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ΕΚΕ

Νοέμβριος 2020 | Τόμος 61

CARDIOVASCULAR DISEASE IN WOMEN:
Expert Panel Statement of Women in Cardiology of Hellenic Cardiological Society. Main Text

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OFFICIAL PUBLICATION OF THE HELLENIC CARDIOLOGICAL SOCIETY

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Abstract

The perception that women represent a low risk population for cardiovascular disease (CVD) needs to be reconsidered. Starting from risk factors, women are more likely to be susceptible to unhealthy behaviors and risk factors that have different impact on CV morbidity and mortality compared to men. Despite the large body of evidence as regards the effect of lifestyle factors on the CVD onset, the gender-specific effect of traditional and non-traditional risk factors on the prognosis of patients with already established CVD has not been well investigated and understood. Furthermore, CVD in women is often misdiagnosed, underestimated and undertreated. Women also experience hormonal changes from adolescence till elder life that affect CV physiology. Unfortunately, in most of the clinical trials women are under-represented, leading to limited knowledge of CV and systemic impact effects of several treatment modalities on women's health. Thus, in this manuscript a group of female Cardiologists from the Hellenic Society of Cardiology present the special features of CVD in women: the different needs in primary and secondary prevention, as well as therapeutic strategies, that may be implemented in daily clinical practice in order to eliminate underestimation and undertreatment of CVD in female population.

Keywords:
Women; gender; cardiovascular disease; risk factors; menopause; pregnancy; breast cancer

Abbreviation list

AAOCA= anomalous aortic origin of a coronary artery
ACS= acute coronary syndrome
AH=Arterial Hypertension
AF=atrial fibrillation
ARD=Autoimmune rheumatic disease
CAD=coronary artery disease
CVD=cardiovascular disease
CCTA=coronary computed tomography angiography
DCM=dilated cardiomyopathy
DM=Diabetes mellitus
ET= essential thrombocythemia
FH= Familial hypercholesterolemia
HF=heart failure
HFpEF=heart failure with preserved ejection fraction
HFrEF=heart failure with reduced ejection fraction
HCM=hypertrophic cardiomyopathy
LDL= low density lipoprotein
MB=Myocardial bridging
STEMI= ST-segment elevation myocardial infarction
MINOCA= myocardial infarction with nonobstructive coronary arteries
SCAD= Spontaneous coronary artery dissection
PPCM=peripartum cardiomyopathy
TAVR= transcatheter aortic valve replacement
SAVR=surgical aortic valve replacement
PAD=peripheral artery disease
PAH=primary pulmonary hypertension
PCOS=polycystic ovary syndrome
PMW =post menopause women
PPCM=Peripartum cardiomyopathy

Introduction

Over the last decades, epidemiological data have demonstrated high incidence of cardiovascular disease (CVD) in women. It seems that the current theory that women represent a low risk population needs to be reconsidered. Women are more likely to be susceptible to unhealthy behaviors and risk factors have different impact on CVD morbidity and mortality between sexes [1]. Despite the large body of evidence as regards the effect of lifestyle factors on the CVD onset, the sex-specific effect of traditional and non-traditional risk factors on the prognosis of patients with already established CVD has not been well investigated and understood. Furthermore, CVD in women is often misdiagnosed and underestimated and subsequently undertreated; while women also experience hormonal changes from adolescence till elder life that affect CVD physiology. Unfortunately, in most of the clinical trials women are under-represented, leading to limited knowledge of CVD and general effects of several treatment modalities on women's health. It is utmost important to gather more scientific data on women with the potential to depict the progressive change in the lifestyle impact on cardiac health, from first to recurrent CVD events, guiding prevention, therapeutic and rehabilitation strategies, tailor-made for the specific needs of women population [2-5].

Thus, in this manuscript a group of female Cardiologists present the special features of CVD in women; the different needs in primary and secondary prevention, in therapeutic strategies, that maybe helpful for colleagues in daily clinical practice, in order to eliminate underestimation of CVD diagnosis in female population. For the present Expert Statement > 500 PubMed articles from January 2011 to August 2020 were considered in the context of a main text.

A. Coronary artery disease (CAD) in women. Genetic disorders and traditional risk factors

A1. Arterial Hypertension

Arterial hypertension (AH) is a major risk factor for CVD morbidity and mortality and is usually accompanied by other important risk factors like obesity, hyperlipidemia, diabetes mellitus (DM) [5]. AH prevalence increases over time, while, it often remains undiagnosed for a long time, especially in women. Moreover, it seems that there are multi-factorial sexual differences in the pathophysiology of AH which include the role of sex hormones, sympathetic nervous system activation and variations in arterial stiffness [6] Women younger than 40 years of age have a lower systolic (SBP) and diastolic (DBP) blood pressure than males. This trend is reversed after 55 years of age [5]. Androgens and estrogens affect CV function and regulate BP levels acting on the renin-angiotensin-aldosterone system (RAAS). While androgens increase BP by RAAS stimulation, estrogens have the opposite effect reducing plasma renin and angiotensin converting enzyme (ACE) activity. Estrogens protect against the salt-induced increase in BP, diminish the sympathetic nervous system activity and stimulate the production of nitric oxide (NO) leading to vascular stiffness reduction. Additionally, estrogens increase the elastin production and decrease the deposition of collagen in human arteries and subsequently they influence the remodeling of arterial wall, **Table 1** [7-11].

Table 1. Gender Differences in Arterial Hypertension

	Males	Females (premenopausal)
Sex Hormones	Testosterone	Estrogens and Progesterone
	▪ RAAS stimulation	▪ PRA and ACE levels reduction ▪ Protection against Salt-induced BP ▪ SNS activity suppression ▪ NO production stimulation ▪ Elastin production increase
Blood Pressure	Increased	Decreased
SNS and RAAS activity	Increased	Decreased
Arterial stiffness	Increased	Decreased

After menopause plasma renin increases, angiotensin I receptors are up-regulated while angiotensin II receptors are down-regulated and arterial stiffness increases. The rate of SBP increase tends to be accelerated in postmenopausal women (PMW) until the sixth decade of life and then it slows down [12-3]. In terms of medical therapy, no differences have been shown in the prevention of major CVD events between males and females with all the antihypertensive drug classes. However, women take more medications than men, usually diuretics and angiotensin receptor blockers (ARB), but they are less likely to achieve the recommended BP goals. Regarding adherence to treatment, female sex is a negative predictor probably due to older age, depressive symptoms, and dissatisfaction with the communication with their care provider [14]. Pharmacokinetics in women may depend on the menstrual cycle, pregnancy, lactation, and menopause. It should be mentioned that there are sex differences regarding drug metabolizing enzymes (cytochrome P450), transporters and multiple drug-resistance proteins [6]. The different classes of antihypertensive drugs are:

a. Thiazide diuretics. Older women have a greater prevalence of reduced glomerular filtration rate so they must be aware that an appropriate use of thiazide diuretics might worsen it. Additionally, women are at a higher risk for thiazide-induced hyponatremia and hypokalemia, serum urate increase leading to glucose intolerance as well as uric acid increase with a deleterious action on vessel wall.

b. Beta blockers. Several beta blockers have sex specific pharmacokinetics (women experience greater exposure in propranolol and metoprolol but similar one compared with men for carvedilol, nebivolol and atenolol). Labetalol is generally considered well tolerated in pregnant women.

c. RAAS inhibitors. Men may require larger dosages of ARBs than women while women develop more angioedema and cough than men in response to treatment with ACE inhibitors. All RAAS inhibitors are contraindicated in women who intend to become pregnant due to their potential teratogenic effect.

d. Calcium channel blockers. BP response to amlodipine as well as in the risk of peripheral edema is higher in women than men and particularly in elderly.

It's obvious that men and women differ regarding BP pathophysiology and response to medical treatment. In the future, the sex parameter should be included in all stages of scientific research as well as in medical practice since a sex-dependent approach might lead to more appropriate therapy.

A1.1. Pharmaceutical treatment of AH in women

Despite the magnitude of their impact on health systems, treatment and control of AH remain suboptimal in women. There is currently no strong evidence for differential effects of antihypertensive therapy based on sex and AH guidelines do not differ among men and women[15]. However, most clinical trials on which guidelines were based, do not include risk stratification by sex. Although the Systolic Blood Pressure Intervention trial (SPRINT) confirmed that a lower BP goal is better, outcome differences in women were not statistically significant [16]. Notably, enrollment of women was only 36% and event rates were low. Thus, some believe that optimal BP goals for women have not been established as well as for men. There is evidence from smaller studies that hypertensive women appear to have a better BP response than men to diuretics, ACE inhibitors, and beta-blockers [17-9]. In addition, a meta-analysis has revealed that calcium channel blockers may be more beneficial in women than ACE inhibitors for stroke prevention [20]. Although pathophysiologic mechanisms for this are still obscure it is apparently related to different impact of pharmacokinetics of some drugs in the female population. For example, sex hormones may affect drug metabolism and efficacy. On the other hand, women may experience more antihypertensive side effects than men, and this may impact the choice of treatment and adherence [21]. Women are more likely to develop hyponatremia, hypokalemia, or arrhythmia with diuretics.

Furthermore, the existence of multiple comorbidities in women may influence the choice of antihypertensive treatment. It is worth noting that findings from a large randomized clinical trial provide evidence of a beneficial effect of thiazide-type diuretic therapy in reducing hip and pelvic fracture risk, compared with treatment with other antihypertensive medications[22]. Finally, women seem to have a different profile in terms of their pharmaceutical compliance to men's AH, with key negative factors in this include dissatisfaction with their health care providers and depressive symptoms[23].

The cornerstone of differential pharmaceutical management of AH in women pertains to those who are pregnant or about to become pregnant. Although antihypertensive therapy reduces risk of severe AH, there is a paucity of data to guide pharmaceutical treatment [24].

A2. DM and Metabolic Syndrome (MetS)

MetS is defined as a constellation of 3 out of 5 CV risk factors which include: a) increased waist circumference (WC) with specific cutoffs based on the population and sex b) elevated triglycerides (TG) > 150mg/dL (1.7mmol/L), c) reduced high density lipoprotein cholesterol (HDL-C) <40mg/dL (1.0mmol/L) in males and <50mg/dL (1.3mmol/L) in women, d) BP >130/85 mmHg and e) elevated fasting glucose >100mg/dl [25],. Other CV risk factors such as age, sex, family history, smoking and levels of LDL-C are not included in the definition. The prevalence of the MetS defers based on the country, however it rises worldwide [25] and some data suggest that is more common in women. Mets is associated with increased CV mortality and development of DM type 2[26].

Women with polycystic ovary syndrome (PCOS) have greater prevalence of MetS in the setting of insulin resistance which is frequently present in both conditions[27]. The more common components of the MetS present in women with PCOS are increased WC, TG and decreased HDL-C[28]. Metabolic disturbances are present even in non-obese women with PCOS[29]. HRT which is used for treatment via its effects on BP, lipoprotein levels, body weight and insulin sensitivity may increase even more the risk for MetS[29]. During normal pregnancy weight gain, progressive decrease in insulin resistance, increase in LDL-C and TG levels and a decrease in HDL-C levels occur[30]. Establishing the diagnosis of MetS in pregnancy is controversial since the aforementioned changes in normal pregnancy coincide with the diagnostic criteria of MetS, however modified criteria have been proposed for the diagnosis of MetS during pregnancy[31]. Women diagnosed with MetS found to have an increased risk for pulmonary embolism (PE) and gestational diabetes mellitus (GDM), which have been linked to development of DM type 2 and CVD later in life[32]. Identifying those women early, altering their diet and exercise habits can potentially decrease the adverse outcomes[33], Women with history of GDM and PE during pregnancy have been shown to have increased prevalence of MetS later in life [34-5].

During menopause, and especially at the menopausal transition, there is an increase in the incidence of MetS secondary to the unfavorable effects of menopause on the different components of MetS (increase in WC, TG levels, fasting glucose and BP and decrease in HDL-C)[36]. HRT provided no evidence for the primary or secondary prevention of adverse cardiovascular events [37]. Lastly sparse data suggest that pre and post-menopausal women (PMW) who are breast cancer survivors receiving chemotherapy have a high risk of developing MetS [38].

Screening of MetS in women throughout the different phases in their life is mandatory since in can potentially decrease their long-term morbidity and mortality.

Table 2: Lifestyle Changes in women with MetS

Recommendation	Class	Level
Management of the individual components of the MetS with emphasis on lifestyle modification (weight loss and physical activity) before initiating medical therapy is recommended.	I	A
In women with diagnosis of MetS the physician is useful to encourage individuals to join comprehensive programs that support the adoption of healthy lifestyles, including diet and physical activity, aiming for moderate but sustained weight loss.	I	C
At least 150 minutes a week of moderate aerobic PA (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination is recommended.	I	A
Body weight control is indicated to avoid obesity (BMI >30 kg/m2, or waist circumference >88 cm in women) and aim for healthy BMI (about 20–25 kg/m2) and waist circumference values <80 cm in women to reduce BP and CV risk.	I	A
For women with excess weight; aiming to achieve a weight loss of 5-10% of initial body weight during the first year is useful.	I	C
Following a diet based on the published guidelines emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended.	I	B
Following the Mediterranean diet on MetS is useful.	IIα	B

Table 3: Medical/Surgical management of MetS Ref#41-44

Recommendation	Class	Level
Management of the different components of the MetS based on published guidelines is useful.		
Dyslipidemia in women with MetS should be treated according to the published guidelines.		
Statin therapy is not recommended in premenopausal patients who are considering pregnancy or are not using adequate contraception.	III	C
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk women with hypertriglyceridemia [TG levels >2.3 mmol/L (>200 mg/dL).	I	B
In high-risk (or above) women with TG levels between 1.5-5.6 mmol/L (135-499 mg/dL) despite statin treatment, n-3 PUFAs (icosapentethyl 2 2 g/day) should be considered in combination with a statin.	IIa	B
In high-risk women who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	IIb	C
In women with MetS and concomitant increase in the LDL cholesterol management based on the recently published guidelines is recommended with statins, ezetimide and PCSK 9 inhibitors if necessary tailored on the individual CV risk assessment.	I/IIb	A/B/C
Diuretics (thiazides/thiazide-like, e.g. chlorthalidone and indapamide) and beta-blockers are possibly contraindicated in patients with metabolic syndrome because of their unfavorable effect on glucose tolerance.	II a/b (table 20 at ESC guidelines	C
In women with gestational hypertension, pre-existing hypertension (can be component of the MetS) superimposed by gestational hypertension, or with hypertension and subclinical organ damage or symptoms, initiation of drug treatment is recommended when SBP is >140 mmHg or DBP >90 mmHg. In all other cases, initiation of drug treatment is recommended when SBP is >150 mmHg or DBP is >95mmHg.	I	C
Methyldopa, labetalol, and CCBs are recommended as the drugs of choice for the treatment of hypertension in pregnancy.	I	B (methyldopa) C (labetalol or CCBs)
ACE inhibitors, ARBs, or direct renin inhibitors are not recommended during pregnancy.	III	C
Increased glucose/Diabetes in MetS should be treated according to the published guidelines/consensus.		
Metformin should be considered in women with the diabetic/prediabetic component of the MetS.	I	A
Bariatric surgery causes long-term weight loss, and reduces DM and risk factor elevations, with effects that are superior to lifestyle and intensive medical management alone.	IIa/b	A

A3. Women smokers and CVD

Smoking is an important cardiac risk factor for development of CVD in both women and men. Although there are fewer adult women smokers there is evidence that women have a 25% increased risk for CAD compared with men in all age groups, except for the youngest (30-44 years) [39]. Recent studies indicate that the proportion of young patients particularly women (<60 years), who present with smoking and/or obesity as their only risk factors at the time of their hospitalization for ST-elevation myocardial infarction (STEMI), has continuously increased between the years 1995 to 2010. The cardio protective effects of female hormones are well studied and recognized but it is important to emphasize that women smokers lose overtime their 'gender' protection against CVD. This is the result of the antiestrogenic effect of smoking and the alteration of the lipid profile in women smokers. The impact of smoking is more evident in PMW due to the lack of natural estrogen protection, or women at risk of thrombosis such as women taking oral contraceptives. The combination of smoking with oral contraceptive use has a synergistic effect on risk of acute MI, stroke, and venous thromboembolism [40-1]. High prevalence and the increased risk both passive and active smoking is one of the most important known modifiable risk factors for CVD.

Women should be advised to quit smoking and to avoid environmental tobacco smoke exposure. All cardiologists should provide counseling at each encounter and approved pharmacotherapy for smoking cessation (nicotine replacement therapy, bupropion and varenicline) must be discussed unless contradicted [40].

A4. Familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a common autosomal dominantly inherited disorder, characterized by cholesterol deposits in the corneas, eyelids and extensor tendons, elevated plasma low density lipoprotein (LDL) cholesterol (LDL-C) concentration and rapidly progressing vascular disease, especially premature CAD [46]. The aortic valve may also be affected [41] Heterozygous FH affects one per 200-500 births (according to the race and ethnic origin) [42]. The plasma total cholesterol concentration is usually more than 290 mg/dL. The triglycerides concentration is normal or moderately elevated [42]

In its heterozygous form, the clinical manifestation of CAD may become obvious after the second decade of life. In untreated patients, the disease will eventually lead to death the 50% of men and 15% of women until the age of sixty; it is noteworthy that the 85% of men will experience a myocardial infarction (MI) within the same period of time [43-4]. The most prevalent underlying molecular defect of FH consists of one of several mutations in the gene coding for the LDL receptor protein. There are also other genes involved in LDL metabolism, which mutations may lead to the clinical manifestation of FH [45]. In rare cases (1:250,000-600,000 births) a child may inherit the abnormal gene from each parent (homozygous FH) [46]. In these patients, the plasma total cholesterol concentration may be >600mg/dL and in some cases the concentrations more than 1000mg/dL or even 1500mg/dL were reported. Clinically evident atherosclerosis (i. e. MI, occlusion of carotid artery or aortic valve stenosis) is usually present at the age of 4-10 years.

Women with FH should be treated according to specific guidelines [46].

