

Cardiovascular multimodality imaging in women.

A scientific statement of the European Association of Cardiovascular Imaging (EACVI) of the ESC

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1 Abstract

2 Cardiovascular diseases (CVD) represent an important cause of mortality and morbidity in
3 women. It is now recognized that there are sex differences regarding the prevalence and the
4 clinical significance of the traditional cardiovascular (CV) risk factors as well as the pathology
5 underlying a range of CVDs. Unfortunately, women have been underrepresented in most CVD
6 imaging studies and trials regarding diagnosis, prognosis and therapeutics. There is therefore a
7 clear need for further investigation of how CVD affects women along their life span.
8 Multimodality CV imaging plays a key role in the diagnosis of CVD in women as well as in
9 prognosis, decision-making and monitoring of therapeutics and interventions. However,
10 multimodality imaging (MMI) in women requires specific consideration given the differences in
11 CVD between the sexes. These differences relate to physiological changes that only women
12 experience (e.g. pregnancy, menopause) as well as variation in the underlying pathophysiology
13 of CVD and also differences in the prevalence of certain conditions such as connective tissue
14 disorders, Takotsubo and spontaneous coronary artery dissection, which are all more common
15 in women. This scientific statement on cardiovascular multimodality in women, an initiative of
16 the EACVI of the ESC, reviews the role of multimodality CV imaging in the diagnosis,
17 management and risk-stratification of CVD, as well as highlighting important gaps in our
18 knowledge that require further investigation.

19

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21 Keywords:

22 Cardiovascular diseases; Women diseases; Multimodality Imaging; Cardiovascular Imaging.

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Abbreviations

ACS	Acute coronary syndromes
AD	Aortic dissection
AMI	Acute myocardial infarction
ANOCA	Angina with non-obstructive coronary arteries
ARD	Autoimmune rheumatologic diseases
AS	Aortic stenosis
AVR	Aortic valve replacement
CA	Coronary angiography
CACS	Coronary artery calcium score
CAD	Coronary artery disease
CCTA	Cardiac computed tomography angiography
CHT	Chemotherapy
CMD	Coronary microvascular dysfunction
CMR	Cardiac magnetic resonance
CV	Cardiovascular
CVD	Cardiovascular disease
DCM	Dilated cardiomyopathy
ECV	Extracellular volume
HPD	Hypertensive disorder
IHD	Ischaemic heart disease
INOCA	Ischaemia with no obstructive coronary arteries
GLS	Global longitudinal strain
HCM	Hypertrophic cardiomyopathy
HFpEF	Heart failure with preserved EF
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MMI	Multimodality imaging
MINOCA	Myocardial infarction with no obstructive coronary artery disease
MR	Mitral regurgitation
PAH	Pulmonary arterial hypertension
PPCM	Peripartum cardiomyopathy
RA	Rheumatoid arthritis
RT	Radiotherapy
SCAD	Spontaneous coronary artery dissection
SLE	Systemic lupus erythematosus
TOE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
TTS	Takotsubo syndrome

INTRODUCTION

Cardiovascular diseases (CVD) remain the number one cause of mortality globally both in males and females (1). Across the EU, 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 EF (HFpEF) are also both more prevalent in women than men as the first event (3). Sex-related 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 (ANOCA) and ischaemia (INOCA) resulting from non-obstructive coronary artery disease are more prevalent in women and is associated with adverse outcomes (5). The same is true of myocardial infarction in the absence of obstructive coronary artery disease (MINOCA), or spontaneous dissection of the coronary arteries (SCAD), as well as non-ST segment elevation MI (6).

There is also a higher prevalence of Takotsubo syndrome 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 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 to 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 to 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. 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

Coronary artery disease (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 to men, women – especially younger (< 55years 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 postmenopausal 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, as well as a sex bias in treatments. Women with diabetes have a 2-4-fold excess risk of CAD and are at an increased relative risk of heart failure compared to 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). 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 genetics/epigenetics 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 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 signaling 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.

MULTIMODALITY IMAGING 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 regards to patients with valvular heart disease, the increased cardiac output will increase gradient across stenotic valves and , whilst 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 in normotensive pregnancy (with a mean increase of 92 g in hypertensive pregnancy) and an increase 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 uteroplacental 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.

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

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

21 Women with HPD also have an increased risk of insulin resistance and of developing
22 diabetes later in life. A large Canadian study including 1 million women with a median follow-up
23 of 8.5 years (39) found that women without gestational diabetes, were more likely to develop
24 diabetes after gestational hypertension (3.9%) or pre-eclampsia (6.6%) than after a normotensive
25 pregnancy (2.5%). A register-based cohort study also demonstrated that the fully adjusted risk of

1 type 2 diabetes 14.6 years after pregnancy was 3.1-fold for women with gestational hypertension
2 and 3.7-fold after preeclampsia (27).

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

7 **Menopause and cardiovascular disease**

8 Despite recent improvements in mortality, CAD continues to be the leading cause of death and
9 disability among elderly and middle-aged women, with a mortality rate that increases 3 to 5-fold
10 times with each decade of life. It has been reported that women with intact ovarian hormonal
11 function have a lower incidence of coronary disease up to 15 years after menopause (41). A sub-
12 analysis of the multicentre study WISE study also showed that premenopausal women with
13 hypo-oestrogenaemia had more angiographic coronary disease (42). The life expectancy of a
14 woman in Europe is currently around 80 years. Therefore, almost half of an average women's
15 life is spent in menopause and without the potentially protective effects of oestrogen. Lower
16 oestrogen levels after menopause are related to vascular dysfunction, inflammation, and up-
17 regulation of both the renin–angiotensin–aldosterone and the sympathetic nervous systems all-
18 contributing to increased CV risk (43). Early menopause has also been linked to increased heart
19 failure risk (44).

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

23 Depending on symptoms, women will be risk stratified and follow the IHD diagnostic
24 pathway, as it is described below regardless of there menopausal state. It has been advised to

1 assess the coronary artery calcium score (CACS) in women at intermediate CV risk, since this
2 technique has been found to have a higher prognostic value than in men (46) (Table 1).

