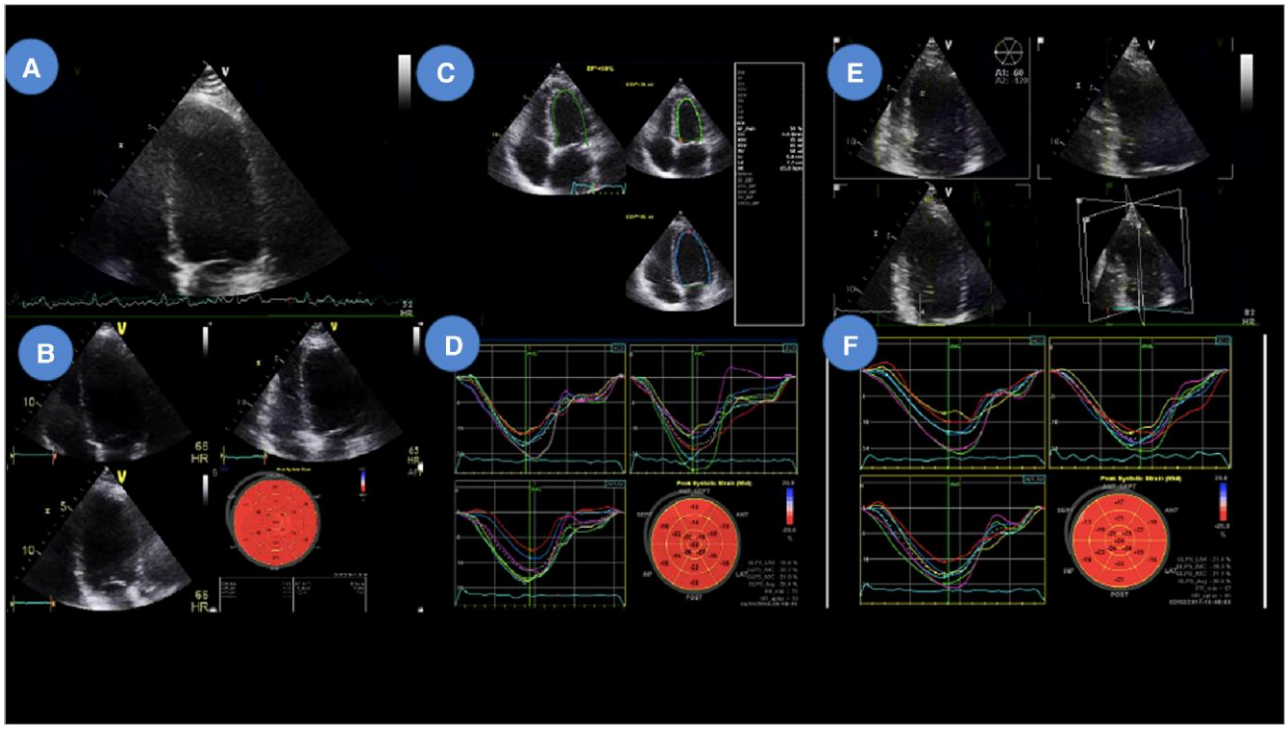


Figure 4 Case of a 37-year-old woman with pre-eclampsia in the last 10 weeks of the pregnancy with heart failure symptoms at 3–4 h after delivery. (*A* and *B*) TTE on the second day after delivery with dilated LV, LVEF 46%, and GLS −13.1%; (*C* and *D*) TTE at 1 month follow-up with LVEF 59% and GLS −20.1% (*E* and *F*). TTE, transthoracic echocardiography; LV, left ventricle; LVEF, left ventricle ejection fraction; GLS, global longitudinal strain.

thickening and stenosis. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET imaging allows assessment of inflammation activity in the vessel wall and myocardium.[200] Native T1 and ECV values are useful markers for monitoring the progression of the disease.

Interestingly, the development of focal fibrosis in myocarditis seems to be related to sex, with women overall developing less scar than men.[201] More subtle changes in T2 mapping parameters may therefore be helpful to identify and follow myocarditis in women although these should always be compared with appropriate reference ranges in age- and comorbidity-matched patients. That underlines the need of a careful assessment of diffuse inflammatory changes as done by T2 sequences to show and monitor the full picture of the disease.