B. CAD in young women-Non-traditional risk factors

B1. CV involvement in autoimmune rheumatic diseases

Autoimmune rheumatic diseases (ARDs) affect 8% of the population; while 78% of patients are women [47]. Sex differences are the result of various causes including sex hormones, microchimerism, genes on X or Y chromosomes, X chromosome inactivation and environmental factors [48]. Estrogens can increase directly the incidence of ARDs in women by elevating auto-antibodies and amplifying T- and B-cell responses [48]. Although ARDs affect several organs and tissues, their prognosis is mainly linked to CVD. However clinically overt heart involvement is not typical and can be misinterpreted as a demonstration of the underlying systemic disease [49]. Therefore, CVD in ARDs is commonly neglected as the interest of rheumatologists is mainly attracted by the systemic disease [50]. The chronic effect of systemic inflammation on CV system results in endothelial dysfunction, myocardial/vascular inflammation and accelerated atherosclerosis that contribute to the increased CVD mortality and morbidity in ARDs [51]. Besides the inflammation, the cardiotoxic effects of some anti-rheumatic drugs can also contribute to the high incidence of CVD in ARDs [51]. Women preponderance is observed in rheumatoid arthritis (RA) (9 women/1 men), systemic lupus erythematosus (SLE) (9 women/1 men), systemic sclerosis (SSc) (3 women/1 men), mixed connective tissue diseases (MCTD) (3.3 women/1 men) and dermatomyositis/ polymyositis (2 women/1 men) [52-3]. In some types of systemic vasculitis there is a female preponderance as in Takayasu vasculitis [52], while in others a male preponderance as in Kawasaki disease [53]. CVD is increased in RA, SLE, SSc, inflammatory myopathies, MCTD, and systemic vasculitis [62-3]. CVD in ARDs is the result of various pathophysiologic processes including myo-pericarditis, atherosclerotic or inflammatory CAD and/or spasm, microvascular disease, valvular heart disease and also the effect of immunosuppressive medication. Heart Failure (HF) in ARDs at early stages is typically presented as diastolic dysfunction, a precursor of HF with preserved ejection fraction (HFpEF), which is typical in all ARDs, irrespective of the underlying mechanisms. Recently, a study of 275 SSc patients documented that left ventricular (LV) diastolic dysfunction is as an independent predictor of mortality [54-5]. Concerning RA, CVD occurs a decade earlier than age- and sex-matched controls and RA patients are twice more likely to develop MI and HF irrespective of age, past CVD or traditional CV risk factors [56-7]. Furthermore, RA increases the risk of non-ischemic cardiomyopathy (CM), valvular heart disease and myo-pericarditis. Additionally, silent diffuse myocardial fibrosis may lead to left ventricle (LV) dysfunction and consequent HF [56]. CVD in SLE includes myo-pericarditis, dilated CM (DCM), macro-micro-CAD, diastolic dysfunction, vasculitis or valvular disease and represents an important contributor to increased mortality [57]. Specifically, CVD accounts for 20-30% of all SSc deaths[58]. Heart involvement in dermatomyositis, polymyositis (PM) is the major causes of death, but the early detection is difficult, because overt cardiac involvement is rare. The most frequent clinical presentation includes HF (associated or not with myocarditis) and conduction abnormalities [59]. MCTD is a distinct systemic autoimmune disease, characterized by an overlap of SEL, SSc, PM/ dermatomyositis and RA, in association with antibodies against the U1 small nuclear ribonucleoprotein autoantigen (U1snRNP). According to the literature, 1/3 of MCTD patients had an excellent prognosis; however, continuous treatment with corticosteroids and/or immunosuppressive medication was needed in another 1/3 and a more aggressive disease in the remaining 1/3. Inflammation and fibrinoid necrosis of blood vessel wall are the typical characteristics of systemic vasculitis, which can be either primary or secondary, due to underlying SLE/RA. The classification of systemic vasculitis according to Chapel Hill Consensus Conference depends on the predominant type of vessels affected. They can involve the aorta and its major branches, as in giant cell arteritis and Takayasu arteritis, medium-sized vessels, as in polyarteritis nodosa and Kawasaki disease and small-sized vessels (arterioles, capillaries and venules), as in granulomatosis with polyangiitis (GPA), formerly known as Wegener granulomatosis, microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome and in mixed cryoglobulinemic vasculitis (MCV). GPA, MPA and EGPA are characterized by anti-neutrophil cytoplasmic antibodies (ANCA) and grouped as ANCA-associated systemic vasculitis [56-60]. CVD in systemic vasculitis may present as valvular heart disease, myocarditis and microvascular CAD.

B2.1. Idiopathic thrombocythemia

B2.1. Idiopathic thrombocythemia

Idiopathic thrombocythemia is a rare blood clotting disorder that produce too many platelets and mainly affects women. It's also known as essential thrombocythemia (ET). The incidence of ET for all races and ethnicities is approximately 2.2 per 100,000 population each year. ET is one of a related group of blood cancers known as "myeloproliferative neoplasms" (MPNs) that share several features, notably the "clonal" overproduction of one or more blood cell lines. About half of individuals with ET have a mutation of the JAK2 (Janus kinase 2) gene. Patients are particularly exposed to risk of thromboembolic events and evolution into more aggressive disorders (myelofibrosis, myelodysplastic syndromes and acute myeloid leukemia), with a consequent heavy burden of morbidity and mortality. Treatment should be adapted according to a classification into low risk or high risk based on the patients' age and history of thrombosis or hemorrhage (prescription of aspirin and cytoreductive drugs). Uncontrolled ET can cause pregnancy complications, including spontaneous abortion, fetal growth retardation, premature delivery, placental abruption. Pregnant women may be treated with low-dose aspirin to reduce the risk complications. Aspirin should be avoided for at least one week prior to delivery to reduce any risk of bleeding complications. Janus kinase inhibitor, given by mouth, is being evaluated to find the efficacy and safety of daily oral doses in patients who are resistant to cytoreductive drugs [61-7].

B2.2. Fibrinolysis disorders

Fibrinolysis disorders leading to the hyper-fibrinolytic bleeding can be caused by a deficiency of one of the inhibitors of fibrinolysis (plasminogen activator inhibitor type 1 [PAI-1] or α2-antiplasmin [α2-AP]), or an excess of one of the activators of fibrinolysis: tissue-type plasminogen activator or urokinase-type plasminogen activator. They are characterized by delayed bleeding after trauma, surgery and dental procedures. Bleeding in areas of high fibrinolytic activity is also common, such as menorrhagia and epistaxis. Patients with α2-AP deficiency present with the most severe bleeding episodes. Recently, it was discovered that hyper-fibrinolytic disorders are associated with a high rate of obstetric complications such as miscarriage and preterm birth, especially in a PAI-1 deficient patient. Hyperfibrinolytic disorders are probably underdiagnosed because of lack of knowledge and lack of accurate diagnostic tests. Bleeding complications can be very severe and can lead to increased morbidity and mortality if not treated adequately with antifibrinolytic therapy [68-9].

B2.3. Contraceptives drugs

Contraceptives are one of the most frequently used drugs by women. Its use can lead to increased prothrombotic risk due to activated protein C resistance, increase prothrombin levels and decrease protein S levels. The use of oral contraceptives initially was associated with a three-fold increased risk of vein thrombosis and pulmonary embolism. With lower levels of estrogen, the risk of thrombosis is 1.5 to 2 times that over control patients. In women with inherited disorders of coagulation the risk for thrombosis due to contraceptive drugs increases 30- 50-fold [70].

C. Non-atherogenic causes of ischemic heart disease

C1. Myocardial bridging

Myocardial bridging (MB) is a congenital benign abnormality in which a segment of an epicardial coronary artery runs deep and for varying lengths through the myocardial fibers, causing a systolic narrowing of the affected coronary, and that could have only a blunted impact on total effective myocardial perfusion [71], **Table 4**.

Table 4. Myocardial bridging

Prevalence
• 0.5% - 16.0% on angiography • 40% – 80% in autopsy studies
Morphology/Histology
• 67%-98% middle segment of the LAD • MB depth 1-10mm, length 4-80 mm Two subtypes • "superficial" subtype: 75% of cases, myocardial fibers traverse over the coronary artery • "deep" subtype: fibers encircle the coronary artery, more often hemodynamic consequences • The bridged segments typically spared from atherosclerosis • Flow disturbances promote accelerated atherosclerosis to the vessel segment proximal to the bridge
Pathophysiology of Ischemia
• Vessel compression during systole, which may persist into diastole and reduce the early diastolic flow • Altered intracoronary hemodynamics
Diagnosis
• Coronary angiography: "milking effect" (systolic compression of MB with ubsequent increase in vessel lumen diameter during diastole) • ICD: 'fingertip' phenomenon (a sharp increase in coronary velocity in early diastole, with a rapid deceleration and a subsequent 'plateau' in mid-late diastole) • IVUS: 'half-moon' phenomenon (echolucent area surrounding the MB throughout the cardiac cycle) • Intracoronary pressure devices (FFR, iFR) • CCTA: anatomic assessment for MBs and concomitant CAD
Treatment
For symptomatic patients • Medical therapy – first line therapy - beta-blockers (mainstay of treatment) - non-dihydropyridine calcium-channel blockers - antiplatelet therapy - nitrates are contraindicated For refractory symptoms • Surgical myotomy (MBs >5 mm deep are less amenable to surgical myotomy) • CABG (risk of graft occlusion in the presence of competitive flow) • PCI with stent (high rates of TLR, coronary perforation, stent fracture)

CABG indicates coronary artery bypass grafting; CCTA, coronary computed tomography angiography; ICD, intracoronary Doppler; IVUS, intravascular ultrasonography; LAD, left anterior descending artery; MB, myocardial bridging; PCI, percutaneous coronary intervention; TLR, target lesion revascularization.

The most frequently involved artery is the left anterior descending coronary (LAD) artery but virtually MB can be found in any coronary artery, to a varying length (4-80mm). Although, flow disturbances seem to have a protective role against atherosclerosis, likely through favorable histopathological changes, in the bridged segment, conversely, appear to promote accelerated atherosclerosis at increased rates (up to 90%) to the vessel segment proximal to the bridge [72-4].

MB remains clinically silent, being an incidental finding on angiography or autopsy, in the vast majority of cases. However, stable angina, acute coronary syndromes (ACS), ventricular rupture, life-threatening arrhythmias, hypertrophic CM (HCM), apical ballooning syndrome or sudden death have been described as rare clinical consequences of MB without a clear pathophysiological explanation.

Coronary angiography is the most common technique for diagnosing MB with the typical "milking effect" and a "step down–step up" phenomenon induced by systolic compression of the tunneled segment. Adjunctive morphological and functional features can be visualized and quantified with the use of intravascular ultrasonography (IVUS), intracoronary Doppler ultrasound, intracoronary pressure devices and coronary computed tomography angiography (CCTA). Patients with HCM and orthotopic heart transplantation have higher reported prevalence of MB. Medication is considered first-line therapy for symptomatic patients with beta-blockers (mainstay of treatment) and non-dihydropyridine calcium channel blockers, while nitrates are contraindicated accentuate systolic compression of bridged segments. For refractory symptoms when symptoms are recalcitrant to medical therapy, surgical intervention such as supra-arterial myotomy or coronary artery bypass surgery (CABG), or less preferably percutaneous coronary intervention (PCI) with drug-eluting stents (DES), can be considered. A prospective randomized trial is required to identify the best treatment strategy for patients with myocardial bridging.

There does not appear to be a difference in prevalence of MB by sex or age.

C2. Anomalous aortic origin of a coronary artery (AAOCA)

The true prevalence of AAOCA in both adults and children, although difficult to ascertain, is estimated between 0.1-1.0%. This rate ranges from 0.3-5.6% in studies of patients undergoing coronary angiography, and in approximately

1% of routine autopsy. The risk of sudden death amongst individuals with AAOCA is reported low throughout literature between 0.0001-0.35%. There has been no documented difference between male and female sex. In general, sudden cardiac death is very rare, mostly in children <10 or adults >30 years of age. Predisposing factors for myocardial ischemia have been incriminated in AAOCA patients. These include slit-like ostium and oblique take-off from the aorta which both cause ostial stenosis, intramural or interatrial course and vessel spasm. Of note is that about 26% of coronary anomalies involve some kind of aortic root abnormality (such as bicuspid aortic valve); or at least asymmetry of the aortic sinuses. Despite, the very low risk of sudden death, the consensus statement in the Guidelines for Management of Adults with Congenital Heart Disease supports that all cases of anomalous aortic origin of the left coronary artery (AAOLCA) and the symptomatic patients with right coronary artery (AAORCA) should undergo surgical treatment[87-88]. Symptomatic are considered patients with chest pain, dyspnea, palpitations, syncope, CM, arrhythmia and MI. With regards to MB, an extremely common variant, most patients are asymptomatic and when no abnormalities are observed during functional stress testing, no need arises for corrective repair. Tables 5 provides a summary of the investigations required in each main entity of AAOCA, but it has to be stated that perioperative testing is often inconclusive in risk stratification [75-6].

Table 5
Recommendations for Congenital Coronary Anomalies of Ectopic Arterial Origin

CLASS I

1. The evaluation of individuals who have survived unexplained aborted sudden cardiac death or with unexplained life- threatening arrhythmia, coronary ischemic symptoms, or LV dysfunction should include assessment of coronary artery origins and course. *(Level of Evidence: B)*
2. CT or magnetic resonance angiography is useful as the initial screening method in centers with expertise in such imaging. *(Level of Evidence: B)*
3. Surgical coronary revascularization should be performed in patients with any of the following indications:
   1. Anomalous left main coronary artery coursing between the aorta and pulmonary artery. *(Level of Evidence: B)*
   2. Documented coronary ischemia due to coronary compression (when coursing between the great arteries or in intramural fashion). *(Level of Evidence: B)*
   3. Anomalous origin of the right coronary artery between aorta and pulmonary artery with evidence of ischemia. *(Level of Evidence: B)*

CLASS IIa

1. Surgical coronary revascularization can be beneficial in the setting of documented vascular wall hypoplasia, coronary com- pression, or documented obstruction to coronary flow, regardless of inability to document coronary ischemia. *(Level of Evidence: C)*
2. Delineation of potential mechanisms of flow restriction via intravascular ultrasound can be beneficial in patients with documented anomalous coronary artery origin from the oppo- site sinus. *(Level of Evidence: C)*

CLASS IIb

1. Surgical coronary revascularization may be reasonable in pa-tients with anomalous left anterior descending coronary artery coursing between the aorta and pulmonary artery. *(Level of Evidence: C)*

or symptomatic AAOCA, as well as for all cases of AAOLCA, surgical intervention is recommended. In asymptomatic, AAORCA, therapy is tailored towards assumed risk profile. No sex differences have been reported.

C3. Coronary artery embolism

Coronary artery embolism (CE) is a nonatherosclerotic cause of acute coronary syndrome (ACS) ranging from 3-13% according to angiographic or autopsy studies [89]. CE is classified into a) direct embolism when a thrombus arises from cardiac structures such as ventricles, valves or coronaries aneurysms, b) paradoxical embolism when a clot transits from the venous to the systematic circulation through a patent foramen ovale (PFO) or atrial septal defect, c) iatrogenic when it occurs during coronary intervention procedures and d) hypercoagulability related embolism, **Table 6.** Embolic tissue may consist of platelets, fibrin, valvular material, infected vegetation or even neoplasm. Coronary or surgical intervention and atrial fibrillation (AF) are the most frequent causes of CE[77]

Table 6
Prevalence, causes, diagnosis and prognosis of Myocardial Infarction Due to Coronary Artery Embolism in the general population.

ACS indicates acute coronary syndrome; AF, atrial fibrillation; CE, coronary artery embolism; IVUS, intravascular ultrasonography; LAA, left atrial appendage; MINOCA, myocardial infarction with nonobstructive coronary arteries; OCT, optical coherence tomography; PFO, patent foramen ovale; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram.

[1] Recommendations for thrombophilia testing are extrapolated from the data for strokes.

Prevalence

- 3-13% of ACS
- High prevalence of MINOCA in women.

Causes

- **Direct embolism**
  - Left atrium
  - Left ventricle
  - Pulmonary veins
  - Endocarditis of the aortic/mitral valve
  - Valvular prosthesis
  - cardiac tumors
- **Paradoxical CE**
  - Deep vein thrombosis
  - PFO
  - Atrial septal defect
- **Iatrogenic CE**
  - Cardiothoracic surgery
  - Percutaneous interventions/ rotablation
  - Aortic/mitral valvuloplasty
- **Hypercoagulable states**
  - Cardiothoracic surgery
  - Percutaneous interventions/ rotablation
  - Aortic/mitral valvuloplasty

Embolic tissue

- **Platelets**
- **Fibrin**
- **Valvular material**
- **Infected vegetation**
- **Neoplasm**

Diagnosis

- **Coronary angiography**

Following investigation with:

- **OCT/IVUS in equivocal cases**
- **TTE (ventricular thrombus)**
- **TEE (LAA clot)**
- **Telemetry (AF episodes)**
- **Thrombophilia screen**

Prognosis

Patients with ACS due to CE have worst long term outcomes compared with the no-CE patients.

All patients post-ACS require close follow-up.

CE is suspected when there is angiographic evidence of coronary embolus/thrombus in an artery without significant atherosclerosis while patients should be investigated with other imaging modalities such as transthoracic and transesophageal echocardiogram for LV and atrial appendage thrombus respectively and with telemetry for AF. Intravascular ultrasound (IVUS) or optical computerized tomography (OCT) invasive coronary imaging can be used selectively in determining if there is underlying atherosclerosis adapting the therapeutic approach. Thrombophilia screen can be performed in selected patients. Because of the rarity of CE there is no consensus regarding treatment of ACS, but anticoagulation is the cornerstone including a) heparin, glycoprotein IIb/IIIa inhibitors, bivalirudin, thrombolytic agents with or without simple wire manipulation, thrombus aspiration and angioplasty in cardiac catheterization laboratories and b) warfarin or a novel oral anticoagulant for long term use. The duration of oral antithrombotic treatment remains unclear [77-80].

Table 7
Empiric Recommendations for the Management of ACS Due to Coronary.

Treatment *

Anticoagulation is the cornerstone of treatment

Acute phase

- heparin, glycoprotein IIb/IIIa inhibitors, bivalirudin, thrombolytic agents
- aspiration thrombectomy
- simple wiring

Post-ACS therapy

- If persistent risk factors for CE ➠ long-term oral anticoagulation.
- If reversible cause of CE ➠ oral anticoagulation for 3 months.
- If AF with low HAS-BLED score ➠ long-term oral anticoagulation (regardless CHADS2-VASc score).
- If recurrence of CE with low HAS-BLED score ➠ long-term oral anticoagulation.
- No recommendation for the optimal regimen and duration of antiplatelet therapies.
- If PCI (stenting) is required ➠ guideline-based therapy after PCI in addition to oral anticoagulation.
- If high HAS-BLED score ➠ individual risk stratification (thrombophilia screen should be considered).

ACS indicates acute coronary syndrome; CE, coronary artery embolism; PCI, percutaneous coronary intervention.

*** There is no consensus regarding treatment of ACS due to CE.**

Patients with ACS due to CE have worse long-term outcomes compared with the non CE patients, with higher all-cause and cardiac mortality during 5-year follow-up and, therefore, require close follow-up.

C4. Coronary Artery Dissection (SCAD)

SCAD is a rare condition, accounting only the 1-4% of overall ACS cases [81]. The female sex, the pregnancy and fibromuscular dysplasia (FMD) are the most important risk factors for SCAD, **Table 8**. SCAD often affects young women and is the main cause of MI in pregnant women in the third trimester or early postpartum period. The SCAD has multiple underlying causes, other than traditional CV risk factors, such as genetics, hormonal in-

Table 8
Prevalence, risk factors, mechanism, causes and diagnosis of Spontaneous Coronary Artery Dissection (SCAD)

ACS indicates acute coronary syndrome; CCTA, coronary computed tomography angiography; FMD, fibromuscular dysplasia; IVUS, intravascular ultrasonography; MRA, magnetic resonance angiography; OCT, optical coherence tomography; SCAD, spontaneous coronary artery dissection.