4 **Radiotherapy and chemotherapy for cancer**

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

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

19 The EACVI has proposed that cancer patients should be assessed before receiving
20 particular potentially cardiotoxic therapies in order to stratify their risk of cardiotoxicity based
21 on both therapy- and patient-related factors (47,51). Cardiotoxicity may be studied with various
22 imaging techniques. 2D and 3D transthoracic echocardiography (TTE) is the method of choice for
23 the evaluation of cardiotoxicity in cancer patients before, during and after cancer therapy. LVEF
24 and LV GLS are the best-established echocardiographic parameters of systolic function.

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

23 TTE image quality may be inadequate due to the effects of RT, left-sided mastectomy, or
24 a left breast prosthesis. Therefore contrast echocardiography or CMR, according to guidelines,
25 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 check point 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).

Transesophageal echocardiography (TOE), 2D and real time 3D echocardiography, are excellent imaging modalities for the diagnosis of nonbacterial 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 were found in women irradiated for left breast cancer compared to 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 characterisation 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 visualisation 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.

Auto-immune 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). ESC 2021 primary prevention guidelines highlight a disproportionately increased risk of CVD in the setting of ARD (68). Notably, cardiovascular 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 (69), and premature MI and stroke in systemic lupus erythematosus (SLE) (70). Significant underestimation of CV event risk by classical risk scoring systems (71), atypical presentations, resting ECG abnormalities, limited exercise capacity, silent episodes and sudden cardiac death (72) (67) justify the diagnostic role of MMI and suggest 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).

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

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

15 ARD can lead to myocardial damage including inflammation, microvascular dysfunction
16 and fibrosis. These can lead to CV complications and symptoms in women with ARD including
17 the development of heart failure (78) (79). Echocardiography with strain is very sensitive for
18 detecting subclinical myocardial dysfunction and monitoring anti-inflammatory treatment
19 effects in ARD (80). CMR allows detection of patchy perfusion defects as well as differentiation
20 of ischaemic and non-ischaemic patterns of myocardial fibrosis. CMR, PET and PET/CMR can add
21 information about ongoing inflammatory activity in the heart muscle as well as the vasculature
22 in cases of suspected vasculitis or myocarditis (81).

23 Acute valvular pathology is sometimes the initial presentation in ARD, particularly in SLE
24 and ankylosing spondylitis (82). Patients also carry a high risk of infective endocarditis because
25 of immunosuppressive therapy. As well as being an independent cause of stroke and mortality,

antiphospholipid antibody positivity increases the risk of valvular heart disease and non-bacterial vegetations, often requiring the use of TOE to confirm the diagnosis in suspected cases. Pulmonary arterial hypertension is also an important cause of mortality in women with ARD, particularly in systemic sclerosis where yearly screening is recommended by the 2022 ESC/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.

Ischaemic heart disease and chronic coronary syndromes

Coronary atherosclerotic disease - obstructive and nonobstructive

Invasive coronary angiography is used as a first line diagnostic procedure for high-risk women presenting with chronic chest pain. For the lower/intermediate risk woman, noninvasive CCTA or 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 noninvasive coronary angiography, the frequency of

1 nonobstructive CAD is decidedly higher than in men (86). For women referred to invasive coronary
2 angiography, about half have nonobstructive CAD; this rate is much higher for lower risk women
3 undergoing CCTA and is generally in the range of 80-90% (87). Importantly, the burden of non-
4 obstructive plaque is also associated with risk of future cardiovascular events.

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

11 Suspected CAD in women may be assessed both by anatomic and functional testing. There
12 have been several studies comparing risk associated with anatomic tests as compared to
13 ischaemic tests. In the PROMISE trial (n=8,966), 92% of women in the CCTA arm of the trial had
14 nonobstructive CAD while 88% of women in the functional testing arm had an abnormal stress
15 test ($p<0.001$) (91). Additionally, the relative hazard for risk for outcomes was 10 fold increased
16 in the presence of obstructive CAD as compared to normal coronaries on CCTA ($p<0.001$) whereas
17 the hazard ratio for an abnormal versus normal stress test was only 5 ($p=0.002$). When examining
18 an interaction, event risk was significantly elevated with CCTA as compared to stress testing for
19 women ($p=0.043$). These findings suggest that CCTA provides better prognostic information than
20 functional testing in women. In the CE-MARC trial, in patients with suspected angina and with a
21 prevalence of obstructive CAD of 23% in women versus 50% in men, sensitivity and specificity of
22 CMR was similar in women and men. In contrast, sensitivity was significantly lower for SPECT in
23 women than in men, with similar specificity (92). Interestingly, in FFR_{CT}-positive CAD, women have
24 less obstructive CAD at coronary angiography and less revascularization showing the need for
25 different interpretation in both sexes (93).

Also, there is increasing evidence with regards to sex differences in atherosclerotic plaque, namely a different aetiology for ACS with plaque erosion versus rupture occurring more in women versus men (95,96). A smaller plaque burden with less calcification and less positive remodelling (97,98) occurs in women in comparison to men.

Using noninvasive CCTA for anatomic assessment, data is available with regards 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 nonobstructive CAD, as precursor features of an acute coronary syndrome (96,99,100). 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) (101,102). Whilst 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, women undergoing invasive or noninvasive coronary angiography, the frequency of nonobstructive CAD is higher than in men moreover in FFR_{CT}-positive CAD, women have less obstructive CAD at coronary angiography 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 coronary artery disease (ANOCA/INOCA) as confirmed from CCTA than men (103). In a study of stable angina and

1 ANOCA/INOCA, 70.2% of female versus (104) 43.1% of male patients had coronary microvascular
2 dysfunction (CMD) or epicardial artery vasospasm (105), the two main endotypes of
3 ANOCA/INOCA, according to the current concepts as proposed by the COVADIS group (106).
4 INOCA is associated with a significant risk of major adverse CV events (86,104) with an annual
5 major adverse cardiovascular event rate of 2.5% present in women with CMD (107). Of note, CMD
6 is a strong determinant of prognosis, even in patients with coronary stenosis of intermediate
7 severity.