Valvular heart dsease

Aortic stenosis

There are important sex-specific differences in AS that may in the future necessitate tailored imaging approaches and which may have important implications regarding management and risk stratification, as well as the development of novel drug therapies.

The differences that can be identified using MMI are summarized as follows: (i) for the same severity of AS, women display less valve calcifications of the leaflets even after adjusting for their smaller BSA or aortic annulus area.[202] This may be because they have more valve fibrosis. This difference is reflected in international recommendations where different CT calcium score thresholds are recommended in men and women to identify likely severe AS [for the integrative approach for low-flow low-gradient AS, with different threshold values using computed tomography; measurement of aortic valve calcification (Agatston units): men > 3000 and women > 1600, highly likely; men > 2000 and women > 1200, likely; men < 1600 and women < 800, unlikely].[203,204] (ii) Since women usually have smaller aortas and inner aortic root dimensions and, therefore, higher pressure recovery, this may influence the grading of AS, although the true impact of pressure recovery requires further study. (iii) Because flow is indexed to BSA and women have higher rates of obesity, this may introduce an error in classification of low flow. This may partially explain the higher prevalence of women in the category of preserved EF normal-flow/low-gradient AS.[205] (iv) CMR has brought new insights about sex differences regarding the LV remodelling in AS. In response to overload related to AS, women often exhibit lower LVM with more often a normal geometry and LV concentric remodelling pattern than men.[205] They also present smaller LV cavity volumes for similar AS severity and comorbidities that may also contribute to the higher prevalence of low-flow states in women.[204,206] CMR studies have also demonstrated a sex difference regarding the pattern of myocardial fibrosis. Women appear to present with more diffuse fibrosis, quantified with ECV fraction by T1 mapping, but similar or less focal fibrosis identified by LGE compared with men.[204]

Regarding aortic valve replacement (AVR), it is clear that women (especially elderly women) with AS have lower rates of specialist visits, diagnostic testing, and surgical AVR (SAVR).[207] They are therefore usually referred late for AVR, at a more advanced stage than men, and this may convey a poorer outcomes post-SAVR, with more symptoms.[208] Transcatheter AVR (TAVR) has been a game-changer regarding the referral pattern in AS, and more than 50% of the AS patients referred for TAVR are women.[209] Importantly, outcomes are generally better in women than in men when TAVR is performed. Fewer traditional risk factors, higher indexed valve areas after TAVR implantation, and earlier remodelling in women are potential reasons for this observation.[209]

Imaging plays a pivotal role in decision-making regarding the need for AVR and whether to perform SAVR or TAVR, by assessing the valve

leaflet morphology of the leaflets, the amount and distribution of calcifications, and the extravalvular consequences of AS and assessing the anatomy of the aorta and vascular access. The aortic annulus is usually smaller and the coronary height lower in women than in men. All this information is crucial for planning the aortic valve intervention. Imaging is routinely used for the follow-up of patients and to predict regression of LV hypertrophy, which is a strong predictor of good functional recovery. Interestingly, reverse remodelling of the LV is more likely in women, especially after TAVR.[209]

The prevalence of bicuspid aortic valve (BAV) is three-to-four-fold more common in men than in women, but women with BAV are more likely to develop AS than men, regardless of age of presentation. Fusion between the right and non-coronary cusps may be more common in women, and they also have less aortopathy.[210]

In summary, there are differences in AS, and its consequences between men and women can be identified using CV imaging. These differences need to be considered when assessing women with AS so that they can be managed using a tailored imaging approach and a sex-specific evaluation strategy. It is important that this be undertaken in the correct time frames to ensure optimal outcomes. Further research to explore the mechanisms of sex differences in patients with AS is warranted, with new imaging technologies under development to deliver these insights.