Prevalence

- 1% - 4% of ACS
- 2.7% of FMD

Risk factors

- Women (> 90%, 10–35% of ACS in women <50 y)
- Pregnancy (43% of ACS)
- FMD (typically affects middle-aged women)

Mechanism

- Intramural hematoma
  - spontaneous hemorrhage of the vasa vasoRum
  - disruption in the tunica intima

Causes

- Traditional cardiovascular risk factors
- Genetics
- Hormonal influences
- Inflammatory diseases
- Internal mechanical stress

Diagnosis

- **Coronary angiography**
  Three angiographic types
  - **type 1 (25%):** classic appearance of multiple radiolucent lumens or arterial wall contrast staining
  - **type 2 (70%):** diffuse smooth stenosis (usually >20 mm in length) which is either bordered by normal proximal and distal segments (type 2A) or extended to the distal tip of the artery (type 2B)
  - **type 3:** focal or tubular stenosis (usually <20 mm in length), mimics atherosclerosis, requiring intracoronary imaging for the diagnosis
- **OCT/IVUS in equivocal cases**
- **CCTA if proximal lesion and for noninvasive follow-up of the coronary arteries**
- **CCTA / MRA angiographic vascular screening for FMD and non-coronary arterial abnormalities**

fluences, inflammatory diseases, and internal mechanical stress. The main mechanism of SCAD is intramura hematoma in the vessel wall caused by either spontaneous hemorrhage of the vasa vasorum, or the disruption in the tunica intima.

There is a strong link between FMD and SCAD. FMD is a segmental non-inflammatory, non-atherosclerotic arteriopathy of unknown etiology that typically affects middle-aged women. The most frequently involved arteries are the renal and cervico-cranial arteries, but virtually any arterial bed can potentially be affected. Although, coronary involvement is not common (accounts the 2.7% of FMD cases), FMD is highly prevalent (up to 63%) among patients with SCAD [95]. Post-mortem histopathological studies and studies employing intracoronary imaging, demonstrated that coronary FMD severely disrupts the normal architecture of the coronaries and weakens the arterial wall [82-3]. It usually affects the LAD coronary artery, the middle or distal segments, with a multivessel involvement of 9-23%. Three angiographic types of SCAD have been proposed with type 2 to be the more common. CCTA may be useful for noninvasive follow-up of the coronary arteries. Due to the high prevalence of FMD, an extensive vascular screening with CCTA or contrast enhanced magnetic resonance angiography (MRA), for non-coronary arterial abnormalities is recommended at least once. SCAD is usually diagnosed angiographically, although intracoronary imaging (mainly OCT or IVUS) can be useful.
Conservative therapy is generally the preferred strategy in patients with SCAD who are clinically stable, with no high-risk anatomy and has been associated with favorable outcomes.

Although, a spontaneous angiographic healing is observed in most of the patients (70-97%) by one month, 5-10% of medically managed patients may develop recurrent MI related to extension of dissection during hospitalization. In high-risk patients with ongoing ischemia, LAD coronary artery dissection, extension of dissection or hemodynamic instability there is consensus that urgent intervention with PCI or CABG should be considered. Both invasive strategies are associated with suboptimal outcomes, because there is risk of the extension of the dissection during PCI and a high rate of both venous and arterial conduit failure as a consequence of competitive flow from the healing native arteries, after CABG [84-5],
The optimal regimen and duration of antiplatelet therapies in conservatively managed SCAD remains unclear.

Table 9
Recommendations for the management of coronary artery dissection (SCAD)

Treatment	
Non-pregnancy associated SCAD Acute phase • **Conservative therapy** - clinically stable - no high risk anatomy - favorable outcomes • **CABG** - clinically stable with - left main or proximal 2-vessel dissection • **CABG or Urgent CABG (should be individualized)** - ongoing ischemia, - hemodynamic instability	**Pregnancy associated SCAD** Acute phase • **Conservative management if feasible** • **Largely the same management as in non-pregnancy SCAD**
Post-SCAD therapy* • **Following conservative therapy** - Aspirin use for at least 1 year - Clopidogrel use is uncertain (1) - b-blockers (standard guideline-based therapy after ACS) - ACE inhibitors/ARBs (standard guideline-based therapy after ACS) - Statins not recommended routinely • **Following PCI** - Antiplatelet therapy (standard guideline-based therapy after PCI)	**Post-SCAD therapy*** • **Following conservative therapy** - Low-dose aspirin use is safe during pregnancy and breastfeeding - Clopidogrel is not recommended (2) - Labetalol is preferable (3) - ACE inhibitors /ARBs not recommended (4)

ACE indicates angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection.

[1] Recommendations for thrombophilia testing are extrapolated from the data for strokes.

* expert opinions, no evidence-based approach

1. Dual antiplatelet therapy should be individualized
2. no clear safety data for clopidogrel use during pregnancy or breastfeeding
3. metoprolol and atenolol are more highly associated with lower placental and fetal weights at delivery. Atenolol should also be avoided during breastfeeding.
4. ACE inhibitors and ARBs are associated with an increased risk of fetopathy during the second and third trimesters of pregnancy.

C5. Women with nonobstructive CAD (MINOCA)

Women have a high prevalence of MI with MINOCA which varies from 6-30% and tends to affect young women. In CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines) Danish registry women were two times more likely to have non–ST-segment elevation MI (NSTEMI) with nonobstructive CAD, while there was no sex difference in outcomes. Consistent with these results, Swedish Coronary Angiography and Angioplasty Registry (SCAAR) reported higher prevalence of nonobstructive arteries in women compared with men and in patients with NSTEMI than those with STEMI and similar future risk for MI between sexes. Furthermore, in Reasons for Geographic and Racial Differences in Stroke (REGARDS) prospective registry the risk of MI associated with atrial fibrillation (AF) was significantly higher in women than in men. There is a lack of sex-specific data in ACS due to CE [86].

C6. Kounis Syndrome

Kounis syndrome was initially described by NG Kounis in 1991, as an 'allergic angina syndrome' progressing to acute MI induced by an acute allergic reaction. Kounis syndrome represents a form of an often-underdiagnosed ACS in the setting of an allergic, hypersensitivity anaphylactic or anaphylactoid reaction [87]. Kounis syndrome is classified into three subtypes. Type I is the most common variant and refers to patients with an ACS-like presentation due to coronary artery spasm, in the absence of atherosclerotic risk factors and normal or near normal coronary arteries in the setting of acute allergy. Coronary artery spasm can be reversed without cardiac enzymes and troponin elevation or can progress to acute MI and associated troponin elevation. Type II includes patients with pre-existing atherosclerotic coronary artery lesions where inflammatory mediators induce coronary artery spasm with normal troponin levels or coronary artery spasm and associated plaque rupture or erosion and progression to MI. Type III includes patients with stent thrombosis, where the aspirated thrombus material reveals on histologic examination the presence of mast cells and eosinophils [88]. The incidence of Kounis syndrome in Achaia, Greece (the region that was first described as a distinct entity) has been reported as 10 cases in 300.000 inhabitants in 2 years. There is a 3 times higher prevalence in men than women. In 175 cases reported up to March 2016, 74.3% were men, whereas only 25.7% were women. A large number of etiologic factors have been described broadly categorized into drug-related, environmental factors, food products and various conditions [89]. Kounis syndrome is a result of coronary artery spasm with/or plaque rupture or erosion during an allergic reaction. The antigen-antibody reaction leads to degranulation of mast cells and basophils or activation of the complement system. The release of inflammatory mediators such as histamine, cathepsin-D, chymase, tryptase, heparin lead to vasoconstriction, platelet activation, plaque rupture, plaque erosion and

Table 10
Prognosis of coronary artery dissection (SCAD)

Prognosis
• 70-97% spontaneous angiographic healing by one month • 5%-10% of medically managed pts develop recurrent MI related to extension of dissection during hospitalization • Risk of the extension of the dissection during PCI • High rate of both venous and arterial conduit failure as a consequence of competitive flow from the healing native arteries, after CABG • 15%-25% recurrence of SCAD at 3 years • 50% major adverse cardiac events is at 10 years • All patients post-SCAD should be referred for cardiac rehabilitation and should be followed-up at least annually. • Avoidance of further pregnancy is advised * if the patient elect to attempt subsequent pregnancy, close monitoring is recommended.

CABG indicates coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection.
***There is no definitive evidence that previous pregnancy-SCAD increases recurrence risk; there are few data to support this recommendation.[136]**

SCAD occurs overwhelmingly in women (> 90% female), with a 10% of the cases to occur during or after pregnancy. It accounts for 10–35% of ACS in women <50 years of age, is the most common cause of pregnancy-associated ACS (43%), with 50% of them occurring in the post-partum period. There is a strong link between FMD and SCAD; although the first is a segmental non-inflammatory, non-atherosclerotic arteriopathy of unknown etiology that typically affects middle-aged women.

thrombus destabilization and maturation, respectively. The most common symptom of Kounis syndrome is chest pain followed by palpitations or shortness of breath. Cardiac symptoms are often accompanied with a skin rash, hives or wheezes or a true anaphylactic reaction. Pulmonary edema develops in a minority of patients. A detailed clinical history as to identify any causative factors or a history of allergy should be taken. Laboratory work-up includes increased eosinophil levels. Increased IgE levels can be present, although the absence of this finding does not exclude diagnosis.

C-reactive protein (CRP) although a non-specific inflammatory marker, is often elevated. Troponin levels are elevated in 60% of patients. Treatment is largely based on individual case reports and case series. Therefore, there are no published guidelines for the treatment of Kounis syndrome. Treatment goals are directed towards alleviation of the allergic reaction and coronary revascularization when needed. Therefore, in patients presenting with ACS, guideline-directed treatment should be applied. In type III aspiration of the stent thrombus during coronary angiography is necessary for histologic examination and tailoring of treatment. In Kounis type I corticosteroids could be administered (hydrocortisone at a dose of 1-2mg/kg/day) to suppress the allergic reaction. Nitrates, either sublingually at a dose of 0.3-0.4mg every 5 min or intravenously at a dose of 5-10mcg/min titrated every 5 minutes remain the cornerstone for treating coronary artery spasm. Calcium channel blockers (verapamil, diltiazem) could represent an alternative to nitrate treatment. B-blockers are contraindicated to Kounis syndrome since unopposed a-activity can aggravate coronary artery vasoconstriction. Patients already receiving β-blockers may benefit from glucagon. Opioids (morphine, meperidine, codeine) can induce mast-cell degranulation. Therefore, there should be given with caution to Kounis syndrome.
According to sex differences there is a 3 times higher prevalence of Kounis syndrome in men than women. Treatment is largely based on individual case reports and case series.

C7. Takotsubo syndrome in women
Takotsubo syndrome, initially described in a Japanese patient in 1990, represents an acute myocardial disease mimicking an ACS with no identifiable culprit atherosclerotic coronary lesion. The syndrome is triggered by physical or emotional stress. Takotsubo syndrome mainly affects post-menopausal women (PMW), although 5-11% of cases have been reported in younger women <50 years old [90]. The classical syndrome's phenotype evident on echocardiography, cardiac magnetic resonance (CMR) or on a left ventriculogram, is transient (up to 3-6 months), apical and with mid left ventricular hypokinesia/akinesia/dyskinesia and basal hyperkinesia or less frequently a reverse Takotsubo pattern of basal hypokinesia/akinesia and apical hypercontractility.
A third variant of left ventricular phenotype is circumferential midventricular akinesia with apical and basal hyperkinesia, although other less frequent variants have been described. Dysfunctional segments extend beyond the region of a single coronary artery territory. Other important diagnostic criteria of the syndrome, apart from the absence of significant coronary artery pathology, are new and transient (up to 3 months) electrocardiographic abnormalities (ST elevation/depression, new left bundle branch block, T–wave inversion and/or QTc prolongation), significantly elevated NT-pro BNP (brain natriuretic peptide) or BNP levels and a relatively small cardiac troponin elevation disproportionate to the amount of affected myocardium [91], **Table 11**.

Table 11
Takotsubo syndrome
Diagnostic criteria

1. **Clinical presentation**
   Cardiac symptoms; mainly in primary TTS: Chest pain, dyspnea, syncope, Cardiogenic shock with the identification of a physical or emotional trigger
2. **ECG abnormalities**
   ST elevation, ST depression, QT prolongation, LBBB
3. **Coronary angiography**
   Absence of a culprit coronary artery lesion

Imaging criteria
Echocardiography, left ventriculography, CMR
- Transient LV regional wall motion abnormalities [a] extending beyond the distribution of a single coronary artery territory.
- CMR usually shows absence of LGE in abnormal LV segments

4. **Biomarkers**
   - Cardiac troponins; relatively small elevation disproportionate to the amount of the affected myocardium
   - BNP or NT-pro BNP levels; significantly elevated in the acute phase

a. Typical variants include apical and mid akinesia with basal hyperkinesia or a reverse Takotsubo pattern of basal akinesia and apical hypecontractility
b. CMR is also indicated for the differential diagnosis between TTS and acute myocarditis or acute MI with normal coronaries depending on the LGE presence and pattern of distribution

The InterTAK diagnostic score was developed to assess the likelihood of Takotsubo syndrome on presentation and to distinguish between Takotsubo syndrome and NSTEMI. It includes 7 parameters. Those are female sex, physical trigger, emotional trigger, neurologic disorders, psychiatric disorders, absence of ST depression (except in lead avR) and QT prolongation. An increased score of 70 points increases the probability of Takotsubo syndrome [92-3].

Takotsubo syndrome is related to an increased catecholamine surge produced by the adrenal medulla as a response to severe physical or emotional stress. Excess catecholamine production leads to abnormal vascular and myocardial response. Multivessel coronary artery spasm and myocardial stunning are predominant features of the syndrome. The strikingly increased incidence of Takotsubo syndrome among PMW may be partly explained by estrogen deficiency. Estrogen loss leads to a dominant sympathetic nervous system response. It is also hypothesized, based on human and animal studies, that decreased estrogen production may be linked to increased extracellular matrix components accumulation in the myocardium. Extracellular matrix contributes to diastolic LV dysfunction and to the development of acute HF during a stressful event. Moreover, estrogen deficiency is a cause of vascular endothelial dysfunction. Lastly, inherent autonomic nervous system dysregulation has been observed in some studies comparing PMW long after Takotsubo syndrome with age–matched women without Takotsubo syndrome. Takotsubo syndrome patients presenting with ACS symptoms are treated according to the existing guidelines in terms of time to coronary angiography. Pharmacologic treatment for hemodynamically stable patients without heart failure symptoms includes ACE inhibitors or ARB's and β-blockers. A recent analysis of the InterTAK Registry has not shown any association between aspirin use in TTS patients and a reduced risk of cardiovascular events at 30-day and 5-year follow-up [93]. Cardiogenic shock is treated with mechanical circulatory support devices, keeping in mind that intra-aortic balloon pump is not indicated in patients with left ventricle outflow tract obstruction. It is recommended to keep long term treatment up to three months post Takotsubo syndrome or until LV ejection fraction recovery is observed. Mortality rates are higher for men than women (8.4% vs. 3.6%, p<0.0001) attributed to the increased incidence of a severe physical illness in men and to the increased rate of complications such as cardiogenic shock, respiratory failure and cardiac arrest.

Takotsubo syndrome mainly affects PMW, although 5-11% of cases have been reported in younger women <50 years old. The strikingly increased incidence of Takotsubo syndrome among PMW may be partly explained by estrogen deficiency. Mortality rates are higher for men than women.

C8. Coronary microvascular dysfunction causing cardiac ischemia in women

About 2/3 of women with ischemia symptoms do not present CAD in cardiac catheterization. Those women may have been presented with symptoms of effort angina or dyspnea, ECG alterations and segmental hypokinesis at rest or during exercise at cardiac imaging. Although the negative findings of coronary angiography provoke relief; one out of 13 of those women will express CV death and generally they face a high probability of hospitalization with symptoms of HF with HFpEF. This situation is due to coronary microvascular dysfunction which are the small blood vessels in the heart, called the coronary microvasculature, which carry most of the blood flow to the heart muscle, delivering oxygen. These blood vessels can become unhealthy when

there is damage to their inner lining, causing chest pain, shortness of breath, heart attack, and HF. Conditions that increase the likelihood of coronary microcirculation dysfunction are AH, DM, high cholesterol, smoking, autoimmune disease, and prior breast cancer treatment, as well as other unknown factors [86]. The use of traditional noninvasive diagnostic testing can include exercise ECG, stress echocardiography, and single-photon emission tomography; however, these modalities have shown low sensitivity and moderate specificity for the diagnosis of microvascular dysfunction causing cardiac ischemia, **Table 12**.

Table 12
Proposed Approach for the Diagnosis of Coronary Microvascular Dysfunction (CMD) in Women With Ischemia With No Obstructive Coronary Artery Disease (INOCA)

- Presentation Woman with signs and symptoms of INOCA
- Exclusion of secondary CMD
- If CMD is not confirmed, consider epicardial coronary vasospasm, microvascular coronary vasospasm, heightened cardiac nociception, or myocardial bridge.
- Myocardial disorders (eg, hypertrophic, restrictive, and dilated cardiomyopathies) Valvular heart disease (eg, severe aortic stenosis) High-output states (eg, anemia and hyperthyroidism)
- Consider in women with elevated atherosclerotic cardiovascular risk scores
- Empirical therapy Low-dose aspirin Statin Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker Vasodilating β - blockers (eg, carvedilol) Calcium channel blockers (eg, ditiazem) Ranalozine.
- If Angina not improved Consider in women with persistent symptoms who are inappropriate for invasive and Noninvasive testing
  - Pharmacologic stress cardiac positron emission tomography
  - Pharmacologic cardiac magnetic resonance imaging
  - Pharmacologic transthoracic Doppler echocardiography Coronary flow If CMD not confirmed Consider reserve assessment via invasive testing
- in women with persistent symptoms, of reproductive age, or who have had a previous myocardial infarction with no obstructive coronary artery disease Invasive testing Response to intracoronary adenosine Response to intracoronary acetylcholine
- If CMD is not confirmed, consider epicardial coronary vasospasm, microvascular coronary vasospasm, heightened cardiac nociception, or myocardial bridge.

Pre-existing hypertension	Precedes pregnancy or develops before 20 weeks of gestation. It usually persists for more than 42 days post-partum and may be associated with proteinuria.

Management of CV risk factors includes control of dyslipidemia, DM, and AH, in addition to therapy with low-dose aspirin. ACE inhibitors have been shown to improve coronary flow reserve, exercise tolerance, and angina symptoms. Carvedilol improves endothelial function. Patients with abnormal vasodilator reserve have improved symptoms, less nitrate usage, and improved exercise tolerance after being treated with verapamil or nifedipine. Statins not only lower cholesterol, but they also improve coronary flow reserve (CFR). The use of nitrates may or may not improve patients' symptoms due to lack of smooth muscle in the microvasculature. Ranolazine improves symptoms in patients with low CFR [86].