8 Patients with coronary vasospasm are frequently younger and have fewer CV risk factors
9 than patients with effort angina (4,64). Diagnosis is based on ST segment elevation on the ECG (or
10 Holter monitoring) during the chest pain episode, but confirmation needs angiographic
11 documentation of coronary spasm upon a provocation test with intracoronary administration of
12 acetylcholine or ergonovine (108).

13 The WISE study, among others, showed that CMD plays an important role in INOCA in
14 women, suggesting the need for a different diagnostic and therapeutic strategy in females (107).
15 CMD is defined as limited coronary flow reserve and/or coronary endothelial dysfunction at
16 microvascular level, underlying myocardial ischaemia in the absence of significant obstructive
17 epicardial CAD. Microvascular remodelling, microembolization, as well as the smaller calibre of
18 coronaries and lower vascular density are proposed as the main mechanisms associated to CMD
19 in women (109).

20 For the diagnosis of CMD, general recommendations propose the following criteria (110):
21 (a) presence of symptoms and objective evidence of ischaemia; b) absence of obstructive
22 coronary disease; c) evidence of impaired coronary microvascular function: impaired coronary
23 flow reserve; abnormal coronary resistance indices; coronary microvascular spasm; coronary slow
24 flow phenomena. So far, the reference method is the invasive testing of coronary flow reserve
25 (CFR) and the index of microvascular resistance (IMR) using acetylcholine and adenosine to assess

1 for endothelial-dependent and endothelial-independent dysfunction (109). Thresholds for an
2 abnormal CFR cut-off have been defined as <2.0 and > 25 units for microvascular resistance > 25
3 units. This assessment is, however not routinely used in the clinical setting in most centres with
4 non-invasive testing often preferred.

5 Among the non-invasive techniques, PET with vasodilator stress is considered the gold-
6 standard non-invasive method to diagnose CMD, although it uses radiation, has limited availability
7 and is costly. Myocardial flow reserve (MFR) by PET has been validated against both invasive
8 assessments (111) and against outcomes. Indeed, PET assessments of MFR are independently
9 associated with increased CV risk in women (112).

10 An alternative non-invasive modality for assessing CFR is CMR, which allows the
11 qualitative diagnosis and quantitative assessment by measuring the CFR, MPI (microcirculatory
12 perfusion index) and MPRI (perfusion resistance index) all of which correlate well with invasive
13 measurements and provide important prognostic information (113,114).

14 CFR may also be assessed by stress Doppler echocardiography, which can measure the
15 maximal diastolic flow in the left anterior descending coronary artery at rest and during adenosine
16 or dipyridamole stress. This technique has been validated against intracoronary Doppler
17 measurements and outcomes, with cut-offs similar to invasive testing however it can be
18 challenging to perform and is not widely used (115). Myocardial contrast echocardiography also
19 shows a particular value for CMD evaluation, delivering myocardial blood flow velocity and CFR,
20 but the lack of widespread experience and absence of approval from the regulatory agencies for
21 this purpose has presented a limitation for its universal use.

22 Cut-offs for diagnosis of CMD using the available non-invasive techniques are currently
23 being reviewed, and consideration is being given to the possible differences between women and
24 men (116), with smaller vascular diameter in women and suggested higher resting coronary blood
25 flow than in men. This will likely influence the values of CRF in women but there is a need for

further studies for cut-offs establishment in women.

In the last years, elevated pro-inflammatory mediators were found to be associated with lower CFR (109). 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 ischemia from clinical and ischemia 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

Acute coronary syndromes (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 versus plaque rupture in men (94-96).

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 (96,97). In a subanalysis from the PROSPECT study, plaque rupture occurred less often in women ($p=0.002$) (89,94). Additional contributors to the unique risk profile in women include smaller vessel size as well as the role of microvascular disease.

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

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

17 **Myocardial infarction with non-obstructive coronary arteries (MINOCA)**

18 Myocardial Infarction with non-obstructed coronary arteries (MINOCA) is present in up to 6-15%
19 of patients with ACS and non-obstructive coronary arteries on invasive coronary angiography,
20 and has a non-negligible 12-month all-cause mortality rate of 4.7% (119)(114). It
21 disproportionally affects women, with women having 5 times higher odds of having MINOCA
22 than men, according to the VIRGO study (120).

23 Suspected MINOCA is a working diagnosis with multiple potential causes requiring
24 further evaluation and often reflects the group of patients with a suspected ACS diagnosis who
25 are then found to have non-obstructive plaque on invasive angiography. The differential

1 diagnoses is wide and includes patients who have a true final diagnosis of MINOCA (type 1 MI:
2 plaque rupture/erosion, type 2 MI: coronary spasm, spontaneous coronary artery dissection,
3 coronary emboli) and those with non-ischaemic aetiologies (myocarditis, Takotsubo syndrome
4 and non-ischaemic cardiomyopathies).

5 The management and prognosis differ significantly depending on the underlying
6 aetiology of the final diagnosis of ischaemic and non-ischaemic aetiologies and are independent
7 from sex (121). Establishing an accurate final diagnosis is therefore crucial for both sexes and
8 differ significantly with the worse prognosis seen in patients presenting with ST-elevation on
9 ECG coupled and those with a CMR diagnosis of cardiomyopathy (121). The 2017 ESC STEMI
10 guidelines presented two diagnostic pathways for MINOCA: a non-invasive approach using
11 echocardiography and CMR or an invasive approach using intravascular ultrasound and/or
12 optical coherence tomography (122). The 2018 4th definition of myocardial infarction (123)
13 further emphasized the crucial role of imaging (particularly CMR) in identifying the correct
14 underlying condition. Finally, the 2020 ESC NSTEMI guidelines (65) now recommend CMR in all
15 MINOCA cases without an obvious underlying cause.