Mitral valve regurgitation

Significant sex differences have been reported in primary MR. As compared with men, women more frequently have a rheumatic aetiology of primary MR and, therefore, more often present with concomitant MV stenosis.[211,212]

When primary MR is due to MV prolapse, men are more frequently affected by a single scallop prolapse, while women present with more complex MV lesions, including anterior or bi-leaflet prolapse, thicker leaflets, and more calcified MV annuli.[213] These differences might also explain the reported higher proportion of men undergoing MV repair and women requiring MV replacement.[214] Importantly, several studies have suggested that, similar to AS, women are referred to MV interventions at a more advanced stage of the disease.[215] The most probable explanation for this finding is the challenge in the assessment of MR severity in women, crucial when trying to establish an indication for intervention.[215] In women, symptoms are subtler and less typical. MR is less often diagnosed as severe, and LV dilatation and dysfunction are less easily identified when using traditional cut-off values without correction for BSA.[213] According to the current 2017 ESC/European Association of Cardio-Thoracic Surgery (EACTS) VHD guidelines, diagnosis of primary MR is crucial, and it is recommended that close follow-up should be performed using TTE as the first-line imaging technique.[216] When indicated (e.g. in cases of suspected severe MR), TOE should be advised for a better quantification of MR severity.[216] TOE better characterizes the complex MV lesions frequently present in women, particularly when including 3D acquisitions, providing a good estimate of the likelihood of a durable surgical repair, and the eligibility criteria for specific transcatheter interventions (for some, a combination of measurements obtained from CCTA is required).[217] CMR can also provide an accurate assessment of MR severity when echocardiographic measurements are inconclusive as well as of LV size and function.[218] Although in current guidelines, imaging-based criteria for MV interventions are not sex-specific and not indexed to BSA, further research is required to assess if women might benefit from earlier referral for surgical MV treatment.

Recently, more attention has been given to a specific presentation of MV prolapse characterized by malignant ventricular arrhythmias.[218–220] Arrhythmic MV prolapse has been described in several studies as being more frequent in young women[219,220] but in other studies was reported as being more frequent in men with comorbidities.[218] The association between women and arrhythmic MV prolapse could be explained by the fact that this syndrome seems to be associated with more complex MV lesions, such as a bi-leaflet prolapse. The presence of mitral annular disjunction (MAD)[221] and the presence of LGE at the level of the papillary muscles on CMR have been also associated with malignant ventricular arrhythmias in patients with MV prolapse.[219] Echocardiography plays an important role, identifying the typical MV lesions and the presence of MAD, while CMR can be used to better characterize MAD and myocardial fibrosis distribution.

Tricuspid regurgitation and pulmonary hypertension

While sex differences have been studied in tricuspid regurgitation, a recent study by Scotti and colleagues[222] highlighted that after transcatheter tricuspid valve intervention in high-risk patients, there were no sex-related differences in terms of survival, heart failure hospitalization, functional status, and reduction of tricuspid regurgitation up to 1 year.

Female sex is a well-known major risk factor for pulmonary hypertension.[223] Women are more susceptible to develop PAH, but they have a better haemodynamic profile, better RV function, better response to treatment with endothelin receptor antagonists, and better survival. Women have greater vascular remodelling and plexiform lesions in PAH, suggestive of better adaptation[224,225] and greater improvement after targeted therapeutic compared with men. While echocardiography is the first-line method for cardiac assessment, CMR is a reference method to evaluate the RV in PAH patients and can be used to predict prognosis.[226]

Women have better RV systolic function in both health and PH, including Group 1 (PAH), Group 2 (left heart disease), and Group 3 (chronic lung disease/hypoxia) patients. Both the Multi-Ethnic Study of Atherosclerosis (MESA)-RV[227] and Framingham[225] studies showed age to be an important modifier of the relationships between sex and measures of RV morphology.