Microvascular dysfunction is common in women, with one out of 13 diseased women having increased risk to face adverse events. Traditional noninvasive diagnostic testing shows low sensitivity and moderate specificity. Therapy consists on atherosclerotic risk factors stick modification. In women with persistent symptoms noninvasive and invasive testing should confirm the diagnosis.

D. Pregnancy

Pregnancy induces changes in the CV system to meet the increased metabolic demands of the mother and fetus. Plasma volume and cardiac output reach a maximum of 40–50% above baseline at 32 weeks of gestation, while 75% of this increase has occurred by the end of the first trimester. The increase in cardiac output (CO) is achieved by an increase in stroke volume in the first half of pregnancy and a gradual increase in heart rate thereafter. Atrial and ventricular diameters increase while ventricular function is preserved. In women with heart disease, LV and right ventricular (RV) adaptation to pregnancy can be suboptimal. Maternal cardiac dysfunction is related to impaired uteroplacental flow and suboptimal fetal outcome. Systemic and pulmonary vascular resistances decrease during pregnancy. Pregnancy is a hypercoagulable state associated with increased risk of thrombo-embolism. Increased activity of liver enzyme systems, glomerular filtration rate, and plasma volume, protein binding changes, and decreased serum albumin levels contribute to changes in the pharmacokinetics of many drugs [94].

D1. Aortic dissection

Aortic dissection is a rare but catastrophic event, being the third cause of CV death during pregnancy. Its prevalence is 4 in a million pregnancies [95]. Risk factors include known aortopathies, namely Marfan, vascular Ehlers-Danlos and Turner syndromes (risk of rupture 1-10%), bicuspid aortic valve (risk of rupture 1%), AH and advanced age. Pregnancy is a high-risk period due to hemodynamic and hormonal changes and dissection is more likely to occur in the 3rd trimester and early postpartum period. The presenting symptoms as chest or abdominal pain, dyspnea and fainting, can be misjudged as more innocent pregnancy symptoms. Women with aortopathies must be advised of the dangers of pregnancy and perform a whole aorta imaging [CCTA or magnetic resonance images (MRI)] before conception. Women with Marfan and ascending aorta diameter >45mm (>40mm in family history), bicuspid aortic valve and ascending aorta diameter >50mm and all women with vascular Ehlers-Danlos should be advised against pregnancy [94-6]. Management of type A aortic dissection in pregnancy includes emergency caesarean section if the fetus is viable and then repair of the dissection, otherwise direct aortic surgery. In the case of uncomplicated type B aortic dissection, the management includes conservative treatment or thoracic endovascular aortic repair [95].

D2. Pregnancy and AH

AH can complicate up to 10% of pregnancies and is responsible for up to 20% of maternal deaths. The risk factor, classification and definitions of AH and its complications during pregnancy is presented in **Table 13**.

Table 13
Classification and definitions of hypertensive disorders in pregnancy

Gestational hypertension	Develops after 20 weeks of gestation and usually resolves within 42 days post-partum
Pre-existing hypertension plus superimposed gestational hypertension with proteinuria	
Antenatally unclassifiable hypertension	When BP is first recorded after 20 weeks of gestation and hypertension is diagnosed; re-assessment is necessary after 42 days post-partum
Pre-eclampsia	Gestational hypertension with significant proteinuria [>0.3 g/24 h or ACR (Albumin: Creatinine Ratio) >30 mg/mmol]. It is often associated with fetal growth restriction due to placental insufficiency and is a common cause of prematurity. The only cure is delivery.
Severe pre-eclampsia	Pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or hematological impairment
Eclampsia	A convulsive (grand mal seizures) condition associated with pre-eclampsia
HELLP syndrome	Haemolysis, elevated liver enzymes and low platelet count

Most women with pre-existing AH and normal renal function have non-severe AH (140-159/90-109mmHg) and are at low-risk for CV complications. Despite a lack of evidence, the guidelines of European Society of Cardiology (ESC) [95], recommend the initiation of drug treatment in all women with persistent elevation of BP >150/95mmHg and at values >140/90 mmHg in women with:

- gestational AH (with or without proteinuria)
- pre-existing AH with the superimposition of gestational AH
- AH with subclinical organ damage or symptoms at any time during pregnancy.

Tight control of BP is still debatable although severe AH is associated with adverse maternal and foetus outcomes. If the BP reaches 170/110mmHg, is an emergency that needs hospitalization and either oral or intravenous low-

ering of BP. The definitive solution is the removal of the placenta through delivery. Management of hypertensive disorders in pregnancy is presented in **Table 15**.

Table 15
Management of hypertensive disorders in pregnancy

Methyldopa (B), labetalol (C), and calcium antagonists (C) are recommended for the treatment of hypertension in pregnancy	**IB and IC**
In women with gestational hypertension or mild pre-eclampsia, delivery is recommended at 37 weeks	**IB**
It is recommended to expedite delivery in pre-eclampsia and with adverse conditions such as visual disturbances or hemostatic disorders	**IC**
In pre-eclampsia associated with pulmonary edema, nitroglycerin given as an intravenous infusion is recommended C	**IC**
In severe hypertension, drug treatment with intravenous labetalol, or oral methyldopa or nifedipine, is recommended	**IC**
Limitation of weight gain to <6.8 kg should be considered in obese women	**IIaC**
ACE inhibitors, ARBs, or direct renin inhibitors are not recommended	**IIIC**
In eclampsia the administration of intravenous magnesium sulfate is recommended	**IA**
In severe preeclampsia the administration of peripartum intravenous magnesium sulfate to prevent preeclampsia is recommended	**IA**

Table 14
Risk factors for preeclampsia

High risk factors	Moderate risk factors
Hypertensive disease during a previous pregnancy Chronic kidney disease Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome Type 1 or type 2 diabetes Chronic hypertension	First pregnancy Age 40 years or older Pregnancy interval of more than 10 years BMI of >_35 kg/m2 at first visit Family history of pre-eclampsia Multiple pregnancy

Table 14 presents the risk factors for pre-eclampsia. Women with one high risk or 2 moderate risk factors must be prescribed aspirin 100-150 mg from the 12th up to 36-37th week of pregnancy. Calcium supplementation also helps in prevention [96-7]. Eclampsia is a potentially catastrophic complication of AH in pregnancy. Serious headache, eye symptoms, thoracic or abdominal pain in a preeclamptic woman can precede eclampsia. Prevention can be attempted by infusion of MgSO4 and urgent delivery of the foetus.

Follow-up of women with hypertensive disorders of pregnancy includes weekly visits for 6 weeks to ensure BP and proteinuria return to normal and counselling for modification of general CV risk.

D3. Peripartum Cardiomyopathy (PPCM)

The etiology of CMs occurring de novo in association with pregnancy is diverse. CMs cause severe complications, making a substantial contribution to maternal morbidity and mortality during pregnancy, in the immediate peripartum period, and up to months later.

Definition of PPCM includes:

1. HF secondary to LV systolic dysfunction with LVEF <45%
2. Occurrence towards the end of pregnancy or in the months following delivery (mostly in the month following delivery)
3. No other identifiable cause of HF

Possible factors leading to PPCM include genetic pre-disposition, low selenium levels, viral infections, stress-activated cytokines, inflammation, autoimmune reaction, pathological response to hemodynamic stress, unbalanced oxidative stress and induction of antiangiogenic factors. An important differential diagnosis in patients presenting with acute HF at the end of pregnancy or directly post-delivery is severe (pre-)eclampsia leading to pulmonary edema mainly due to diastolic dysfunction. While antiangiogenic state might provide a theoretical basis to link preeclampsia and PPCM, not all women with preeclampsia go on to develop superimposed PPCM. Identifying women with preeclampsia who are at highest risk of PPCM may lead to targeted quality improvement care interventions to facilitate early detection of this CM and decrease the burden of adverse outcomes related to late presentation. Genetically transmitted DCM may manifest during early adulthood and is sometimes difficult to distinguish from PPCM.

Differential diagnosis should include cardiac and extracardiac causes of acute dyspnea and discomfort and include PE, pregnancy related ACS, Takotsubo CM, myocarditis, pre-existing idiopathic/familial dilated or acquired CM and amniotic fluid embolism.

Management of PPCM depends on the severity of presentation. Mild PPCM is defined as hemodynamically stable subacute HF, moderate PPCM as hemodynamically stable acute HF while severe PPCM as cardiogenic shock.

In cases when PPCM presents with acute, decompensated HF/cardiogenic shock, the guidelines for the management of acute HF apply.

For rapid diagnosis and decision making in all pregnant women with acute HF, a pre-specified management algorithm and the establishment of a multidisciplinary team is crucial. Multidisciplinary care includes cardiologists, intensivists, obstetricians, neonatologists, anesthetists and cardiac surgeons. Medical treatment options include the standard HF treatment with beta blockers, diuretics, mineralocorticoid receptor antagonist, ACE inhibitors, ARBs, ivabradine, angiotensin receptor–neprilysin inhibitor (ARNI). There is evidence that bromocriptime may be beneficial in PPCM via inhibiting prolactin, in a starting dose of 2.5 mg bid to 10-20 mg daily. Bromocriptine has related to increased thromboembolic events and at least prophylactic anticoagulation during bromocriptine treatment is mandatory. Several HF drugs (ACE inhibitors, ARB, ARNI, ivabradine, new oral anticoagulants, mineralocorticoid receptor antagonists) are not recommended during pregnancy while ARB, ARNI, ivabradine, new oral anticoagulants are not recommended during lactation. It is proposed that tapering of medical treatment should be attempted 12-24 months post full LVEF recovery; while wearable defibrillator for the prevention of sudden cardiac death, could be considered. There is a wide variation in reported mortality rates of PPCM, ranging from 2% in Germany, to 12.6% in South Africa. African American women were more likely to worsen after initial diagnosis, had a lower chance to recover despite apparent adequate treatment. Even after full recovery of LVEF, subtle diastolic dysfunction and reduced maximal exercise capacity (peak oxygen uptake) was reported recently in a Danish PPCM cohort. All patients with a previously diagnosed PPCM and their partners should receive careful counseling (class I recommendation) about the long-term prognosis and undergo a risk stratification if further pregnancies are considered. Women with an impaired LV systolic function are at substantial risk of relapse and death and should therefore be strongly advised against future pregnancy [97].

D4. Valvular heart disease in pregnancy

At childbearing age, valvular heart disease is often due to rheumatic heart disease, particularly in low–middle-income countries. In stenotic valve diseases, increased cardiac output causes an increase in transvalvular gradient of up to 50%, mainly between the first and second trimesters, which increases the risk of maternal and fetal complications. Mild mitral valve stenosis is generally well tolerated. Sustained atrial fibrillation, although rare (<10%), may precipitate heart failure symptoms and thrombo-embolic events. Mortality is between 0-3% in western countries and higher in low-middle-income countries. NYHA class ≥II, pulmonary artery systolic pressure >30mmHg, severe mitral valve stenosis, and older age are associated with maternal complications. Percutaneous balloon valvuloplasty may be performed preferably after 20th week of pregnancy in patients with severe mitral stenosis and symptoms to allow pregnancy to continue. Aortic valve stenosis even severe is well tolerated if the patient was asymptomatic prior to pregnancy. Cardiac morbidity is related to the baseline severity of aortic valve stenosis and symptoms. HF is rare (<10%) in women with moderate aortic valve stenosis and in those who were asymptomatic before pregnancy, while it occurs in one out of four symptomatic patients. Women with bicuspid aortic valve have a low risk of aortic dissection if the aortic diameter is <50 mm. During pregnancy in patients who are severely symptomatic despite medical therapy, percutaneous valvuloplasty can be undertaken by an experienced operator. In severe symptomatic mitral and aortic valve stenosis caesarean delivery should be preferred. An individual approach is recommended for asymptomatic severe aortic valve stenosis as well as for significant mitral valve stenosis. HF occurs in 20-25% of women with moderate or severe rheumatic mitral valve regurgitation. Acute severe valve regurgitation is poorly tolerated. It considers tricuspid regurgitation usually when is severe or is a part of a complex congenital heart disease with RV dysfunction In the case of tricuspid valve, secondary regurgitation is more frequent than primary regurgitation which is usually due to endocarditis or Epstein's anomaly. Maternal risk is usually determined by left-sided valve disease or pulmonary hypertension. Pulmonary stenosis and regurgitation are mainly due to congenital heart disease and will be discussed at the specific session [94].

D5. Prosthetic cardiac valves in pregnancy

When implantation of a prosthetic cardiac valve is unavoidable in a woman who wants to become pregnant in the future, valve selection is challenging. Cardiac mechanical valves offer excellent hemodynamic performance and long-term durability, but the need for anticoagulation increases maternal and fetal mortality and

morbidity, and the risk of major cardiac events during pregnancy is much higher than with bioprosthetic valves. However, bioprosthetic valves in young women are associated with a high-risk of structural valve deterioration resulting in the risk of going through pregnancy with a dysfunctional valve, and eventually in the inevitable need for re-operation. In women with cardiac mechanical valves, pregnancy is associated with a very high-risk of complications [World Health Organization (WHO) risk classification III]. In the Registry Of Pregnancy And Cardiac disease (ROPAC) registry, the chances of an event-free pregnancy with a live birth were 58% for women with a mechanical valve, compared with 79% for women with a bioprosthesis and 78% for women with heart disease but no valve prosthesis. Optimal anticoagulation is a still matter of debate but there is some recommendation from recent guidelines. In patients treated with high dose vitamin K antagonist, as there is a risk of embryopathy during the first trimester, should be counseled, and either switch to low-molecular-weight heparin (LMWH) or unfractionated heparin with risk of valve thrombosis, either continue with vitamin K antagonist with the risk of embryopathy [94].
In general, women with severe native valvular disease or mechanical valves should be followed in high risk pregnancy centers by expert team of obstetrician, cardiologist, anesthesiologist and neonatologist.

D6. Congenital heart disease in pregnancy

All women with known congenital heart disease who wish to embark on pregnancy require timely pre-pregnancy counseling. Maternal risk, fetal risk, obstetric risk and risk of transmission should be discussed. In most women with congenital heart disease, pregnancy is well tolerated. The risk of pregnancy depends on the underlying heart defect as well as on additional factors such as ventricular function, functional class, and cyanosis. Maternal cardiac complications are present in about 10% of completed pregnancies and are more frequent in mothers with complex disease. Patients who experience complications during pregnancy may also be at higher risk of late cardiac events after pregnancy. To assess the maternal risk of cardiac complications during pregnancy, the condition of the woman should be assessed, taking into account medical history, functional class, oxygen saturation, natriuretic peptide levels, echocardiographic assessment of ventricular and valvular function, intrapulmonary pressures and aortic diameters, exercise capacity, and arrhythmias. Disease-specific risk should be assessed using the modified WHO classification, presented in latest ESC guidelines [94]. A multidisciplinary team is required to care for the pregnant high-risk congenital heart disease (CHD) patient. A delivery plan should be made with details of induction, management of labor, delivery, and post-partum surveillance. Specific expertise and collaborative management by a pregnancy heart team in specialist centers is mandatory for all moderate- and high-risk patients.
Clinical considerations: The impact of pregnancy in a woman with congenital or aortic valve disease on the long-term maternal and foetal outcome is not well studied. In women with mechanical valve prostheses, no prospective studies are available that compare different anticoagulation regimens. There are unresolved questions concerning LMWH, including optimal antiXa levels, the importance of peak vs. pre-dose levels, the best time intervals for anti-Xa monitoring, and the duration of use (first trimester or throughout pregnancy). The safety of antiplatelet agents used after PCI in pregnancy is not well known. The impact of fertility treatment on pregnancy complications and maternal outcomes remains unknown.

E. Cardiomyopathies (CMs) in women

CMs are a heterogeneous group of heart muscle diseases with a variety of specific phenotypes [99]. They are classified into hypertrophic (HCM), dilated (DCM), Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), and unclassified CMs [114]. Each phenotype can be classified into inherited (familial) and non-inherited (non-familial) forms. Most forms of CMs have a genetic basis, but single mutations may cause different forms of CMs. There is increasing evidence that sex plays a role in CMs, in terms of prevalence, clinical expression and outcome [99-109]. Although most cases of familial CMs follow an autosomal dominant inheritance pattern, prevalence is not similar in both sexes [104]. In almost all forms there is a male predominance, indicating that other factors may play a role. In X-linked recessive forms of CMs, i.e. Becker's dystrophy or Anderson-Fabry disease, males are primarily affected whereas women may present with mild forms of the disease [104]. Experimental work and animal studies indicate a protective effect of estrogens in females in terms of hypertrophy and HF [119]. Behavioral and social factors may also be responsible for the sex related differences in CMs. Women are more reluctant in seeking medical care whereas men are earlier diagnosed with CMs through CV screening before entering the army or participating in sports.

E1. Hypertrophic cardiomyopathy

HCM is the most common genetic heart muscle disease with a prevalence of 0.2%. It is characterized by LV hypertrophy that is not solely explained by abnormal loading conditions and a great diversity in morphological and clinical expression [99]. In up to 60% of adolescents and adults with HCM, the disease is an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes. Five to ten percent of adult cases are caused by other genetic disorders including inherited metabolic and neuromuscular diseases, chromosome abnormalities and genetic syndromes. Sudden cardiac death is the most devastating complication. A large amount of data consistently indicates differences between male and female patients with HCM [99-103].

Table 16
Female HCM patients' characteristics

- Lower disease prevalence (2:1 predominance in males)
- Diagnosis made due to onset of symptoms
- Older on the time of diagnosis
- More symptomatic on diagnosis
- Greater risk of heart failure and worse outcome
- LVOTO is significantly more frequent
- More severely impaired diastolic and systolic function
- More fibrosis
- No difference in sudden death rates or atrial fibrillation
- The risk for heart failure deterioration and death is greater in female patients older than 50 years compared to younger female and male patients.
- Pregnancy: Absolute maternal mortality is low and confined to women at particularly high risk.