16 Data on comparative imaging approaches and sex differences in suspected MINOCA is
17 limited, but whilst echocardiography and CMR are most used in clinical practice, the nuclear
18 cardiology techniques and CCTA also can also prove helpful with a distinctive role.
19 Echocardiography can assess the presence and extent of global and regional wall motion
20 abnormalities, and the presence of pericardial effusion and other forms of cardiomyopathy, as
21 well as the characteristic appearances of Takotsubo syndrome. CMR is a critical diagnostic
22 imaging tool in the assessment of patients with a working diagnosis of MINOCA, due to the
23 unique myocardial tissue characterization (myocardial inflammation/oedema, scarring/fibrosis),
24 and the ability to discriminate between each of the possible underlying ischaemic and non-
25 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 versus men, sex-differences are noted, in particular related to the subsequent risk of chronic dilated cardiomyopathy. 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 (TTS) is an increasingly recognised 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 of the basal or mid-cavity segments can be observed. Echocardiography can detect additional specific findings such as LV outflow tract obstruction, mitral regurgitation, and RV involvement (128), whilst serial speckle echocardiography can document the progressive functional LV recovery in left ventricular 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 characterisation is time sensitive so that prompt appropriate imaging, ideally whilst the patient is in patients 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, Galibazzi et al. recently showed evidence of altered peri-coronary fat attenuation detected by CCTA in patients

with TTS, a finding typically associated with coronary artery inflammation (131). 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 underdiagnosis. 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 hours

1 before presentation supports the hypothesis of a catecholaminergic surge similar to TTS (139).
2 Fibromuscular dysplasia in non-coronary arteries is commonly observed in patients with SCAD,
3 which also demonstrates a strong predilection for females (>90% of cases) (140). Uncommon
4 genetic predispositions for SCAD have also been described, including genes for inherited
5 connective diseases (141) and systemic inflammatory diseases, but not with autoimmune
6 diseases (142).

7 Acute myocardial infarction (AMI) in female patients with SCAD has a 7-fold higher rate
8 of adverse CV events compared to atherosclerotic AMI (44% vs. 6%, $p < 0.001$). Pregnancy -
9 associated SCAD carries a poorer prognosis than with SCAD unrelated to pregnancy (135,143)
10 probably related to hormonal effects on the arterial vasculature and the hemodynamic stress
11 associated with pregnancy.

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

1 **Takotsubo Syndrome**

2 Takotsubo syndrome is an acute heart failure syndrome that predominantly affects post-
3 menopausal women and is characterized by substantial morbidity and mortality (144,145).
4 Patients with TTS show typical regional wall motion abnormalities that reflect impairment of
5 myocardial contractility in the absence of culprit epicardial CAD. The clinical presentation of TTS
6 is generally similar to AMI, with chest pain, transient ECG changes, and elevation of serum
7 cardiac troponin (146). Acute complications are not infrequent and can be severe, including a
8 4% to 5% in-hospital mortality related to cardiogenic shock, cardiac rupture, and cardiac arrest
9 (146,147).

10 MMI plays an important role in the evaluation of TTS (132). Echocardiography can be
11 used as first technique, particularly in the acute care setting, allowing for the assessment of LV
12 systolic and diastolic function and the identification of the typical apical-mid ventricular
13 ballooning pattern, as well as the circumferential pattern of wall motion abnormalities
14 (148,149). It is also useful in the early detection of complications and monitoring of systolic
15 function recovery. However, CMR provides a more comprehensive depiction of cardiac
16 morphology and function alongside tissue characterization (oedema and myocardial lesion) and
17 offers additional value to other imaging modalities for differential diagnosis (myocardial
18 infarction and myocarditis) (148,149). CCTA has a substantial role in the diagnostic workup of
19 patients with acute chest pain and a doubtful TTS diagnosis to rule out other medical conditions
20 and it can be considered as a non-invasive appropriate alternative to coronary angiography in
21 several clinical scenarios (150).

22 Finally, nuclear cardiology can play a very important role by adding different
23 information, not available from other techniques. Quite recently, an association between
24 dysfunctional sympathetic nervous system and TTS has been suggested, with initial reports
25 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 nor-epinephrine (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 norepinephrine 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).

Imaging ischaemic heart disease 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 nonobstructive CAD on coronary angiogram (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 underestimation, missed diagnosis, and treatment. All these factors can contribute to the higher morbidity and mortality due to IHD in women compared to 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 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-intermediate risk of IHD, CCTA can be used as a first-line test to assess the coronary anatomy, to detect the presence of atherosclerotic plaque and detect 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 single-photon emission computed tomography (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 positron emission tomography (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 coronary flow reserve (CFR) and myocardial blood flow (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 the progression of atherosclerotic disease. Positive results from the PROMISE and SCOTHEART trial suggest this technique might significantly improve diagnosis and risk stratification in young women with angina and non-obstructive disease (99). A summary of MMI use in chronic chest pain syndromes in women is presented in Table 5.

Heart failure and cardiomyopathies

Heart failure with preserved ejection fraction

In contrast to heart failure with reduced ejection fraction, which is more widespread in males, life-time 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, have higher comorbidity load, in particular, hypertension, anaemia, diabetes and 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

1 importantly, despite its high prevalence, the female HFpEF phenotype has been consistently
2 underrepresented in HFpEF trials (171).

