Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Hellenic Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Hellenic Journal of Cardiology

journal homepage: http://www.journals.elsevier.com/hellenic-journal-of-cardiology/

Review Article

Cardiovascular disease in women: Executive summary of the expert panel statement of women in cardiology of the hellenic cardiological society

Christina Chrysohoou [1, *], Constantina Aggeli [2], Catherine Avgeropoulou [3], Maria Aroni [4], Maria Bonou [5], Maria Boutsikou [6], Stella Brili [2], Eftyhia Chamodraka [7], Anna Dagre [8], Panagiota Flevari [9], Aikaterini Fountoulaki [8], Alexandra Frogoudaki [10], Aggeliki Gkouziouta [11], Julia Grapsa [12], Eleni Hatzinikolaou-Kotsakou [13], Kallirroi Kalantzi [14], Anastasia Kitsiou [15], Panagiota Kostakou [8], Roy Kourea [9], Paraskevi Koutrolou-Sotiropoulou [16], Maria Marketou [17], Sophie Mavrogeni [11], Katerina K. Naka [14], Maria Nikolaou [18], Ourania Papazachou [19], Lida Pieretta Papavasileiou [20], Eftihia Simeonidou [9], Artemisia Theopistou [21], Helen Triantafyllidi [9], Chrysanthi Trikka [22], Dorothea Tsekoura [2], Aphrodite Tzifa [23], Sophia Vaina [2], Agathi Rosa Vrettou [24], Theodora Zaglavara [25], Genovefa Kolovou [26], Reviewers

[1] *1st Cardiology Clinic, University of Athens, Hippokration Hospital, Athens, Greece*
[2] *1st Cardiology Clinic, University of Athens, Hippokration Hospital, Athens, Greece*
[3] *Cardiology Clinic, Hippokration Hospital, Athens, Greece*
[4] *Iaso General Hospital, Athens, Greece*
[5] *Laiko Geniko Nosokomeio: Athens, Greece*
[6] *Mediterranean Hospital, Attica, Greece*
[7] *Asklipeion Voula, Greece*
[8] *Thriaseio Geniko Nosokomeio Elefsinas, Greece*
[9] *Panepistemiako Geniko Nosokomeio Attikon, Greece*
[10] *Panepistemiako Geniko Nosokomeio Attikon, Greece*
[11] *Onasseio Cardiosurgical Center, Athens, Greece*
[12] *Guy's and Saint Thomas' Hospitals NHS Trust:, UK*
[13] *General Hospital of Thessaloniki Papageorgiou: Geniko Nosokomeio Thessalonikis Papageorgiou, Greece*
[14] *University of Ioannina: Panepistemio Ioanninon, Greece*
[15] *Sismanoglio General Hospital, Greece*
[16] *Ygeia General Hospital, Athens, Greece*
[17] *Panepistemiako Geniko Nosokomeio Erakleiou Crete, Greece*
[18] *Cardiology Clinic, Sismanogleio Hospital, Greece*
[19] *Helena Venizelou general and Maternity District Hospital: Geniko Nosokomeio Elena Benizelou, Greece*
[20] *Ygeia General Hospital, Greece*
[21] *Athens, Greece, Greece*
[22] *Alexandra General Hospital, Athens, Greece*
[23] *Ygeia General Hospital, Athens, Greece*
[24] *Panepistemiako Geniko Nosokomeio Attikon, Greece*
[25] *European Interbalcan Medical Center, Thessaloniki, Greece*
[26] *Metropolitan Hospital Center, Greece*

Abbreviations: CVD, cardiovascular disease; AH, Arterial hypertension; FH, Familial hypercholesterolemia; DM, Diabetes mellitus; LDL, low density lipoprotein; ACS, acute coronary syndrome; HCM, hypertrophic cardiomyopathy; STEMI, ST-segment elevation myocardial infarction; CAD, coronary artery disease; AAOCA, anomalous aortic origin of a coronary artery; MINOCA, myocardial infarction with nonobstructive coronary arteries; SCAD, Spontaneous coronary artery dissection; HF, heart failure; AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PPCM, peripartum cardiomyopathy; DCM, dilated cardiomyopathy; TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; PAD, peripheral artery disease; PAH, primary pulmonary hypertension; ARD, Autoimmune rheumatic disease.