Anatomic differences in women	Imaging implications
LV size	Reduced accuracy of radionuclide magnetic resonance imaging (MPI) (180)
Diameter of coronary arteries	Coronary artery computed tomography (CCTA): Inaccessibility to coronary segments especially mid and distal segments (180)
Increased chest wall attenuation due to breast tissue	Radionuclide MPI: attenuation artifacts at LAD territory Application of gating and attenuation correction techniques and use of 99mTc-sestamibi radiotracers
Estrogen – digitalis like effect	ETT: may potentiate false positive exercise ECG changes
Obesity	CTCA/MPI Increased radiation dose needed Presence of artifacts
Radiation	
Increased exposure due to breast tissue	Cranial breast displacement and organ-based dose modulation
Exposure during pregnancy/ fetus exposure	Consider non-ionizing imaging modalities Use IV contrast when necessary
Sex based differences in presentation and pathogenesis of CAD	
Higher mortality form CAD in women despite decreased severity of CAD	ETT: Reduced exercise capacity in older women may fail to identify CAD (181)
Older age at presentation and atypical symptoms	Cardiac imaging may be delayed (181)
Potential role of microvascular disease in the pathogenesis of CAD	Non-invasive quantification of MBF and coronary fractional reserve (CFR) may identify microvascular disease

E2. Dilated cardiomyopathy (DCM)
DCM is characterized by an enlarged and poorly contractile LV in the absence of abnormal loading conditions or CAD. The prevalence of familial DCM is assumed to be at least 30%. Forty per cent of these patients have an identifiable genetic cause. The majority of genetic DCM is inherited in an autosomal dominant pattern caused by mutations in several genes coding for the cytoskeleton, sarcomeric protein/Z-band, nuclear membrane and intercalated disk proteins but specific forms of autosomal recessive, X-linked recessive and mitochondrial inheritance also occur. In general, familial DCM primarily affects males (1.5:1), while emerging data agree that women have less severe systolic dysfunction and a more favorable outcome than men [104-5].

E3. Arrhythmogenic RV cardiomyopathy (ARVC)
ARVC is characterized by global or regional RV dysfunction, caused by progressive RV adipose and fibrous replacement of the myocardium [106-7]. The LV is so frequently involved as to support the adoption of the broad term arrhythmogenic CM. It is a hereditary CM with a high risk of ventricular arrhythmias and sudden cardiac death. In over 50% of the cases ARVC is familial. The underlying genetic causes are mutations in several genes encoding desmosomes. Inheritance in ARVC is predominantly autosomal dominant but autosomal recessive transmission has also been described, i.e. Naxos disease [108-10].
Sex differences in the prevalence, phenotypes and clinical course of ARVC have been described and differences in the degree of physical exercise between men and women might play a role. ARVC is more prevalent in males than females with a ratio of 3:1. ECG abnormalities and late potentials are more common in male than in female patients suggesting more severe disease [110]. Male sex has been found to be an independent arrhythmic risk predictor in ARVC-associated desmosomal mutation carriers. In conclusion, the diagnosis of ARVC is less common in female patients who present with mild forms of the disease.

E4. Restrictive CM (RCM)
RCM refers to restrictive ventricular physiology at normal or reduced ventricular volumes and normal wall thickness. Although the disease rarely is familial it can result from autosomal dominant, autosomal recessive or X-linked inheritance [110]. Data on sex differences in familial RCM are scarce.

There is increasing evidence that biological sex plays a role in CMs, in terms of prevalence, clinical expression and outcome. In X-linked recessive forms of CMs, i.e. Becker's dystrophy or Anderson - Fabry disease, males are primarily affected whereas women may present with mild forms of the disease. Experimental work and animal studies indicate a protective effect of estrogens in females in terms of hypertrophy and HF. Sex differences in the prevalence, phenotypes and clinical course of ARVC have been described and differences in the degree of physical exercise between men and women might play a role.

F. Menopause

F1. Effects of menopause on the CV system
Postmenopausal status is identified as a risk factor for CVD. Furthermore, the incidence of traditional CVD risk factors is also increased in PMW [112].

Alteration in BP: PMW lose the cardioprotective effects of estrogen and have an elevated risk of developing AH. SBP tends to increase with menopause and this effect is believed to be mediated through an increase in plasma-renin activity but also through the loss of estrogen mediated vasodilation [112]. Several other factors, such as obesity, aging and salt sensitivity contribute to the increased prevalence of arterial hypertension in PMW; thus, all should be addressed in order to reduce CV risk,
PMW are more likely to have undiagnosed or poorly treated AH despite medication compared with age matched men. Multi-drug therapy may be necessary to control hypertension as women age and should be combined with lifestyle interventions, such as weight control, a low-sodium diet and systematic exercise [113]. A beneficial effect in NO mediated vasodilation of estrogen hormones has been demonstrated in experimental studies, but multiple clinical trials including Women's Health Initiative have failed to demonstrate a role of HRT for the prevention of hypertension and CVD risk in PMW [112-4].
An optimal BP<120/80 mmHg should be encouraged through lifestyle approaches (weight control, increased physical activity, alcohol moderation, salt restriction, and a healthy Mediterranean type diet) (Class I). For those requiring pharmacological therapy, the target BP

should be<130/80 mmHg (Class I). HRT is not indicated and should never be prescribed for prevention of hypertension and CVD risk (Class III).

Alteration in Body Weight and Plasma Glucose:
Menopause results in slower metabolism and weight gain but also changes the body fat distribution towards a more central pattern, due to increase in visceral adiposity. Even when PMW do not gain additional weight, there is a redistribution of fat to the abdomen. Thus, combining waist circumference (WC) and body mass index (BMI) may be the best approach for assessing obesity-related risk. Abdominal obesity and insulin resistance subsequently increase the incidence of MetS in PMW,
Weight maintenance or loss through caloric restriction, physical activity and counseling is recommended for PMW (Target BMI<25 kg/m², WC< 88 cm) (Class I). Combining WC and BMI is the best approach for assessing obesity-related risk and metabolic syndrome and is recommended in all women with BMI<35 kg/m² (Class I). Lifestyle intervention is recommended to delay/prevent conversion from pre-DM to T2DM (Class I). Moderate-vigorous physical activity (≥150 min/week) is recommended unless contraindicated (Class I).
The impact of obesity on the development of CVD seems to be greater in PMW [170]. Diabetic women are also more likely to both develop and die from CVD than their male counterparts. Impaired fasting glucose alone causes increased CVD risk in women to a similar extent as DM does, an association not observed in men [114].

F2. Hormone replacement therapy (HRT)
The average age of menopause is 49-51 years, while the life expectancy of women in European countries is about 76-81 years. In recent years, a great debate was raised on benefits and risks of HRT. The International Menopause Society (IMS) in 2007 and 2009 for the first-time reviewed studies and published guidelines, to achieve a balanced approach and interpretation of all scientific data on HRT [115-7]. The most recent IMS guidelines were issued in 2016.

F2.1. Basic principles on HRT
HRT should be part of a holistic therapeutic approach-if there are not contraindications that aims to maintain the PMW health. HRT includes improving lifestyle taking care of proper nutrition, exercise, smoking cessation and alcohol reduction. HRT should be personalized, and symptoms should be tailored based on medical history, blood tests, accepting each woman's preferences and expectations and combining with regular follow-up. Menopausal women before the age of 45, but even more before the age of 40, have a high risk of developing CVD and osteoporosis. These women are recommended to be given HRT at least until the normal age of menopause, in the lowest effective dose [115-7]. Progesterone should be added to estrogen (except vaginal estrogen) in all women who maintain the uterus to prevent endometrial hyperplasia and cancer. Although progesterone protects the endometrium, it has major disadvantages regarding breast cancer.

F2.2. Effects of HRT
In general, HRT remains the most effective treatment for vasomotor and urinary track symptoms due to estrogen deficiency. Other conditions related to menopause such as myalgies, emotional and sleep disorders can also be improved with HRT. Beneficial effects on connective tissue, skin, joints, and intervertebral discs, as well as sexuality have been reported with HRT. Recent studies appear to reduce the risk of colon cancer while continued administration of estrogen and progesterone may reduce the risk of developing endometrial cancer. HRT improves insulin resistance and reduces the risk of DM and has a positive effect on lipids and MetS [115-7]. In several studies and in a large meta-analysis, it has been observed that estrogen administration to women aged 50-59 years for approximately 7 years had caused less coronary calcification 1 year after discontinuation of treatment compared with untreated women. It is possible that HRT will slow atherosclerosis process. However, HRT administration 10–20 years after menopause when the endothelium is already atherosclerotic, may be harmful. Based on existing data, HRT should not be administered to older women with known CAD.
HRT is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks in symptomatic women before the age of 60 years or within 10 years after menopause. Despite the proven benefits MHT is not indicated for the primary prevention of chronic conditions (CAD, stroke etc) in PMW.

G. Cardiovascular disease in women

G1. How to diagnose CVD in women?

CVD is the leading cause of death in both sexes. Women usually present CAD in the form of ACS approximately 10 years later compared with men, probably due to the protective effects of oestrogen during the reproductive years [118]. The absolute number of annual CVD deaths among the female sex has exceeded that of the male sex since 1984. These data are often confused with CVD mortality rates, which, when adjusted for differences in age distribution, reveal that the CVD mortality rate is substantially higher in men than women. In 2007, the age-adjusted CVD death rate in men was 300 per 100 000 compared with 212 per 100 000 women. The 2007 CVD mortality rate in women represents a 43% reduction from the rate in 1997. From 1980 to 2000, the age-adjusted death rate for CHD fell from 263 to 134 per 100 000 women; during the same time, the rate fell from 543 to 267 per 100 000 men [118]. Angina pectoris is the predominant initial and subsequent presentation of CV ischemic disease in women, in contrast to MI and sudden death for men. Several studies describe women presenting with less typical symptoms including fatigue, sleep disturbance, shortness of breath, back pain, tooth ache, indigestion, weakness, nausea/vomiting, and weakness [119]. In the Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome (GENESIS PRAXY) study although chest pain was the prevalent symptom among women, was less common compared with men. [120] In women <45 years old presenting with acute MI, chest pain is the less frequent symptom [119]. Women compared with men, more commonly present with NSTEMI and non-obstructive CAD; whereas the pathophysiological mechanisms of CAD differs from the classical plaque rupture predisposing in men; and include plaque erosion, SCAD or coronary artery spasm. Furthermore, women often show increased time delay in presenting to the hospital, attributed to misinterpretation of symptoms, lack of knowledge that women may also have CAD and tendency to avoid disturbing other family members [121-4]. CAD risk factors vary by age and reproductive status. After menopause, the prevalence of cardiac risk factors in women approaches that of men and concurrently increases the risk of CAD. Tobacco use, DM, depression, and other psychosocial influences are stronger predictors of CV risk in women than in men. Inducible ischemia in response to mental stress is associated with a twofold increased risk of mortality and recurrent CV events. Moreover, marital stress has been implicated in the development of subsequent cardiac events [124].

G2. Diagnostic test in women- Imaging modalities

The basis of choosing the appropriate diagnostic test to evaluate existence of CHD in women depends on a number of factors, including test availability, local expertise, patient age, body habitus, ability to exercise, and the individual's risk profile that modifies pretest probability of having CHD. In asymptomatic subjects, the use of risk-estimation systems such as SCORE is recommended [125-7]. Only subjects at high event risk should be considered for further non-invasive or invasive testing. Patients with cancer and undergoing cancer treatment, or chronic inflammatory diseases such as inflammatory bowel diseases, rheumatoid arthritis, and systemic lupus erythematosus, may deserve more intensive risk screening, counselling, and management. In a patient with a high clinical likelihood of CAD, symptoms unresponsive to medical therapy or typical angina at a low level of exercise, and an initial clinical evaluation (including echocardiogram and, in selected patients, exercise ECG) that indicates a high event risk, proceeding directly to invasive coronary angiography (ICA) without further diagnostic testing is a reasonable option. In patients in whom CAD cannot be excluded by clinical assessment alone, non-invasive diagnostic tests are recommended to establish the diagnosis and assess the event risk. The current Guidelines recommend the use of either noninvasive functional imaging of ischemia or anatomical imaging using CCTA as the initial test for diagnosing CAD [126, 128]. There is a need and opportunity for diagnostic and therapeutic modalities in CVD tailored distinctly to women. Early symptom recognition is the key to early diagnosis of CVD in women. When CV risk factors and symptoms are recognized early, women fare better when treated according to existing guidelines [128]. Furthermore, heart conditions unique to women such as those that occur during pregnancy and post-delivery as well as during menopause may warranty special considerations for cardiac imaging. Anatomic differences between men and women related to alterations in diagnostic performance of cardiac imaging modalities are presented in **Table 17** and **Table 18**.

G3. Considerations and challenges in CV imaging related to sex

G3.1. CAD

Table 17
Anatomic differences between men and women are related to alterations in diagnostic performance of cardiac imaging modalities

Anatomic differences in women	Imaging implications
Small LV size	Reduced accuracy of PET MPI
Smaller diameter of coronary arteries	CTCA: Inaccessibility to coronary segments especially mid and distal segments
Increased chest wall attenuation due to breast tissue	SPECT MPI: attenuation artifacts at LAD territory
Estrogen – digitalis like effect	ETT: may potentiate false positive exercise ECG changes
Obesity	CTCA/MPI Increased radiation dose needed Presence of artifacts

Table 18
Recommendations for diagnostic work up for ischemic heart disease in women

Diagnostic work up for IHD in women	
ECG exercise test (ETT) could be the initial diagnostic test in symptomatic women with suspected CAD and intermediate risk and good exercise capacity(>5METS)	Ia
Stress imaging should be reserved for symptomatic women with resting ST abnormalities and unable to exercise adequately	Ib
Stress imaging, SPECT and PET should be the second modality of choice when ETT is indeterminate or abnormal	Ib
Stress echo is comparable between sexes, while its diagnostic performance is better than exercise ECG	Ib
Stress echo is the preferred imaging modality for pregnant women since it does not use radiation	Ic
PET MPI showed improved sensitivity and specificity with lower radiation doses in women over SPECT MPI	IIa
Coronary CT angiography may be reasonable in symptomatic women at intermediate risk of CAD including those with equivocal stress test results	IIb
Coronary CT angiography may be reasonable in symptomatic women of low risk for CAD	IIb
In feminine population stress MRI may be suitable for symptomatic intermediate to high risk women for CAD, for female patients with poor acoustic windows on echo or during pregnancy	IIb
Cardiac MRI can offer quantitative assessment of myocardial blood flow (MBF) which may help in diagnosis of microvascular disease or it can help in the non-invasive identification of significant coronary lesions	IIb

Sex based differences in pathophysiology and clinical presentation of CAD affect the diagnostic performance of different imaging modalities and should be taken into consideration during the diagnostic work up for CAD. For example, sensitivity, specificity, and positive predictive value of exercise ECG is lower in women than in men. This was attributed to the digitalis effects of estrogen, chest wall attenuation and reduced exercise capacity. However negative predicted value of exercise ECG is high (approximately 80%), in both sexes [129, 130]. Dobutamine stress contrast echo has a strong prognostic value for patients with known or suspected CAD, regardless of patient sex. This makes dobutamine stress contrast echo an attractive screening option for women in whom CAD assessment can be challenging [131]. Single photon emission computed tomography (SPECT) or positron emission tomography (PET) MPI imaging can be used for the evaluation of symptomatic women of intermediate risk for CAD. The ability to quantitively assess myocardial blood flow and CFR with PET MPI which are previously associated with the presence of non-obstructive CAD or microvascular disease makes PET MPI a very useful imaging modality for the identification of these entities, especially in women whose prevalence is higher [131-3].

Clinical assessment of asymptomatic or symptomatic CAD is also complicated as women not only underestimate symptoms (as angina, etc) but also remain most frequently underdiagnosed and therefore less likely to receive non-invasive testing or even coronary angiography [135]. It is common knowledge that functional testing in women most often are inconclusive, although women with angina are more likely to present positive functional testing than men. CCTA may be reasonable in symptomatic women at intermediate risk of CAD including those with equivocal stress test results [130]. Calcium score is routinely performed before the contrast –enhanced imaging. The presence of calcium in the coronary arteries at CT imaging has been associated with the presence of obstructive CAD on invasive angiography and with adverse outcome in both sexes. However, the presence of calcium is not linearly associated with the severity of stenosis. On the other hand, absence of calcium does not rule out the possibility of coronary stenosis due to the presence of non- calcifies plaques. Recent studies have showed greater Agaston scores in males and differences in plaque composition between sexes, which could possibly explain the differences in calcium score, clinical presentation and outcomes between males and females. The accuracy of

Coronary CT angiography in detection of obstructive CAD is high and comparable between sexes. Previous data have shown that non-obstructive lesions (<50%) were associated with higher mortality rates only in women. Trial such as the ROMICAT (the Rule Out Myocardial Infraction using Computer Assisted Tomography) and the ROMICAT II showed that CT angiography not only predicts major CV events but women in particular who underwent such assessment had less hospital admissions, shorter hospital stays and lower total radiation dose when compared with men [128]. In addition, the diagnostic performance of CCTA is not significantly different between men and women making the CCTA with CA a valuable tool in the diagnosis and further treatment of women with CAD. Of note, as CCTA exposes to ionizing radiation and women tend to have a higher radiation exposure risk the use of these extremely useful diagnostic tools should be used with relative caution. Otherwise, CTCA is an imaging modality of values especially in investigating the presence and significant of CAD in women as it can recognize the presence of non-flow limiting lesions in women, which may warrant prompt lifestyle modifications [132, 134].

In female population stress MRI may be suitable for symptomatic women in intermediate to high risk for CAD, for those patients with poor acoustic windows on echo or during pregnancy. Sensitivity and specificity of stress MRI for the detection of CAD is comparable between sexes with improved performance over SPECT MPI [131]. Additionally, cardiac stress MRI has the significant advantage of detection of sub-endocardial ischemia due to its excellent spatial resolution. Furthermore, it has been showed that it can offer quantitative assessment of myocardial blood flow which may be useful in diagnosis of microvascular disease or in the non-invasive identification of significant coronary lesions [128], **Table 18 and 19**.

Table 19
Calcium-score by MSCT

Quantitative data that increase the likehood of severe AS in patients with AVA <1.0 cm2 and mean gradient <40 mmHg in the presence of preserved EF

	Men	Women
Severe AS very likely	≥ 3000	≥ 1600
Severe AS likely	≥ 2000	≥ 1200
Severe AS unlikely	< 1600	<800

[a] **Values are given in arbitrary units using Agatston method for quantification of valve calcification**
MSCT: multislice computed tomography
AS:aortic stenosis
AVA: aortic valve area
EF: ejection fraction

Sex differences. Absolute number of annual CVD deaths for women has increased, but age-adjusted death rate in lower than men. Women present less typical symptoms of CAD; more often NSTEMI and on-obstructive CAD. Anatomic differences between men and women related to alterations in diagnostic performance of cardiac imaging modalities. Radiation imaging modalities should be a concern particularly for women with previous breast cancer therapy with radiation. Stress Cardiac stress-MRI shows significant advantage of detection of sub-endocardial ischemia and microvascular disease but it's not widely available.

G4. CAD treatment in women

G4.1. Antiplatelet treatment

Available data shows different responses to antithrombotic therapy between males and females in terms of efficacy and safety, in both primary and secondary CVD prevention. The pathophysiological mechanisms underlying these sex differences are not fully understood and multifactorial. Evidence on antithrombotic therapy is derived from clinical trials where women are less represented than men, while few studies include exclusively female subjects. Women included are older, and have more comorbidities and risk factors than men, with higher risk of both thrombotic and bleeding events [135-136].

Antiplatelets

Females demonstrate higher platelet reactivity on aspirin and clopidogrel therapy [356-137].

Primary prevention

Aspirin for primary prevention is associated with a higher risk reduction for ischemic stroke in females and for MI in males [137-138].