3 MMI is key in the investigation of patients with suspected HFpEF. Echocardiography is
4 the principal imaging modality for the diagnosis of diastolic dysfunction through measurement
5 of mitral inflow and tissue Doppler velocities, tricuspid velocity and left atrial size. New methods
6 of diastolic function assessment include measurement of LV diastolic strain, left atrial stiffness
7 and diastolic stress test (173). CMR also plays an important role in the assessment of HFpEF. It
8 allows precise estimation of LV mass and volumes, systolic function by LVEF and feature tracking
9 or tagging strain imaging, and evaluation of diastolic function by LV time-volume filling curves
10 and phase contrast assessment. Recently, a physiological CMR model was validated invasively
11 for estimating the LV filling pressure in patients with HFpEF (174,175). CMR's principal
12 advantage is its ability to provide tissue characterization and direct assessment of replacement
13 and interstitial fibrosis by T1 mapping and extracellular volume fraction computation. It can help
14 exclude important differential diagnoses (e.g. myocardial disease, pericardial constriction) and
15 elucidate conditions that underlie the development of HFpEF (e.g cardiac amyloid). Further,
16 CMR allows precise estimation of left atrial volume and RV function in HFpEF patients. Elevated
17 T1 and extracellular volume (ECV) expansion indicating myocardial fibrosis have been
18 demonstrated in patients with HFpEF (176), correlate with histologically detected fibrosis
19 (176,177) and are directly associated with LV stiffness and impaired diastolic function (177,178).
20 ECV expansion also correlates with other markers of disease severity such as NT-proBNP, 6
21 minutes' walk test distance, NYHA class, and right atrial pressure. Importantly ECV expansion is
22 also an important predictor of outcome in patients with HFpEF (179). Of note, ECV expansion
23 can be observed prior to the development of overt heart failure in patients with predisposing
24 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 cardiomyopathies

Overall, there are significant sex differences in myocardial imaging parameters at baseline with women having lower LV mass and volumes, and higher right ventricle (RV) function parameters (182), such as RV ejection fraction 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 cardiomyopathy genes have an identified pathogenic mutation, with TTN truncations most commonly implicated (187). Symptoms and signs are typical for heart failure but are also nonspecific with shortness of

1 breath and cough predominating. Therefore, diagnosis can initially be missed when occurring in
2 the last trimester of pregnancy. Patients frequently present with acute heart failure, but also
3 with ventricular arrhythmias and/or cardiac arrest.

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

17 Pre-existing cardiomyopathies, like hypertrophic or dilated cardiomyopathy or
18 conditions occurring during pregnancy like TTS, are possible differential diagnoses for post-
19 partum cardiomyopathy. Echocardiography is the first-line method and CMR the next one for
20 identifying other pre-existing cardiomyopathies without ionizing radiation (160). Other potential
21 differential diagnoses can include pulmonary embolism, CAD, pregnancy-related SCAD (185).
22 Imaging work-up in pregnant patients presenting with breathlessness requires careful planning.
23 Use of radiation, radiopharmaceuticals, and contrast agents should be minimized. Both
24 pulmonary and CCTA are associated with minimal foetal radiation, and ventilation-perfusion
25 scintigraphy offers relatively low foetal irradiation, which may minimised further if the

ventilation part is omitted. Cardiac catheterization and coronary angiography also cause relatively low foetal exposure. Even nuclear cardiology procedures are unlikely to exceed negligible-risk (50 mGy cutoff) 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 cardiomyopathies (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 a left ventricular wall thickness (larger than >15mm) 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/ height or the introduction of sex-specific cut-off values. Further research in this important area is required. Moreover, specific cardiomyopathy types e.g. wtATTR-CM are observed more frequently in men vs. women (~9:1) helping in the diagnosis (196).

Echocardiography is the first line imaging method in all cardiomyopathies. CMR provides added value, contributing to risk stratification, providing precise functional assessments (e.g. ejection fraction 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 dilated cardiomyopathy (DCM) in their primary and secondary forms. In cases of unexplained LVH, HCM should be ruled out as 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 cardiomyopathy (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 ICD implantation, with a high scar burden indicating an increased risk of death in both men and women (198).

DCM may be caused by a variety of underlying diseases. LGE-imaging is crucial in the diagnostic workup of DCM patients as it can differentiate between ischaemic and non-ischaemic causes (199). 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 effusion, 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

1 and nuclear cardiology may provide important information for its diagnosis. Moreover, vasculitis
2 can present with inflammation of the aorta and coronary arteries as well as the pericardium and
3 myocardium(200). A careful stepwise approach using ultrasound, CCTA as well as CMR allows
4 the identification of aortic and coronary wall thickening and stenosis. 18F-FDG PET imaging
5 allows assessment of inflammation activity in the vessel wall and myocardium (201). Native T1
6 and ECV values are useful markers for monitoring the progression of the disease.

7 Interestingly, the development of focal fibrosis in myocarditis seems to be related to
8 sex, with women overall developing less scar than men (202). More subtle changes in T2
9 mapping parameters may therefore be helpful to identify and follow myocarditis in women
10 although these should always be compared to appropriate reference ranges in age and co-
11 morbidity matched patients. That underlines the need of a careful assessment of diffuse
12 inflammatory changes as done by T2 sequences to show and monitor the full picture of the
13 disease.

14 **Valvular heart disease**

15 **Aortic stenosis**

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

19 The differences that can be identified using multimodality imaging are summarized as
20 follows: 1) for the same severity of AS, women display less valve calcifications of the leaflets even
21 after adjusting for their smaller BSA or aortic annulus area (203). This may be because they have
22 more valve fibrosis. This difference is reflected in international recommendations where different
23 CT calcium score thresholds are recommended in men and women to identify likely severe aortic
24 stenosis (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, women >1600 = highly likely; men >2000, women >1200 = likely; men <1600, women <800 = unlikely) (204,205). 2) 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. 3) 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 ejection fraction normal flow / low gradient AS (206). 4) 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 LV mass (LVM) with more often a normal geometry and LV concentric remodelling pattern than men (206). 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 (205,207). CMR studies have also demonstrated a sex difference regarding the pattern of myocardial fibrosis. Women appear to present with more diffuse fibrosis, quantified with extracellular volume (ECV) fraction by T1 mapping, but similar or less focal fibrosis identified by LGE compared to men (205).

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) (208). 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 (209). 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 (210). 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 remodeling in women are potential reasons for this observation (210).

1 Imaging plays a pivotal role in decision making regarding the need for AVR and whether
2 to perform SAVR or TAVR, by assessing the valve leaflet morphology of the leaflets, the amount
3 and distribution of calcifications, the extravalvular consequences of AS, and to assess the
4 anatomy of the aorta and vascular access. The aortic annulus is usually smaller and the coronary
5 height lower in women than in men. All this information is crucial for planning the aortic valve
6 intervention. Imaging is routinely used for the follow up of the patients and using imaging to
7 predict regression of LV hypertrophy, which is a strong predictor of good functional recovery.
8 Interestingly, reverse remodelling of the LV is more likely in women, especially after TAVR (210) .