Atrial tricuspid regurgitation has been associated with female gender. Furthermore, female sex, as well as age, atrial fibrillation (AF), heart failure, and right ventricular systolic pressure, has been significantly associated with tricuspid regurgitation progression.[228,229]

Stroke

There are stroke risk factors unique to women which physicians should be aware of: use of oral contraceptives,[230] occurrence of menopause before age 42,[231] menopause hormone therapy initiated more than 5 years after menopause onset,[232] migraine with aura in women < 55 years,[233] pregnancy, and pre-eclampsia. In comparison with non-pregnant women, pregnancy is associated with a three-fold increased stroke risk (mainly for intracerebral haemorrhage), while pre-eclampsia is associated with a 14.5-fold increased stroke risk within the first 3 years.[234] Furthermore, classical CV risk factors present sex differences in their effects on risk, mostly to the detriment of women.[235]

Cardioembolic stroke represents 20–25% of all ischaemic stroke (IS). The most common major risk source of cardioembolism is AF. Noteworthy, women have lower age-adjusted incidence of AF but when present face a greater lifetime AF-related risk of stroke.[235] Other major risk sources are CMP with LV dysfunction, intracardiac thrombi, cardiac tumours, endocarditis, and prosthetic valves. Minor risk sources include patent foramen ovale (PFO), atrial septum aneurysm (ASA), and calcification of the aortic and mitral valves (MVs).

Once acute IS is suspected, imaging assessment is recommended with no differences between sexes. Emergent brain imaging with non-enhanced CT is advised to exclude intracerebral haemorrhage and determine a patient's candidacy for thrombolysis or mechanical thrombectomy.[236] Magnetic resonance imaging (MRI) is as accurate as non-enhanced CT in detecting hyperacute intracerebral haemorrhage.[237] CCTA with perfusion or MRI angiography with diffusion-

weighted MRI (DW-MRI) is also useful for selecting candidates for mechanical thrombectomy after 6 h.[238] In candidates for thrombectomy and in those with suspected large vessel occlusion, non-invasive imaging of the intracranial arteries with CT or MRI angiography is recommended and imaging of the extracranial carotid and vertebral arteries with MRI, CT, or ultrasound may add information on patient eligibility, procedural planning, and secondary prevention strategies.

Regarding cardiac evaluation, patients with IS should be screened for AF with 12-lead ECG and ECG monitoring for at least the first 24 h. Echocardiography is the first imaging technique in the diagnostic strategy to identify central sources of cardioembolism, help classify stroke aetiology, design secondary prevention, and detect comorbidities, including CAD. Still, its diagnostic capability in unselected patients is limited, with inconsistent results among studies both for TTE and TOE.[239] CMR and CCTA are second-line methods indicated in patients with cryptogenic stroke and a non-conclusive echocardiographic study, providing complementary information useful for secondary prevention.[240] Screening for occult CAD in IS patients either with CMR or CCTA remains a matter of debate.

Final remarks

CVDs in women demonstrate important differences, seemingly related to oestrogens and hormonal differences but also to genetic mechanisms, and this must be acknowledged when findings are generalized to populations of both men and women.

MMI has proven to play a key vital role for diagnosis, decision trees, monitoring, and risk stratification of most major CVD, as well as improving our understanding of the pathophysiology underlying CVD. Current knowledge suggests different MMI approaches should be advised in their use in women, consistent with the clear differences in pathophysiology, clinical presentation, and outcomes for CVD according to sex.

There are currently still significant gaps in our knowledge, and further studies must be undertaken including both men and women in order to fully understand both the differences in CV diseases and the best diagnostic approach according to sex. With improved knowledge, in the future, it is likely that sex differences should be clearly recognized in clinical guidelines and clinical research.

Advances in CV imaging techniques are expected to increase speed, accuracy, and standardization of morphology, function, and prognosis assessments and propose novel therapeutics. This will pair with further progress in the application of artificial intelligence.[241] On this, a word of caution about potential sex bias is warranted given the differences between women and men and the potential for the under-representation of women in the development of AI tools.

To conclude, sex matters in all aspects of cellular function and physiology from the 'womb to tomb', and true sex equity with good outcomes will only be achieved if healthcare disparities are addressed with adequate knowledge and understanding, tailored diagnosis pathways, and appropriate management as well as timely primary prevention. CV imaging is central to all these steps.

Acknowledgements

This scientific statement was an initiative from the Task Force of Women in Cardiovascular Imaging from the EACVI, ESC.

Funding

None declared.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research (scientific statement).

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