Secondary prevention

There is no interaction between sex and efficacy of aspirin for secondary CV prevention [139]. Young women show the lowest use of antithrombotic, lipid-lowering, beta-blockers, and BP lowering drugs after an ACS [140]. Furthermore, the use of CV drugs declines soon after hospital discharge. The efficacy and safety of P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor and cangrelor) are comparable between men and women. Therefore, sex should not influence patient selection for administration of P2Y12 inhibitors. Prasugrel, however, is contraindicated due to an increased risk of bleeding in patients with body weight < 60 kg, a possible profile of an older woman. Regarding hemorrhagic risk of an-

tiplatelet therapy, bleeding during hospitalization in the setting of ACS or PCI is higher [141-2]. Bleeding in the acute phase may result in antithrombotic treatment disruption, increasing the risk of long-term thrombotic events. Table 20 summarizes the suggestions on the use of antiplatelet therapy in women for primary and secondary CV prevention.

Table 20
Suggested antiplatelet strategies for primary and secondary cardiovascular prevention in women

Setting	Suggestions
Primary prevention	
Overall	- Low-dose aspirin (≤100 mg/day) should probably use in women with a risk of >2 major cardiovascular events (death, myocardial infarction and stroke)/100 patients-year (the bleeding risk must be weighted) (6). - Low-dose aspirin may be considered in women with a risk of >1 cardiovascular events/100 patients-year (the bleeding risk increased by aspirin and the risk of cancer, especially colon cancer, likely reduced by aspirin - along with patients' values and preferences, should be considered) (6). - low-dose aspirin may be considered among selected adult women<70 years old at higher cardiovascular risk, but not at increased bleeding risk (4) - No convincing data for clopidogrel use (1)
Specific settings	- Low-dose aspirin is indicated in women with type-1 diabetes and target-organ damage (the bleeding risk must be weighted) (6) - Low-dose aspirin may be considered in diabetic women with a risk of >1 cardiovascular events/100 patients-year (the bleeding risk must be weighted) (6) - Low-dose aspirin may be considered in postmenopausal women on hormone replacement therapy (the bleeding risk must be weighed)(6) - Low-dose aspirin may be considered in pregnant women at high risk of early pre-eclampsia (6) - Low-dose aspirin may be considered in women with breast cancer undergoing radiotherapy (the bleeding risk must be weighed) (6)
Secondary prevention	
Women with CAD	- No gender-specific recommendations in patients with stable or unstable CAD (1)
Women with non-cardio-embolic stroke/TIA	- Low-dose aspirin preferred; clopidogrel may be considered (6)

CAD = coronary artery disease
TIA = transient ischemic attack

Venous Thromboembolism (VTE)

Data suggests that men have a higher risk of recurrent VTE than women after vitamin K anticoagulant treatment is stopped [143]. However, direct oral anticoagulants (DOAC) treatment for acute VTE seems to increase bleeding in women, likely caused by abnormal uterine or menstrual bleeding. Extending treatment of VTE, the risk of VTE recurrence or death in the absence of oral anticoagulants (OAC) seems significantly higher in males, while non-significantly different in patients treated with DOACs [143].

G4.2. Reperfusion and invasive endovascular therapy in ACS

Regarding anatomy and pathophysiology, women present smaller coronary diameter, regardless surface area, as well as smaller in number and diameter collaterals, but also coronary microvascular dysfunction, vasomotor abnormalities, stress induced CM and spontaneous SCAD with an incidence for up to almost 95% of all stable CAD [144-145]. Treatment of ACS in women present a high rate of variability regarding not only treatment strategies, timing but also outcomes and further treatment. In the VIRGO study (The Variation of Recovery: Role of Gender on Outcomes of Young AMI Patients) young women (aged <55 years old) with ST-segment elevation MI were more likely to have reperfusion delays and less likely to receive reperfusion treatment than similar aged men. [146] Overall, women have almost always worse outcomes regardless the choice of treatment (thrombolysis, PCI or CABG) often due to associate comorbidities [147]. Women treated with thrombolytics have increased morbidity and mortality rates due to increased age, presence of DM, AH and HF [148-9]. In addition the GUSTO trial (the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) showed that women have more nonfatal complications such as shock, HF, reinfarction, recurrent ischemia, bleeding, and stroke than men, even if thrombolytic therapy is successful (90-min patency rates and global ejection fraction immediately and day 7) [148]. Women, even with delayed arrival are most likely to benefit from primary PCI when compared with thrombolytic treatment; although they present worst outcomes compared with men [149-150]. An analysis of 22 trials that evaluated STEMI patients randomized in primary PCI and thrombolytic treatment found that women had a 30-day lower mortality rate in the invasive treatment

group despite eventual delays on initial treatment [149]. In the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial (Association between sex and short-term outcome in patients with STEMI participating in the international, prospective, randomized administration of ticagrelor in the catheterization laboratory or in the ambulance for new STEMI to open the coronary artery: a prespecified analysis) women although older at presentation, with higher TIMI risk score, longer prehospital delays but surprisingly better TIMI flow in the culprit artery, had a threefold higher risk for all-cause mortality compared with men (5.7% vs 1.9%, HR 3.13,95% CI 1.78 to 5.51) [151]. Women have been also found to have higher unadjusted mortality compared with men for long follow up periods (>5-10 years) after an ACS [174-5]. In the NSTEMI population, the coronary revascularization group women had a higher risk of death or recurrent ACS within 30 days which remained throughout the first years. Furthermore, a meta-analysis in 2008 comparing outcomes of early invasive versus conservative strategies in NSTEMI showed a significant 33% reduction in death, MI, or rehospitalization for ACS in women treated invasively in unstable angina (UA). Therefore, the present statement regarding NSTEMI patients recommend an early invasive strategy as a Class I, Level of Evidence A recommendation in women with high-risk features [152-9]. Even if the safety and efficacy of drug-eluting stents (DES) for treating CAD in women could not be assessed as there were far fewer female study participants in many randomized controlled trials, a large pooled analysis showed that they are more effective and safe than bare metal stents during long term follow-up [157]. Women treated with DES have significantly lower rates of death or MI as well as a better safety profile, with less stent thrombosis and lower rates of target lesion revascularization [157-8]. Although early trials showed that women have increased periprocedural bleeding and vascular complications (gastrointestinal bleeding, and stroke/transient ischemic attack), after further adjustment for chronic kidney disease and low body surface area, the odds ratios of major adverse cardiac events and death for women were no longer statistically significant [158]. Regarding the access point, the SAFE-PCI for Women trial, a randomized trial comparing radial to femoral access in women, did not show a statistically significant reduction in bleeding or vascular complications in women undergoing radial access PCI, although there was a trend toward benefit. Access site crossover occurred more often in women assigned to radial access due to the fact that women have smaller radial arteries that could make them more prone to spasm, a major cause of radial procedure failure [158-9].

Table 21
Recommendations on invasive treatment in stable coronary artery disease in elderly women

	CABG		PCI	
	Class	Level	Class	Level
One-vessel CAD without proximal LAD stenosis	IIb	C	I	C
	I	A	I	A
Two-vessel CAD without proximal LAD stenosis	IIb	C	I	C
Two-vessel CAD with proximal LAD stenosis	I	B	I	C
Left main disease with low SYNTAX score (0 – 22)	I	A	I	A
Left main disease with intermediate SYNTAX score (23 - 32)	I	A	IIa	A
Left main disease with high SYNTAX score (>_33).	I	A	III	B
Three-vessel disease with low SYNTAX score (0 - 22) without diabetes	I	A	I	A
Three-vessel disease with intermediate or high SYNTAX score (>22) with diabetes	I	A	III	A
Three-vessel disease with low SYNTAX score (0–22) without diabetes	I	A	IIb	A
Three-vessel disease with intermediate or high SYNTAX score (>22) with diabetes	I	A	III	A

Abbreviations: Class of recommendation I, is indicated/is recommended; IIa, should be considered, IIb, may be considered, III in not recommended, Level of evidence A, data derived from multiple randomized clinical trials or meta-analyses; B, data derived from a single randomized clinical trials or large non-randomised studies; C, consensus of opinion of the experts and/or small studies, retrospective studies, registries. CABG, coronary artery bypass grafting; CAD, coronary artery disease; LAD, left anterior descending coronary artery; PCI, percutaneous coronary intervention; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

Table 22
Recommendations on invasive treatment in ACS in elderly women

	PCI Class	PCI Level
Elderly women presenting with NSTEMI and high-risk features benefit from an early invasive strategy	I	A
Elderly women presenting with STEMI fair better with PCI as opposed to thrombolytic therapy	I	A
DES stents have better safety profile, with less stent thrombosis and lower rates of target lesion revascularization	I	A
Radial access is the optimum access site if performed by an experienced radial operator	I	A
Newer antiplatelet agents should be used if there are no contraindications	I	A

Regarding STEMI, women tend to have more complications than men, such as shock, HF, reinfarction, recurrent ischemia, bleeding, and stroke, but use of primary PCI virtually eliminates the risk of intracranial bleeding and is an independent predictor of survival in women. The present statement regarding NSTEMI patients recommend an early invasive strategy as a Class I, Level of Evidence A recommendation in women with high-risk features.

G5. Cardiac surgery in women: Does the sex play a role?

Regarding surgical revascularization in women, once again no specific trials are available, but all data are extrapolated from greater series. Most studies confirm that women are older with many comorbidities at the time of surgical treatment and therefore present a higher in-hospital mortality and frequent post-operatory complications such as renal failure, neurological sequels and postoperative MI [160]. In addition, the left internal mammary artery is used less frequently in women than men.

In stable CAD, clinical studies for the type of revascularization (CABG versus PCI) in the conducted trials [SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery), PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease), BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease), NOBLE (Nordic-Baltic-British Left Main Revascularization Study), EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization)], show limited results as women were underrepresented with a proportion between 22% and 29%. The criteria for decision-making between CABG and PCI (predicted surgical mortality, the anatomical complexity of CAD, and the anticipated completeness of revascularization) were equal in both sexes. However, for the estimation of surgical mortality, the clinical scores EuroSCORE II, and STS as well as the clinical and anatomical score SYNTAX II include the female sex as an independent predictor of increased mortality, after adjustment for all comorbidities [161]. It is well documented that compared with men, women who present for cardiac surgery are older, more frail, have a smaller body surface area, are more likely to require an urgent/ emergent operation, and have a greater burden of comorbid conditions, such as DM, AH, HF, cerebrovascular disease and anaemia. Similar sex differences in comorbidities have been noted in patients presenting for isolated mitral, aortic valve and concomitant CABG and valve surgeries [161-3]. In addition, women with CVD often experience a delay in diagnosis and treatment when compared with men, which may in part, explain the more advanced coronary and/or valvular pathological conditions observed in women at the time of surgery [161-4].

H. Valvular heart diseases in women

In industrialized countries, the prevalence of valvular heart disease is estimated at 2.5% and increases markedly after the age of 65 years, reflecting the predominance of a degenerative etiology [165]; although rheumatic valve disease in younger ages can prove challenging. Aortic valve stenosis and mitral valve regurgitation account for 3 in 4 patients with valvular heart disease [166]. Despite their similar prevalence, sex differences are present in the epidemiology, pathophysiology, diagnosis, treatment and outcomes [167]. However, guidelines do not include specific sex-based recommendations for the diagnosis and management of significant valvular heart disease. Degenerative aortic valve stenosis is the most common cause of aortic valve stenosis secondary to progressive sclerosis and calcification. In general, women tend to be older in age, frailer, sicker,

with higher comorbid burden than men [168]. Distinct sex difference in LV adaptation during progression of aortic valve stenosis have been described in **Table 23**.

Table 23
Sex-related differences in LV adaptation during AS progression

Sex-related differences
1. Women have larger LV wall thickness, more concentric LV geometry, with smaller annular sizes and LV outflow tract dimensions.
2. Women preserve better LV systolic function (measured as EF or GLS), independently of LV size.
3. Women present greater increase in LVMI and LVRI for smaller changes in hemodynamic loads.
4. Men have higher myocardial stiffness, more interstitial fibrosis and abnormal collagen architecture with increased cross-hatching.
5. Women have higher pulmonary pressures.

LV: left ventricular, AS: aortic stenosis, EF: ejection fraction, GLS: global longitudinal strain, LVMI: LV mass index, LVRI: LV remodeling index (= LV mass / LV end-diastolic volume).

Moreover, women have demonstrated a higher prevalence of paradoxical low flow-low gradient aortic valve stenosis, which has been related to worse mortality compared with high-gradient aortic valve stenosis [169-71]. Recommendations on the echocardiographic aortic valve stenosis grading allow for indexed values for body surface area (BSA) (aortic valve area <0.6cm2/m2), a helpful distinction for women [172] Women have lower aortic valve calcification load than men for the same AS severity. Female sex has been shown to be an independent determinant of progression of both aortic valve calcification and mean pressure gradient, a finding which suggests that women may benefit from a closer follow-up time [173]. Surgical aortic valve replacement (SAVR) is less frequently chosen in women with severe symptomatic aortic valve stenosis than in men, reflecting the sex bias that results from the higher in-hospital mortality and complications among women. Contrary to SAVR, improved survival after transcatheter aortic valve replacement (TAVR) has been reported in women, particularly with transfemoral approach [174-8]. However, the optimal treatment choice for women remains undetermined. The most common etiology of degenerative mitral valve regurgitation is mitral valve prolapse. Sex differences in mitral valve pathology have been described, which challenge women's candidacy for mitral valve repair [175], **Table 24**.

Table 24
Sex-related differences in Mitral valve (MV) pathology

Sex-related differences
1. MV prolapse is more common in women, but they present with lesser degree of MR
2. Higher incidence of increased leaflet thickness and anterior and bi-leaflet MV prolapse is more predominant in women, whereas posterior leaflet prolapse which is technically easier to repair is more common in men.
3. Women have higher prevalence of MV calcification, rheumatic MV disease and mixed regurgitation / stenosis.

MV: mitral valve

The smaller LV dimensions among women and the absence of indexed values for BSA may often result in echocardiographic underestimation of mitral valve regurgitation severity. Moreover, elderly women may be less active and have atypical symptoms compared with men, which may lead to misdiagnosis. Women referred for intervention are usually at an older age, with more advanced disease and higher comorbid burden, and have a lower likelihood of undergoing mitral valve repair. [178]. Women are more likely than men to receive an urgent surgery; whereas at the time of MV surgery they are more likely to undergo concomitant operation for AF and tricuspid valve regurgitation. Several studies have suggested higher operative mortality for women, especially for the younger ones, compared with men, and worse long-term survival. With regards to the percutaneous treatment of mitral regurgitation, MitralClip implantation has been demonstrated to be equally effective in both sexes [174].

Sex differences: Current evidence supports the role of worse profiles for women presenting for valve surgery compared with their male counterparts as the main cause of disparity in outcomes. Timely referral to experienced centers and close follow-up may be particularly relevant in elderly women with small body size. Women demonstrate a higher prevalence of paradoxical low flow-low gradient aortic valve stenosis, which has been related to worse mortality compared with high-gradient AS. Future clinical guidelines should address distinct differences between men and women to ensure sex equality in care of valvular heart disease patients.

H1. The impact of procedure type on surgical risk and on survival isolated CABG

H1.1. CABG and mitral surgery

There is a significantly higher age-standardized mortality rate in women undergoing CABG/mitral valve sur-

gery [177]. This could be attributed to the poorer prognosis after CABG in women with HF, as those needing combined CABG/mitral valve surgery are more likely to have HF with reduced ejection fraction. The presence of HF compounds the sex-specific challenges in patients with CAD and further places women at risk.

H1.2. CABG and aortic valve surgery

In a recent cohort of 5867 patients undergoing combined CABG and aortic valve surgery (33% women), the risk of in-hospital mortality was higher in women compared with men. Long term outcomes were not examined. These authors found that substantial sex differences existed in patient presentation and mortality risk. The female patients were older and this age difference could also fuel speculations concerning later presentation of female patients in the disease process or even higher levels of frailty at time of presentation, potentially contributing, in addition to the CABG, to the worse outcomes in female patients after CABG/AV surgery [178].

H1.3. Isolated mitral valve surgery

In a study of 183,792 Medicare beneficiaries, between 2000 and 2009 found that women, compared with men, had worse preoperative characteristics and admission status and were also less likely to undergo mitral valve repair. In addition, women had worse operative mortality and long-term survival. Although mitral valve repair seems to restore life expectancy for men, women do not seem to achieve the full benefit of their mitral valve repair operation. These differences appeared to be largely driven by the worse preoperative characteristics of women; however, after adjustment, female sex was still independently associated with higher operative mortality in mitral valve replacement. Although risk adjustment diminishes or eliminates differences in survival between men and women, it does not mitigate the fact that women present later, more urgently, and with more advanced disease [176].

H1.4. Isolated aortic valve replacement

Several studies have documented no sex differences in isolated aortic valve surgery for both in-hospital mortality as well as long-term survival [172].

More recently the new Euro SCORE II has been developed. Although improvements have been made with this updated model, the risk score was again built using a mixed population of male and female patients who underwent predominantly CABG surgery. However, EuroSCORE II has better predictive discrimination for operative mortality than EuroSCORE I, which greatly overestimated this risk. EuroSCORE II fared well compared with the STS risk score. The inclusive nature of EuroSCORE II for numerous procedures provides more flexibility than the STS score for complex procedures. EuroSCORE II should be considered for calculating risk score for complex cardiac surgical patients [178].

I. Women and Stroke

Stroke is the third leading cause of death for women and by 2030, stroke incidence will be increased. Few years ago, the Global Burden of Disease 2013 Study described that the risk and the absolute number of ischemic and haemorrhagic stroke events were greater in men than in women. However, given that life expectancy is higher in women, females with stroke are more likely to be living alone and/or widowed. Therefore, they are more often institutionalized and have poorer recovery from stroke than men. Moreover, genetic, coagulation, hormonal, reproductive and social factors differ between sexes. AH and AF are the most common factors leading to stroke in women whereas female sex is an independent predictor of stroke in the patients with AF. For those reasons, haemorrhagic stroke, which has higher mortality than ischemic stroke, is more frequent in women. Furthermore, concerning the ischemic stroke, elderly women have higher mortality than men. Although in the era of evidence-based medicine, women are under-represented in clinical trials, it is crucial to identify women at high risk to reduce stroke mortality and morbidity. Women experience symptoms of nausea/vomiting, headache, dizziness, and cognitive dysfunction more often than men which are characterized as non-typical stroke symptoms and could be associated with delayed recognition and treatment, misdiagnosis, and adverse outcome [179]. The increased risk of stroke in pregnancy is well recognized. The period of highest risk of stroke is the peripartum/postpartum phase. The rate of stroke is increased by nine-fold at the time of delivery and three-fold in the early postpartum period, with an increase in the risk of both ischemic and haemorrhagic stroke. For patients with high-risk status such as hypercoagulation state, consider ASA+/-low molecular weight heparin during

pregnancy. Patent foramen oval endovascular closure may be considered for secondary prevention of stroke in such group of patients. Furthermore, hypertensive disorders of pregnancy such as preeclampsia are important contributors to obstetric stroke and predispose women to premature CVD [180-2].