9 The prevalence of bicuspid aortic valve (BAV) is threefold to fourfold more common in
10 men than in women, but women with BAV are more likely to develop AS than men, regardless of
11 age of presentation. Fusion between the right and non-coronary cusps may be more common in
12 women and they also have less aortopathy (211).

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

21 **Mitral valve regurgitation**

22 Significant sex-differences have been reported in primary mitral regurgitation (MR). As
23 compared to men, women more frequently have a rheumatic aetiology of primary MR and,
24 therefore, more often present with concomitant MV stenosis (212,213).

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 (214). These differences might also explain the reported higher proportion of men undergoing MV repair and women requiring MV replacement (215). Importantly, several studies have suggested that, similar to AS, women are referred to MV interventions at a more advanced stage of the disease (216). 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 (216). 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 body surface area (214). According to the current 2017 ESC/EACTS VHD guidelines, diagnosis of primary MR is crucial, and is recommended that close follow-up should be performed using TTE as the first-line imaging technique (217). When indicated (e.g. in case of suspected severe MR), TOE should be advised for a better quantification of MR severity (217). TOE better characterizes the complex MV lesions frequently present in women, particularly when including three-dimensional 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) (218). CMR can also provide an accurate assessment of MR severity when echocardiographic measurements are inconclusive as well as of LV size and function (219). Although in current guidelines, imaging-based criteria for MV interventions are not sex-specific and not indexed to body surface area, 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 (219-221). Arrhythmic MV prolapse has been

described in several studies as being more frequent in young women (220,221), but in other studies was reported as being more frequent in men with comorbidities (219). 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) (222) 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 (220). 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 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 (223).

Female sex is a well-known major risk factor for pulmonary hypertension (224). Women are more susceptible to develop pulmonary arterial hypertension (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 (225) (225-226) and greater improvement after targeted therapeutic compared to 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 (227).

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 (228) and Framingham (226) 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, AF, heart failure and right ventricular systolic pressure have been significantly associated with tricuspid regurgitation progression (229)(230).

Stroke

There are stroke risk factors unique to women which physicians should be aware of: use of oral contraceptives (231), occurrence of menopause before age 42 (232), menopause hormone therapy initiated more than 5 years after menopause onset (233), migraine with aura in women <55 years (234), pregnancy and preeclampsia. In comparison to non-pregnant women, pregnancy is associated with a 3-fold increased stroke risk (mainly for intracerebral haemorrhage) whilst preeclampsia is associated with a 14.5-fold increased stroke risk within the first three years (235). Furthermore, classical CV risk factors present sex differences in their effects on risk, mostly to the detriment of women (236).

Cardioembolic stroke represents 20–25% of all ischaemic stroke (IS). The most common major-risk source of cardioembolism is atrial fibrillation (AF). Noteworthy, women have lower age-adjusted incidence of AF but when present face a greater lifetime AF-related risk of stroke (236). Other major-risk sources are cardiomyopathies 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.

Once acute IS is suspected, imaging assessment is recommended with no differences between sexes. Emergent brain imaging with nonenhanced CT is advised to exclude

intracerebral haemorrhage and determine a patient's candidacy for thrombolysis or mechanical thrombectomy (237). MRI is as accurate as nonenhanced CT in detecting hyperacute intracerebral haemorrhage (238). CCTA with perfusion or MRI angiography with DW-MRI are also useful for selecting candidates for mechanical thrombectomy after 6 hours (239). In candidates for thrombectomy and in those with suspected large vessel occlusion, noninvasive 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 hours. Echocardiography is the first imaging technique in the diagnostic strategy to identify central sources of cardioembolism, and help classify stroke aetiology, to design secondary prevention, and to detect comorbidities, including CAD. Still, its diagnostic capability in unselected patients is limited, with inconsistent results among studies both for TTE and TOE (240). CMR and CCTA are second-line methods indicated in patients with cryptogenic stroke and a nonconclusive echocardiographic study, providing complementary information useful for secondary prevention (241). Screening for occult CAD in IS patients either with CMR or CCTA remains a matter of debate.

Final remarks

Cardiovascular diseases in women demonstrates 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 cardiovascular disease. 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 (242). 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 health care disparities are addressed with adequate knowledge and understanding, tailored diagnosis pathways and appropriate management as well as timely primary prevention. Cardiovascular imaging is central to all these steps.

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1

2 Table 1. Multimodality imaging of coronary artery disease in pregnancy, pre-eclampsia and
 3 menopause

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

4 Echo: echocardiography; CMR – cardiovascular magnetic resonance; CCT – cardiac computed tomography; Nuclear: nuclear cardiology

5 techniques; CO: cardiac output; LVH: left ventricular hypertrophy; LV: left ventricle; RAA: renin-angiotensin-aldosterone; CAD: coronary

6 artery disease

7

8

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.

1 Table 3 – Cardiotoxicity diagnosis using multimodality imaging

	Echo	CMR	CCT	Nuclear
Ventricular volumes and function	+++*	++++	+	++
Ventricular deformation/strain	++++	+++ /++++	-	-
Tissue characterization	++	++++	+	++
Myocarditis	-	++++	-	+++ /++++
Pericardial disease	+++	++	+++	-
Valve disease	++++	++ /+++	+	-
Coronary artery disease	+++	+++	+++	+++

2 * 3D more reproducible than 2D

3 Echo: echocardiography; CMR – cardiovascular magnetic resonance; CCT – cardiac computed tomography; Nuclear: nuclear cardiology
4 techniques

3 Echo: echocardiography; CMR – cardiovascular magnetic resonance; CCT – cardiac computed tomography; Nuclear: nuclear cardiology
4 techniques; CAD – coronary artery disease; CMD – coronary microvascular disease; CRF – coronary reserve flow; SPECT – single photon
5 computed tomography; PET – positron emission tomography

1 Table 5. Chronic coronary syndromes. Comparison of women versus men*

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

2 *Women have lower pretest probability (2019 ESC guideline) which impacts the accuracies of some functional modalities for CAD .
3 Echo: echocardiography; CMR: cardiovascular magnetic resonance; CCT: cardiac computed tomography; Nuclear: nuclear cardiology
4 techniques; CMD: coronary microvascular dysfunction; CFR: coronary flow reserve; CMD: coronary microvascular dysfunction; CAD :
5 coronary artery disease; PET: positron emission tomography.
6
7

Figures Legends:

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 wall (C), increased native T1 values (D) and ECV (34%) representing focal and interstitial fibrosis. A CCTA (E) excluded coronary artery disease.