Prevention of stroke is a complex medical and a political issue. Governments as well as non-governmental organizations must take responsibilities urgently in order to prevent stroke events. Concerning the therapeutic approach, aggressive treatment of obesity (even before pregnancy), hypertension, hyperlipidaemia, DM, smoking and AF in women should be emphasized. It is worth noting the importance of screening and primary prevention of risk factors in early life, especially in the obese, pregnant, and high-risk ethnic/racial groups. Educational campaigns for early stroke recognition in women should be organized.

J. Arrythmias in women

The incidence of certain clinical arrhythmias undoubtably varies between men and women

Clinical and experimental observations suggest that true differences in electrophysiologic variables exist between them and this is a sex hormones' effect through differences in expression of ion channel subunits and channel function modulation. Sex differences have the potential to impact diagnostic and therapeutic interventions in arrhythmias.

Symptoms of supraventricular arrhythmias in women are more likely to be attributed to panic, anxiety, or stress disorders than in men. Women are referred 3-times less frequently for catheter ablation. At the time of referral, they are significantly older, have more co-morbidities, and are more sensitive to amiodarone side effects than men. Sex-related anatomical differences could theoretically affect procedure outcomes [183].

AF incidence and prevalence increase with aging, and it's known to be higher in men than in women; however, because there are almost twice as many women as men aged >75 years, the absolute expected number of men and women affected by AF is equal. In AF patients, female sex is associated with an age-dependent moderate risk of stroke and should be regarded as a stroke risk modifier relevant in the presence of other CHA2DS2-VASc risk stroke factors, rather than an independent stroke risk factor.

Women with AF show a higher risk for AF-related morbidity due to stroke, a poorer tolerance to antiarrhythmic pharmacological therapy and a weaker quality of life; for this reason, a curative, catheter-based approach for AF appears very attractive in women.

Right ventricular outflow tract (RVOT)-ventricular tachycardia is twice more common in females while left idiopathic fascicular ventricular tachycardia is more common in men. Catheter ablation of idiopathic ventricular arrhythmias is equally effective with the same risk of complications in female and male patients. Female patients are under-represented in randomized controlled clinical trials and registries of patients undergoing catheter ablation for ventricular tachycardia with structural heart disease, especially with CAD.

There are sex differences well delineated in the most common channelopathies and it is especially important to be taken into consideration during management. Boys with LQT1 have higher risk of ventricular arrhythmias and fatal events than girls. The risk rate switches in puberty to lower risk in males and higher risk in females. The most important sex differences are found in LQT2.Women with LQTS have an increased risk during the 9month post-partum period, particularly women with the LQT2 genotype. There is conflicting evidence on sex differences in ventricular arrhythmias in LQT3, both indicating higher risk in LQT3 men or indicating no additional risk in LQT3 according to sex. Beta-blocker efficacy may be greater in women with LQT3 compared with men [184-5].

Clinical manifestations of Brugada syndrome are eightfold more frequent in adult men than in adult women. It has been suggested that androgens may affect the Ito channel and aggravate ion channel dysfunction. Additionally, sex differences have been described in various brady-arrhythmias requiring permanent pacing with respect to physiology, utilization, and implant complications. In retrospective and prospective analyses, women have a higher incidence of sinus node dysfunction and men a higher incidence of atrioventricular node dysfunction. A retrospective analysis of >30.000 patients implanted with a permanent pacemaker demonstrated that women on average presented at an older age than men.

J1. Atrial Fibrillation (AF)

AF incidence has been shown to increase disproportionately with increasing age in both women and men, reaching as high as 30.4 per 1,000 person-years in women and 32.9 per 1,000 person-years in men by age 85-89 years. Women with AF show a higher risk for AF-

related morbidity due to stroke, a poorer tolerance to antiarrhythmic pharmacological therapy and a weaker quality of life; for this reason, a curative, catheter-based approach for AF appears very attractive in women. Nevertheless, women with HF and tachyarrhythmia are poor represented and often show delayed referral for interventional procedures. The underlying reason is not completely clarified. It seems that concerns about radiation exposure and potential reproduction-associated consequences in women of childbearing age, children care issues and higher symptom tolerance are possible explanations. Finally, symptoms of supraventricular arrhythmias are more likely to be attributed to panic, anxiety, or stress disorders in women than in men. Women are referred 3-times less frequently for catheter ablation. While the outcome after AF catheter ablation in female does not differ from their male counterparts, the overall complication rate is reported to be two-fold, due to a higher incidence of vascular access complications and possible cardiac tamponade [184-5]. OAC use is similar in AF patients, but women were less often prescribed OAC and were given aspirin more often than male counterparts [186-7]. Anticoagulation with warfarin may be less controlled in female AF patients (lower time in therapeutic range). Moreover, females with AF have a 28-54% higher residual stroke risk than males even with well-controlled warfarin. Available evidence showed no significant sex-specific differences in the warfarin-related risk of major bleeding in AF patients, although overall bleeding rates were higher in females. There are small differences for men and women with AF treated with DOACs. Women experienced similar overall efficacy, but less major bleeding or intracranial bleeding compared with men [187]. Observational data suggests females receive lower dosages of dabigatran (110 mg), and that males have less major bleeding than females. Rivaroxaban 20mg was associated with significant stroke reduction in males and more major bleeding in females compared with warfarin. Indirect comparison of DOACs effects did not reveal any clinically relevant difference in DOACs efficacy and safety relative to female sex [187], suggesting that DOAC in females should follow general principles of personalized AF treatment decision making [187].

Sex differences: Women with AF show a higher risk for AF-related morbidity due to stroke, poorer tolerance to antiarrhythmic pharmacological therapy and weaker quality of life. Women with AF are referred for catheter ablation later than men, which may reflect that AF occurs later in life in women. Women presenting with AF suffer worse symptoms than men; tend to have a less favourable result by PV ablation; suffer significantly more procedural complications from AF ablation including perforation/tamponade.

J2. Paroxysmal supraventricular tachycardia

There is a clear sex-dependent difference in arrhythmia incidence and onset of the three most common types of paroxysmal supraventricular tachycardia (PSVT), i.e. AV nodal re-entrant tachycardia (AVNRT), accessory pathway mediated orthodromic AV re-entrant tachycardia (ORT), and less clear in focal atrial tachycardia (FAT). Inappropriate sinus tachycardia (IST) was previously believed to occur predominantly in young, females from small studies. However, in a later study of 607 patients, the prevalence of asymptomatic IST was 1.16%, in both sexes. Thus, IST might occur equally often in men than in women, but women seem to appear more symptomatic. There is a clear dependence of AVNRT susceptibility on cyclic hormone level changes, with increased number of AVNRT and other PSVT episodes early in hormonal cycle. The overall conclusion is that low oestrogen levels (rather than high progesterone) are the reason for more supraventricular tachycardia in the early menstrual cycle and why AVNRT ablations are more common post-menopause [188-190]. In symptomatic women with documented PSVT, equal access to catheter ablation as appropriate should be provided. A diagnostic electrophysiological study may be offered to women with symptoms strongly suggesting PSVT, even before arrhythmia documentation In women with a previous 'negative' electrophysiology study, a second electrophysiology study timed in the first days of menstrual cycle may be advised to render arrhythmia inducible [191].

J3. Ventricular tachyarrhythmia and catheter ablation

Several aspects of cardiac electrophysiology are influenced by sex. At the 12-lead ECG, females present a higher heart rate at rest, shorter QRS, and longer QTc interval. Incidence of specific arrhythmias and sudden death is also affected by sex, with AVNRT and focal tachycardias occurring more frequently in females while AVRT and AF/flutter and sudden cardiac death are more frequently reported in male subjects. These characteristics are more pronounced in athletes also due to a greater CV remodelling in male subject in response to exercise training [192]. In addition, pregnancy

is a setting for the occurrence of arrhythmias both for diagnosis and treatment [193]. Supraventricular arrhythmias are frequently expressed, while ventricular events are rare. Notably, women with CHD represent a population at higher risk for severe arrhythmic complications. We need further investigations to better define the mechanisms underlying these sex-related differences: physical, autonomic and hormonal effects are certainly involved, but their role still needs to be fully characterized. More importantly, females are seldom represented in clinical research (i.e. one-fifth to one-fourth of the enrolled patients) and are infrequently referred for electrical treatments for arrhythmias and HF in clinical practice.

Sex differences

- RV outflow tachycardia is twice more common in females.
- Female and male patients are equally represented in nonrandomized single centre registries of catheter ablation for idiopathic ventricular arrhythmias.
- Catheter ablation of idiopathic ventricular arrhythmias is equally effective with the same risk of complications in female and male patients
- Female patients are under-represented in randomized controlled clinical trials and registries of patients undergoing catheter ablation for VT with structural heart disease, especially with CAD.
- Lower incidence of sudden cardiac death and CAD and lower incidence and inducibility of ventricular arrhythmias in women with structural heart disease partly explain the under-representation.
- Catheter ablation of VT associated with ischaemic heart disease may be associated with slightly higher VT recurrence rate and has the same risk of complication in female and male patients.
- Catheter ablation of VT associated with non-is chemic cardiomyopathy and arrhythmogenic RV cardiomyopathy is equally effective with the same risk of complications in female and male patients. Catheter ablation should be offered equally to women and men
  with symptomatic ventricular arrhythmias.
- Catheter ablation should not be denied to women with symptomatic ventricular arrhythmias because of feared less success or increased complication rates

K. Heart Failure (HF) in women

K1. HF with reduced Ejection Fraction (HFrEF)

HFrEF is a less common diagnosis in women compared with HF with preserved ejection fraction (HFpEF), as documented in the Framingham Heart Study [194]. However, the in-hospital mortality remains the same among women and men with HFrEF as well as sharing common risk factors and history of chronic renal disease [195].

HFrEF is defined as HF with an ejection fraction < 40%. According to the European Society of Cardiology (ESC) 2016 HF guidelines, transthoracic echocardiography is recommended for the diagnosis of HfrEF and for guidance in therapeutic decision-making [196]. Other imaging modalities such as cardiac magnetic resonance, computed tomography, nuclear stress testing or coronary angiography can be used for the investigation of the etiology. The symptoms and signs of the disease do not differ between sexes, however some differences in their frequencies have been reported [197]. The diagnosis of HfrEF, especially in the acute setting, can be facilitated using biomarkers, like BNP and NT-proBNP. Their reference range should be sex specific given that women tend to have higher values [198]. The established HF treatment consists mainly of b-blockers, ACE inhibitors, ARBs and mineralocorticoid receptor antagonists. Clinical trials regarding b-blockers effectiveness in HF include the COPERNICUS trial, the CIBIS II and the MERIT-HF which studied carvedilol, bisoprolol and metoprolol respectively. All the above trials showed a significant reduction in mortality or hospitalizations in women with HFrEF following treatment with a b-blocker [199-205]. ACE inhibitors have been a cornerstone of HF treatment since the landmark CONSENSUS trial showed the beneficial effect of enalapril [202]. However, women were significantly underrepresented in most trials. A large meta-analysis showed a non-significant trend towards increased survival and reduced hospitalizations with ACEIs treatment [203]. Use of ARBs in indicated when ACEIs cannot be tolerated because of serious side effects. The CHARM trials and the Val-HEFT studied the effects of candesartan and valsartan on HF respectively. Both showed a reduction in either mortality or hospitalizations in female patients. [204-5]. MRAs are recommended in HF patients with ejection fraction ≤ 35%. The RALES and EMPHASIS-H trials studied the effects of spironolactone and eplerenone on HFrEF patients, respectively. They both showed significant reduction in mortality and hospitalization in the female

subpopulation [206-7]. The use of the combination of hydralazine and isosorbide dinitrate is recommended in black HFrEF patients or those who cannot tolerate neither an ACE inhibitors nor ARB. Most studies included only men except for the A-HEFT trial [208] which enrolled 41% African American women and showed a reduction in mortality and hospitalizations in the treated group. Digoxin use is recommended in symptomatic patients despite optimal HF treatment [209]. Analysis of the DIG trial showed reduced mortality when the digoxin serum levels were within therapeutic range for both sexes [210]. Ivabradine use is recommended in symptomatic HFrEF patients in sinus rhythm and resting heart rate ≥ 70 bpm despite optimal HF treatment. A sex-specific subgroup analysis of the SHIFT trial showed similar results between men and women [211]. ARNI is recommended as a replacement to ACE inhibitors in case of a symptomatic HFrEF patient despite optimal medical treatment [212]. The PARADIGM-HF trial, which studied the efficacy of the combination of sacubitril and valsartan in HFrEF patients, used an ACE inhibitor as control medication showed reduced hospitalizations in the female subgroup [211]. Exercise training has been shown to increase exercise tolerance, quality of life and hospitalization rates in HF patients. In particular, the HF-ACTION trial showed significant improvement in mortality and hospitalizations while a sex-based analysis revealed a higher benefit in women [212]. Device therapy [implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT-D) implantation) in women has been shown to decrease mortality especially in women with dilated cardiomyopathy as seen in the sex-specific analysis of the MADIT-CRT trial perhaps due to an increased prevalence of left bundle branch block in women [213]. Long term mechanical circulatory support has evolved dramatically during the last decades. Despite the fewer complications seen in modern LV assist devices such as the H-VAD and HeartMate 3, sex-specific analyses are still required given the usually smaller LV dimensions seen in women.

K2. Heart Failure with preserved LV ejection fraction (HFpEF)

Table 25
Pathophysiologic mechanisms underlying the predominance of HFpEF in women

Pathophysiological mechanisms in HFpeF	What is especially known for women
Cardiometabolic conditions are common risk factors in HFpEF • associated with a systemic inflammatory state that leads to coronary microvascular dysfunction	Obesity and hypertension are more common in women A cardiometabolic phenotype of HFpEF is more commonly seen in women with obesity, hypertension, diabetes mellitus and hyperlipidemia
Chronic Kidney Disease Renal dysfunction is a common risk factor in HFpEF • predisposing to sodium retention and volume expansion	A cardiorenal phenotype of HFpEF is more commonly seen in older individuals who are predominantly women with low estimated glomerular filtration rates
Cardiac radiation exposure may lead to HFpEF • associated with coronary microvascular disease, myocyte dysfunction and interstitial fibrosis	Women with a history of breast cancer who have undergone radiation therapy are at increased risk of HFpEF
Increased arterial stiffness results to chronic pressure overload and LV stiffness	Aging women have higher rates of increased vascular stiffness
Increased left ventricular (LV) stiffness and impaired LV relaxation • leads to LV diastolic dysfunction and increased LV filling pressures causing symptoms and signs of HF	Gender differences in the LV structural remodeling response exist; women develop smaller and stiffer hearts under stress. Increased LV wall thickness (i.e. LV hypertrophy) and smaller LV cavity size occur with aging; these effects are more pronounced in women Post-menopausal women are more vulnerable to negative LV remodeling due to the hormonal modulation on calcium and nitric oxide handling in cardiac myocytes, and on the renin–angiotensin–aldosterone system, with oestrogen serving a protective role Oestrogen receptors play a role in ventricular remodelling Gene expression profiles differ in women; sex differences exist in the endothelin and nitric oxide systems, myocyte remodelling, calcium handling, fibrosis, myocyte adaptation and apoptosis Obesity appears to have a more pronounced effect on ventricular remodeling, leading to stiffer ventricles

Based on the ESC textbook chapter on HF in women, EUGenMed Cardiovascular Clinical Study Group 2016, Westerman 2016, and Tibrewala 2019.

HFpEF, i.e. EF >40%, also including the category of HF with mid-range EF (HFmrEF, with an EF of 40-50%), is an increasingly prevalent condition [239]. More than 50% of HF patients nowadays exhibit HFpEF. HFpEF is more prevalent in women than men and HFpEF is the most common phenotype of HF in women [214]. Women are about 2 times more likely than men to develop HFpEF [215]. Important differences in this syndrome vary with sex. HF in women occurs at an older age and is more often due to non-ischemic causes [215]. Women with HFpEF are also more likely to have obesity and hypertension but less likely to have CAD or AF [216]. The syndrome of HFpEF has historically been considered to be caused by LV diastolic dysfunction that can be demonstrated on echocardiography, but many other contributing factors such as limitations in LV systolic reserve, systemic and pulmonary vascular function, chronotropic reserve, right heart function, autonomic tone, left atrial function, microvascular endothelial inflammation and dysfunction have shown to play an important role [215-6]. Thus, compared with HFrEF, HFpEF seems to be more heterogeneous with various phenotypes. Aging, visceral adiposity, metabolic stress and hypertension are the most common risk factors. Apart from obesity and hypertension that are known to be more prevalent in women, other potentially unique risk factors and pathophysiological mechanisms have been proposed in women, **Table 25**.

The most recent ESC guidelines on HF [221] have introduced diagnostic criteria for HFpEF (and HFmrEF) aiming to reduce misdiagnosis in this complex syndrome.
Sex differences in the diagnosis have been very little studied. Specific points to avoid misdiagnosis of HFpEF (and HFmrEF) in women are shown in **Table 26**.

Table 26
Definitions of HFrEF, HFmrEF, HFpEF and left ventricular diastolic dysfunction; specific points in women

HFrEF	1. Symptoms ± Signs 2. LVEF <40%
HFmrEF or HFpEF	1. Symptoms ± Signs **2. LVEF 40-49% for HFmrEF or LVEF ≥50% for HFpEF** 3. a) Elevated NP levels (BNP >35pg/ml and/or NT-proBNP >125pg/ml) b) At least one additional criterion: - relevant structural heart disease (LVH and/or LAE) - LV Diastolic Dysfunction

Diagnosing LV Diastolic Dysfunction in patients with Normal LV Ejection Fraction

1. **Average E/E' >14**
2. **Septal E' <7 cm/s or Lateral E' <10 cm/s**
3. **TR Vmax >2.8 m/s**
4. **LAVI >34 ml/m2**

→ **<2 positive → Normal diastolic function**
2 positive → Indeterminate
>2 positive → Diastolic dysfunction

Specific points to avoid misdiagnosis of HFpEF (and HFmrEF) in women

- **always index echocardiographic measurements to body surface area**
- **obesity is associated with lower BNP values, while chronic kidney disease with higher natriuretic peptide values. As both conditions are more common in women, care should be taken in the interpretation of natriuretic peptides for the diagnosis of HFpEF in women.**

Modified from the ESC guidelines 2016 on HF and the ESC Textbook chapter on HF in women.

Abbreviations: BNP, B-type natriuretic peptide; ECG, electrocardiogram; HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; LAE, left atrial enlargement; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NP, natriuretic peptides; NT-proBNP, N-terminal pro-BNP; TR Vmax, maximal tricuspid regurgitation velocity

Almost all studies have shown that women with HFpEF show more prominent signs and symptoms of congestion than men and a worse quality of life [216-8]. However, whether mortality in HFpEF differs between sexes is not yet clear. A recent individual patient-level meta-analysis from 3 large clinical trials in HFpEF in nearly 8,500 patients [214] showed that women had similar rates of hospitalization and better survival than men. The risk of CV death was lower in women and their risk of sudden death was half that of men, likely related to a much lower prevalence of CAD.