Abbreviations: 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.

Figure 2. A representative case of MINOCA. A 45 year-old woman with systemic lupus erythematosus 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-C: Coronary angiography with no coronary lesions (B,C). D-E: CMR short-axis images on T2-weighted depicting oedema and subendocardial LGE depicting necrosis at inferior wall; F-G: 3D and 2D TOE showing a marantic vegetation likely cause of coronary embolism. Abbreviations: CMR: cardiac magnetic resonance; T2: myocardial relaxation constant T2; LGE: late gadolinium enhancement; TOE – transesophageal echocardiography

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

Figure 4. Case of a 37 year-old woman with preeclampsia in last 10 weeks of the pregnancy with heart failure symptoms at 3-4 hours after delivery. A-B: TTE 2nd day after delivery with dilated LV, LVEF 46% and GLS -13,1 %; C-D: TTE 1 month follow-up LVEF 59% and GLS -20.1%.

Abbreviations: TTE: transthoracic echocardiography; LV: left ventricle; LVEF: left ventricle ejection fraction; GLS; global longitudinal strain

Figures (attached independently):

Figure 1:

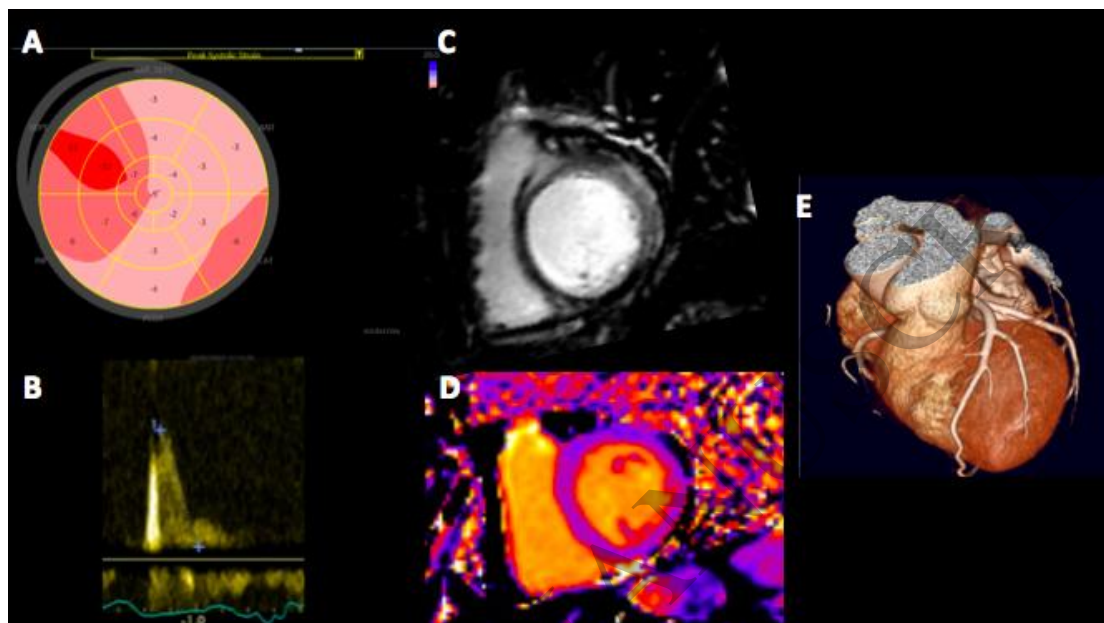


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Figure 2:

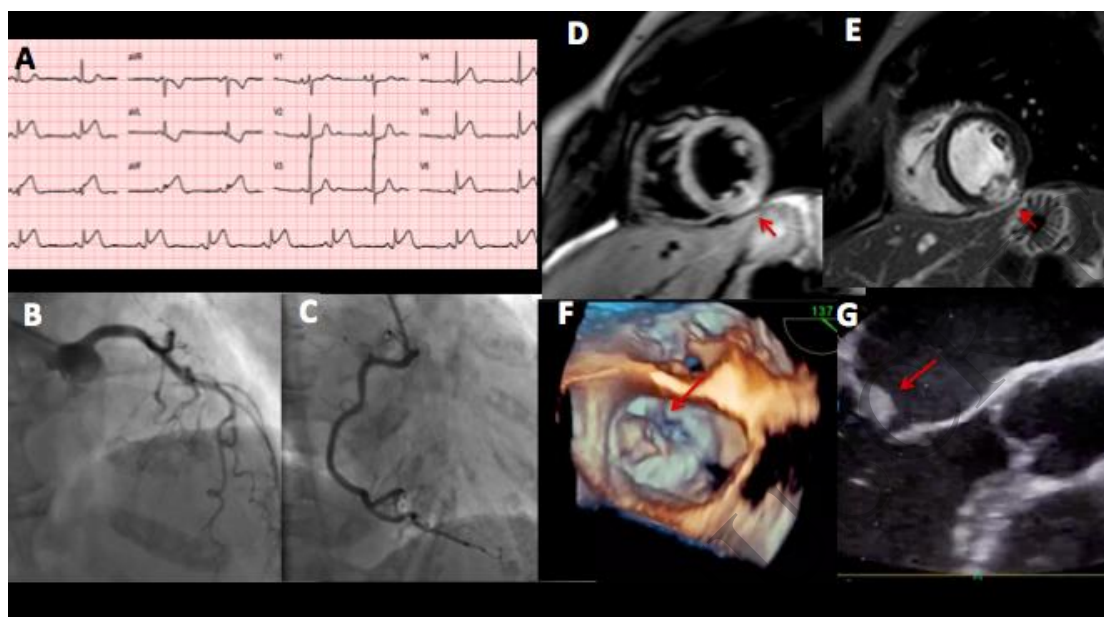




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1 Figure 3

2

	Male HFpEF	Female HFpEF
		
Clinical characteristics	Younger Age	Older Age
Principal mechanism	Hypertension Endothelial dysfunction	Atrial Fibrillation
Comorbidities	Obesity Coronary artery disease	Hypertension Anemia 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

3

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

6

7

Figure 4

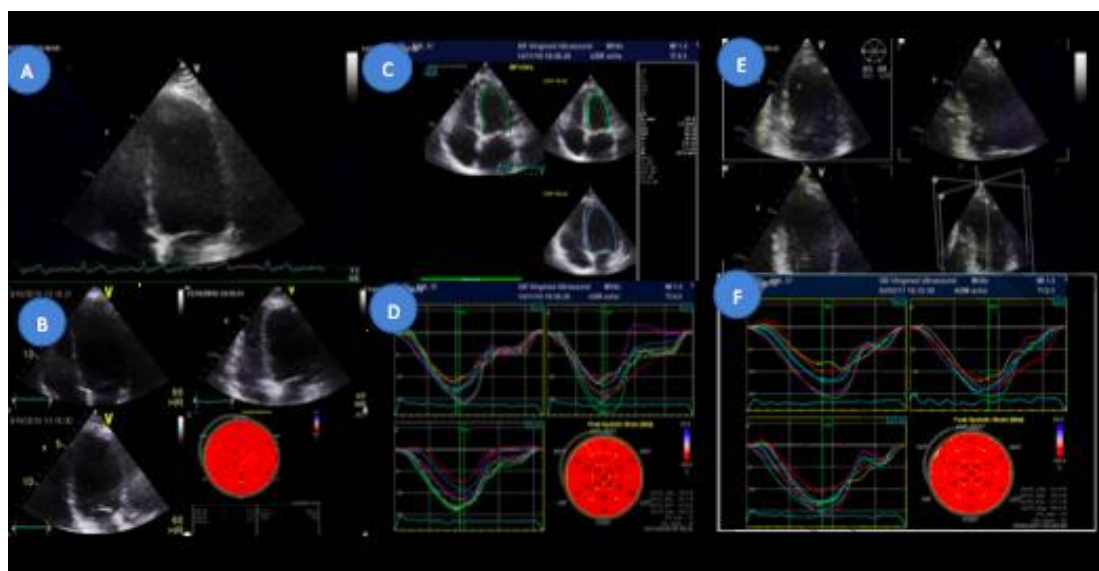
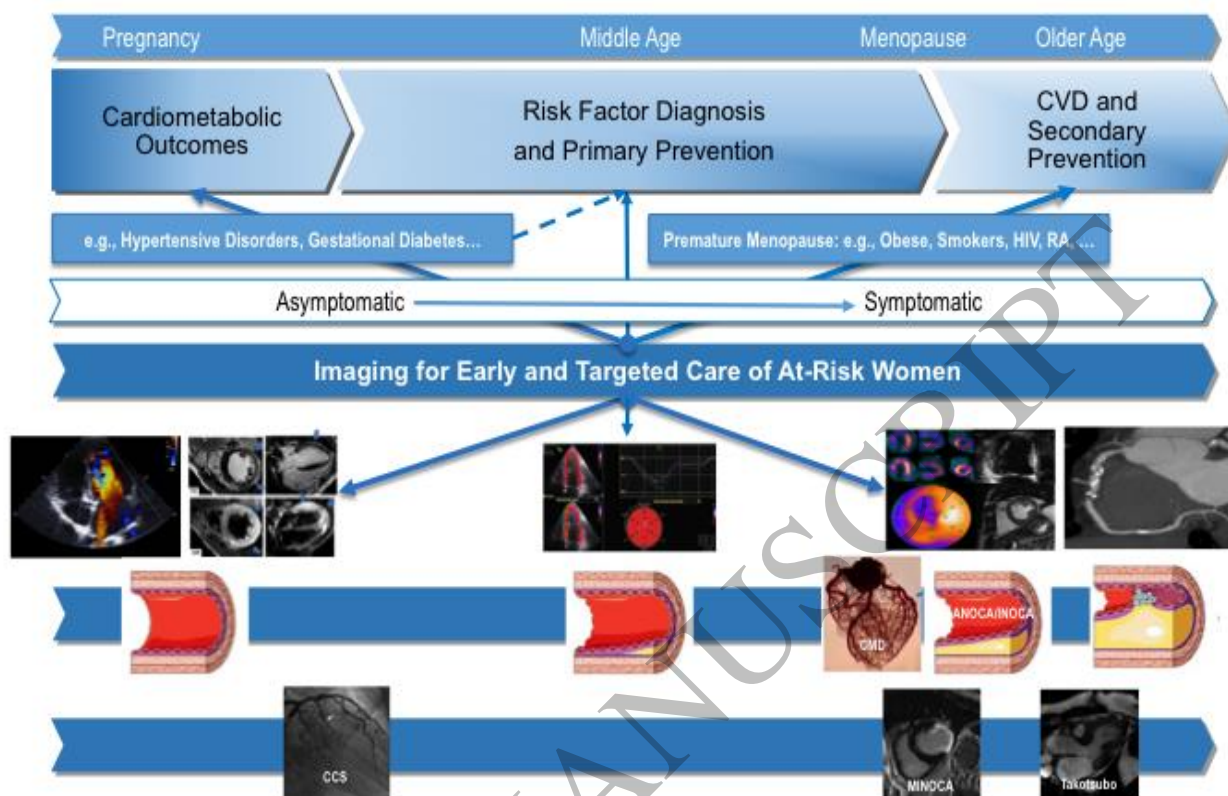


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Graphical Abstract
147x82 mm (x DPI)