Treatment of HFpEF remains a clinical challenge. In contrast to HFrEF, no treatment has been proven effective for HFpEF in clinical trials. Diuretics are the mainstay of treatment while patient phenotyping and specific treatment of comorbidities is emphasized [216-221]. When considering treatment of HFpEF in women, evidence is even less, given the relatively smaller representation in trials and limited analysis of sex differences. Evidence emerging on female-specific aspects of treatment in HFpEF is shown in **Table 27**.

Table 27
Emerging evidence on female-specific aspects of treatment in HFpEF

Nonpharmacologic measures such as dietary modifications and exercise training	In limited studies assessing the effect of caloric restriction and aerobic exercise training in appropriately targeted HFpEF populations in which women were well-represented, a benefit was shown with the interventions
Mineralocorticoid receptor antagonists	In the TOPCAT trial, treatment of HFpEF patients with spironolactone in the Americas was associated with reduced all-cause mortality in women, whereas a significant reduction was not seen in men, suggesting a potential benefit for women with HFpEF
Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors)	In the EMPA-REG OUTCOME(R) trial, treatment of high risk type 2 diabetes patients with empagliflozin was associated with reduced HF hospitalization or cardiovascular death, largely driven by a reduction in HF hospitalization. This difference was seen in women but not in men, suggesting a potential additional benefit for patients with HFpEF and DM, particularly in women
Angiotensin receptor neprylisin inhibitors	In the PARAGON-HF trial that compared sacubitril-valsartan vs valsartan in patients with HFpEF (ca 52% women), sacubitril-valsartan seemed to reduce the risk of HF hospitalization more in women than in men, suggesting that that women may derive benefit at a higher EF than do men

Based on Tibrewala 2019, and McMurray 2019.

The constantly increasing population of elderly women with HFpEF associated with adverse clinical outcomes, in combination with the lack of effective treatments, render HFpEF an important clinical and social problem. Sex differences in demographics, comorbidities and pathophysiology make phenotypes of HFpEF unique in women. Treatments have not been overwhelmingly effective so far, but some small benefits shown only in women hold promise for the future. Further research is needed to improve the understanding of the disease and develop therapies for HFpEF in women.

L. Precapillary PH

PH is classified into five groups based on the WHO classification system. Pulmonary Arterial (pre-capillary) Hypertension (PAH) group I, is a relatively rare condition, estimated to affect 15-50 per million people in the western societies. It is a proliferative vasculopathy of the pulmonary arterioles characterized by vascular remodelling (hyperplasia - hypertrophy of all three vascular wall layers) and neovascularization. Idiopathic, heritable and drugs/toxins related PAH (mainly appetite-suppressants medications) are the major subtypes in this group, accounting for more than 50% of the cases. All these three conditions affect women disproportionally to men, in a fashion more than 2:1. The median age of patients at presentation is 50 years. In early stage, most of the cases report exertional breathlessness [222].

PH group I also includes PAH related to connective tissue diseases, portal hypertension, AIDS, and congenital heart diseases (Eisenmenger's syndrome). 12 % of patients with systemic sclerosis are expected to develop PAH, whereas the incidence of the condition related to other connective tissue diseases is not clear. Connective tissue diseases on the other hand, like systemic sclerosis, rheumatoid arthritis and systemic lupus erythematosus are predominantly affecting women compared with men in a fashion 4/1, 3/1 and 9/1 respectively. Those have been demonstrated in the National French Study [223-5].

Diagnosis is suspected based on Echocardiographic – Doppler findings after the exclusion of other cardiorespiratory condition (chronic thromboembolic disease also included). Right heart catheterization is confirmatory (normal pulmonary capillary wedge pressure – PCWP, increased pulmonary vascular resistance). Based on the DETECT protocol, certain parameters (FVC/DLCO and natriuretic peptide levels) are used to select patients with systemic sclerosis for Echocardiography screening before proceeding to right heart catheterization. Awareness of this uncommon condition among Health Care professionals is of high importance, to enable its timely diagnosis and treatment.

M. Congenital heart disease

Although published literature suggests that prevalence of congenital heart disease is higher in women compared with men in the adult population, aortic coarctation and bicuspid aortic valve are more prevalent in male patients. Furthermore, it has been shown by other studies that morbidity and mortality rates differ between sexes, with the women being in a more favorable state. However, the etiology of this fact remains unclear [226].
Female adult patients with congenital heart disease present higher prevalence of PH compared with males. Data from Mayo Clinic suggest that the ratio of isolated secundum atrial septal defect (ASD) with PH of women to men is 28/1. This phenomenon is striking and could be explained by the "two hit hypothesis": (the higher genetic predisposition -susceptibility for the primary PH for women along with the ASD trigger).
It can be concluded that there is a female preponderance in adult population with congenital heart disease and that the female sex is associated with lower hospital morbidity and mortality [226-7]. The underlying causes behind this might be due to sex differences in genetic polymorphisms or the effect of sex hormones, however further investigation is required to illuminate this.

N. Women and peripheral artery disease (PAD)

Currently, PAD is beginning to be recognized as a life- and lifestyle-threatening disease in women. PAD affects 5-10 million people in the United States, and is associated with similar morbidity, mortality, and economic healthcare costs as both heart disease and stroke. Nevertheless, female peripheral vascular disease remains under-recognized as a cause of significant morbidity and mortality by both the medical community and public [228].

N1. Prevalence
PAD prevalence and incidence are intimately age related. While PAD has typically been thought of as a male-dominant disease process, when accounting for the greater representation of women in the elderly population, there are more women than men with PAD among adults older than 40 years [229]. These findings underline increasing overall prevalence of PAD in women.

N2. Risk factors for PAD among women
Risk factors for PAD are like CAD and other atherosclerotic diseases. DM, AH, hyperlipidemia, and tobacco use have been mostly reported to be similar for men and women, with a few exceptions. However, because women more often present with asymptomatic PAD [230]. and are less often diagnosed with CVD risk factors, they may not receive the same risk factor modification therapy as men. Other conventional risk factors include chronic kidney disease, obesity, and physical inactivity. Sex specific risk factors include use of oral contraceptives, history of complications during pregnancy such as intrauterine growth restriction, preeclampsia, and pregnancy-induced hypertension. HRT does not appear to reduce the odds of developing PAD in PMW and may even increase the risk of morbidity from vascular interventions [231]. Also, neither study demonstrated increased incidence of PAD in women taking HRT [232].
Table 28 outlines the risk factors associated with PAD in women compared with men.

Table 28
Risk factors of PAD in Women

Diabetes	Presence of diabetes doubles the risk of IC as compared with males[4]
Tobacco use	Females are assuming a larger number of smoking-related diseases by percentage[4]
Obesity	Waist circumference required for increased cardiovascular risk is smaller than for males[4]
Chronic Kidney Disease	Women <70 y.o with chronic kidney disease have 1.5 times higher risk of developing PAD than men[3]
Oral Contraceptives	Women aged 18–49y taking any generation oral contraceptives have x3.8 higher odds of having PAD as compared to women taking no oral contraceptives[3]

N3. Clinical presentation of PAD among women

Women are mostly asymptomatic, without an obvious reason, that often leads to delayed diagnosis. Up to 63% of elderly females with an ankle brachial index (ABI) of less than 0.9 demonstrating no exertional leg symptoms. Also, women may present with unusual signs that are ascribed to other comorbidities, such as spinal stenosis. The patient's activity level should be ascertained during screening for those patients who are suspected to have PAD; this will help establish whether a lack of symptoms is an indicator of the presence of disease. When compared with men, data suggest that women more often present with advanced disease, have a poorer quality of life, and baseline lower extremity function as seen by the shorter walking distance to claudication onset and the slower walking speeds than males [231].

Table 29 outlines the clinical presentation of PAD in women [232].

Table 29 Presentation of PAD in women	
Asymptomatic PAD	More common in women[4]
Age at presentation	Women present with symptoms at an older age than men[4]
Claudication distance	Distance to claudication onset is shorter for women[4]
Atypical leg symptoms	More common in women[32,34]
Critical Limb Ischemia (CLI)	Women are more likely to present with CLI[4]
Walking speeds	Slower walking speeds in women diagnosed with IC as compared with males[4]

N4. Diagnosis of PAD

Although patient history and physical examination are helpful for the general diagnosis of PAD and the assessment of CV risk, objective assessments with non-invasive diagnostic tests are invaluable in PAD detection. Most utilized initial diagnostic test is resting arterial brachial index (ABI). Although use of a lower ABI limit in women has been suggested to be necessary due to smaller-sized arteries presence in women or to the relationship between ABI and height, most physicians use an ABI <0.9 to diagnose PAD, regardless of the patient's sex. Exercise ABI, toe-brachial index, transcutaneous oxygen pressure or skin perfusion pressure may be considered based on clinical presentation and resting ABI. Advanced imaging techniques such as duplex ultrasound, MRA, CTA, or invasive angiography are useful in providing anatomic location and severity of disease. Currently, there is no major sex difference in diagnostic sensitivity or accuracy of these tests [232].

N5. Treatment and outcomes

The main management goals for PAD are similar for both sexes, namely, reducing morbidity and mortality and improving symptoms and quality of life. These goals are achieved by aggressive risk factor modification, pharmacotherapy and revascularization.

N6. Medical therapy

Although pharmacotherapy and life-style modification and risk factor modification are imperative for reduction of mortality and morbidity, they may not provide significant reduction of claudication.

Cilostazol, supervised exercise and antiplatelet therapy- aspirin or clopidogrel-have been recommended as first line therapy for the treatment of claudication. None of the studies in this field has reported sex specific outcomes [232].

N7. Lower extremity revascularization

Ischemic ulceration, gangrene, rest pain, or lifestyle-limiting or disabling claudication serve as the primary indications for endovascular or open revascularization [230-2]. Open surgical bypass and endovascular angioplasty and/or stent placement remain options for revascularization in both men and women. It seems that women may be more prone to complications because of either open or endovascular revascularization.

In patients presenting with critical limb ischemia for open revascularization, women were found to be more likely to suffer from wound complications, limb loss, and mortality than their male counterparts. Endovascular intervention generally in females appears to be associated with better patency rates and may be associated with better outcomes in cases of CLI when compared with males presenting with critical limb ischemia [232]. The optimal intervention based on sex and indication is not clearly delineated in the literature and remains a topic for future study.

Table 30

Table 30 Therapy outcomes of PAD in women	
Medical therapy, cilostazol	No gender-based difference to benefit[4]
Supervised exercise	No gender-based difference to benefit[4]
Surgical revascularization outcomes	
Graft failure	Higher incidence in women[5]
Wound infection	Higher incidence in women[5]
Bleeding complications	Higher incidence in women[5]
Limb loss after surgery	Higher incidence in women[5]
Mortality	Higher incidence in women[5]
Endovascular revascularization outcomes	
Technical success	Higher incidence in women[5]
Embolic events	Higher incidence in women[5]
Patency rates after CLI	Higher in women[5]
Limb loss after EVI	Similar for males and females[5]
Outcomes after iliac stenting	Similar primary and secondary patency[5]
Outcomes after SFA POBA/stenting	Improved patency in females[5]
Outcomes after tibial angioplasty	Improved patency in females[5]

Abbreviations: CLI, critical limb ischemia; EVI, endovascular intervention; PAD, peripheral arterial disease; POBA, plain old balloon angioplasty; SFA, superficial femoral artery

O. Cardio-oncology

CVD and cancer are the two main causes of death in both sexes. Over the last decades, the increasing prevalence of cancer therapies along with successful treatment strategies, has created a special population described as cancer survivors. In women, the most common cancer diagnosis is invasive breast cancer with one out of 8 carrying the lifelong risk to develop [233], while the 5-year survival rate of the disease exceeds 90% [233-4]. Consequently, breast cancer patients form an excellent model to study the pathophysiological effects of cancer treatment and cancer itself on CV system. CVD remains a great concern in these patients, as it represents the second cause of death, after cancer itself and in selected subgroups (postmenopausal hormone sensitive breast cancer) the first cause, exceeding cancer.

It has been observed that women with cancer have higher risk of developing CVD. The risk of a CVD event (hospitalization or death) among women with a low Framingham risk (<10%) is 44% higher in women with breast cancer compared with women without breast cancer [235]. Furthermore, women with breast cancer have an adjusted 77% higher risk of death from CVD than women without breast cancer. Although cancer treatment, chemotherapy and radiotherapy, has been associated with accelerated atherosclerosis, there are several other factors that can explain this association. First, breast cancer and CVD share common risk factors such as smoking, family history, obesity, unhealthy diet, hormone replacement and physical inactivity [302]. Obesity and physical inactivity (<150min/week of moderate aerobic exercise) seems to link CV disease and breast cancer [236], while it has been assumed that 20% of cancers have a causal association with obesity. In addition to preexisting risk factors, cancer itself promotes atherosclerosis through a couple of molecular and pathophysiological mechanisms, implicating inflammation, and oxidative stress [237-8]. Finally, common genetic predisposition has also been implicated.

Table 31

Table 31
Baseline risk factors for cardiotoxicity (Ref#270)

Current myocardial disease	Demographic and other CV risk factors
Heart failure (with either preserved or reduced ejection fraction) •	• Age (paediatric population ;>50 years for trastuzumab; >65 years for anthracyclines) • Family history of premature CV disease (<50 years)
• Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide)	Arterial hypertension Diabetes mellitus Hypercholesterolaemia
Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia	
Moderate and severe VHD with LVH or LV impairment	
Hypertensive heart disease with LV hypertrophy	
Hypertrophic cardiomyopathy Dilated cardiomyopathy Restrictive cardiomyopathy Cardiac sarcoidosis with myocardial involvement (e.g. AF, ventricular tachyarrhythmias)	
Previous cardiotoxic cancer treatment	**Lifestyle risk factors**
• Prior anthracycline use	Smoking High alcohol Intake
• Prior radiotherapy to chest	Obesity Sedentary habit or mediastinum

O. Cardio-oncology- screening for heart disease

Patients with reduced or low normal LVEF, known CAD, or AF prior to the initiation of anthracycline or trastuzumab treatment have been shown to be at increased risk of developing HF [239]. In addition, traditional cardiac risk factors for CAD or HF such as AH, DM, tobacco use, hyperlipidemia, obesity and increasing age have been associated with an increased risk of cardiotoxicity with breast cancer therapy that includes anthracyclines, trastuzumab or radiation [240-4]. Given these findings, screening, and treatment of potentially modifiable risk factors to reduce the risk of cardiac events in patients with breast cancer is indicated.

Assessment of CAD should be based on the history, age and sex of the patient, considering the use of chemotherapy drugs as a risk factor for CAD. Clinical evaluation and, when necessary, testing for detection of myocardial ischemia is key to identify patients with latent preexisting CAD. This may have implications in the selection of cancer treatment.

AH should be adequately treated according to the current standing clinical practice guidelines, and BP should be monitored before initiating cancer treatment and periodically during treatment, depending on the patient's characteristics and adequate BP control. AH in patients with cancer is manageable with conventional antihypertensive treatment, but early and aggressive treatment is encouraged to prevent the development of CV complications (i.e. HF). ACE inhibitors or ARBs, beta-blockers and dihydropyridine calcium channel blockers are the preferred antihypertensive drugs. Non-dihydropyridine calcium channel blockers should preferably be avoided due to drug interaction.

While primary prevention of cardiotoxicity is still in the research domain, secondary prevention has already entered clinical practice guidelines despite persistent unresolved questions. [245]. There is some evidence that

good control of common CV risk factors at initiation of chemotherapy mitigates the CV consequences of cancer treatment in patients with a history of AH, DM and HF [245]. Prospectively validated criteria of early cardiotoxicity, which would be representative of late morbidity and mortality, are needed. The sensitivity of the current approach based on serial assessment of LVEF is insufficient [241-2]. The combined biomarker and imaging approach also suffer from a set of limitations. Several circulating biomarkers (troponin I and BNP or NT-proBNP) have been identified as useful for the early detection of myocardial dysfunction and overt HF related to cancer therapies [244]. However, conclusive data are needed to establish whether biomarkers reliably predict clinically relevant late consequences of cancer treatment. The effect of interrupting cancer therapy remains to be determined, but should not be taken lightly, as there are examples in general of interruptions or incomplete treatment courses having an adverse effect on optimal cancer treatment outcomes.

P. Sex differences in COVID-19 Cardiovascular implications

Early reports demonstrated that when compared to women, male COVID positive patients have more severe disease and a higher mortality. According to Global Health 5050, an organization that promotes sex equality in health care, the disproportionate death ratio in men may be explained by the higher contribution of comorbidities (i.e., CVD, hypertension, diabetes, and chronic lung disease), higher risk behaviours (i.e., smoking and alcohol use), and occupational exposure. Another biological difference may relate to sex differences in angiotensin-converting enzyme 2 (ACE2) receptors. Interestingly, there are marked differences in the density of ACE2 receptors in the reproductive organs: the testes have much higher levels of ACE2 than the ovaries [246]. Thus, may explain sex differences on heart injury among patients infected with SARS-CoV-2.

Conclusion

For years heart disease in women has been described as under-researched, under-diagnosed and under-treated even though it is a leading cause of death. Diagnosis of coronary heart disease in women can be challenging due to a higher rate of functional limitations and lower prevalence of obstructive coronary artery disease than in men. Women have less epicardial disease than men suggesting other mechanisms of ischemic heart disease that include endothelial dysfunction, thrombophilia, and microvascular reactivity. Risk factors, reproductive status, clinical symptoms and functional status, help determine which diagnostic modality is best for identifying underlying CHD. In pharmaceutical therapy, available data shows different responses to antithrombotic therapy between males and females in terms of efficacy and safety, in both primary and secondary cardiovascular disease prevention. Additionally, women exhibit higher prevalence of non-atherogenic coronary artery disease than men, while pregnancy and menopause promote alterations in cardiovascular function and physiology. Postmenopausal status is identified as a risk factor for CV disease. Sex-specific patterns of cardiac and vascular ageing play an important role; thus, differences between sex in patterns of age-related cardiac remodelling are associated with the relatively higher prevalence in women than in men of heart failure with preserved ejection fraction. Similarly, sex variation in vascular structure and function changes with ageing contribute to differences in the manifestation of coronary artery disease. Both hormonal and non-hormonal factors underlie sex differences in cardiovascular ageing and the development of age-related diseases. Cancer therapy in women has shown positive results in reducing morbidity and mortality, although cardiotoxicity remains the most important side-effect. While primary prevention of cardiotoxicity is still in the research domain, secondary prevention has already entered clinical practice guidelines despite persistent unresolved questions. There is an ongoing need for greater emphasis on the sex-specific aspects of cardiovascular risk factors, manifestation of cardiovascular disease states, and response to therapies; as well as it is crucial to promote diversity, health equity, and a broad range of perspectives in treating special needs for each sex, age category, demographic and social status.

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