The full article is available at https://www.hcs.gr/cardiovascular-disease-in-women-executive-summary-of-the-expert-panel-statement-of-women-in-cardiology-of-the-hellenic-cardiological-society-hellenic-.aspx.

* Corresponding author. Vasilissis Sofias 114, PO 11528, Hippokration Hospital, Athens, Greece. Fax:+30-2132088676.
E-mail address: chrysohoou@usa.net (C. Chrysohoou).

Peer review under responsibility of Hellenic Society of Cardiology.

https://doi.org/10.1016/j.hjc.2020.09.015

Please cite this article as: C. Chrysohoou, C. Aggeli, C. Avgeropoulou *et al.*, Cardiovascular disease in women: Executive summary of the expert panel statement of women in cardiology of the hellenic cardiological society, Hellenic Journal of Cardiology, https://doi.org/10.1016/j.hjc.2020.09.015

A R T I C L E I N F O

Article history:
Received 12 July 2020
Received in revised form
17 September 2020
Accepted 24 September 2020
Available online xxx

Keywords:
Women
Cardiovascular
Heart disease
Primary prevention
Secondary prevention

A B S T R A C T

The perception that women represent a low-risk population for cardiovascular (CV) 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 as 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 underrepresented, leading to the limited knowledge of CV and systemic impact effects of several treatment modalities on women's health.

Thus, in this consensus, a group of female cardiologists from the Hellenic Society of Cardiology presents 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 to eliminate underestimation and undertreatment of CVD in the female population.

1. Introduction

Over the last decades, epidemiological data have demonstrated the high incidence of cardiovascular (CV) 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 CV morbidity and mortality between genders.[1] Despite the large body of evidence regarding 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 and underestimated and subsequently undertreated; while women also experience hormonal changes from adolescence till elder life that affect CV physiology. Unfortunately, women are underrepresented in most of the clinical trials, leading to the limited knowledge of CVD and general effects of several treatment modalities in women's health. It is of utmost importance 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 CV events, guiding prevention, therapeutic, and rehabilitation strategies, tailor-made for the specific needs of the women population.[2–5]

Thus, in this consensus, 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, to eliminate the underestimation of CVD diagnosis in the female population. For the present, Expert Statement >500 PubMed articles from January 2011 to November 2019 were considered in the context of a main text [in press].

2. Main traditional risk factors for CVD in young women

There are various conditions related to early atherosclerosis, even in young women with a normal endogenous estrogen concentration. Throughout their life women have gender-specific diseases such as polycystic ovary syndrome, gestational diabetes mellitus, preeclampsia, and breast cancer; often use the hormonal replacement therapy and experience pregnancy and menopause.[5,6] Some of them will be briefly analyzed, *for extensive analysis see main text [in press].*

2.1. Arterial hypertension

Arterial hypertension (AH) is a major risk factor for CV morbidity and mortality and is usually accompanied by other important risk factors (dyslipidemia and diabetes mellitus (DM)). Additionally, although AH prevalence increases over time, it often remains undiagnosed for a long time, particularly in women. Moreover, it seems that there are multifactorial sexual differences in the pathophysiology of AH, which include the role of sex hormones, sympathetic nervous system activation, and variations in arterial stiffness. After menopause plasma renin increases, angiotensin I receptors are upregulated while angiotensin II receptors are downregulated, 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. Regarding medical therapy, women are at a higher risk for thiazide-induced hyponatremia and hypokalemia and should be cautious when presenting a lower filtration rate. 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. Women may require larger dosages of angiotensin receptor blockers than men, while they are prone to develop angioedema and cough as compared to 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. Blood pressure response to amlodipine and the risk of peripheral edema is higher in women than men and particularly in elderly.[7–11]

Women with AH should be treated according to guidelines (See Table 1).

2.2. Familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a common autosomal dominantly inherited disorder, characterized by cholesterol deposits in the corneas, eyelids, and extensor tendons, elevated

Table 1
Gender differences in arterial hypertension.[9]

	Males	Females (premenopausal)
Sex Hormones	Testosterone • renin-angiotensin-aldosterone system stimulation	Estrogens and Progesterone • Plasma renin activity and angiotensin-converting enzyme levels reduction • Protection against salt-induced blood hypertension • sympathetic nervous system activity suppression • Nitric Oxide production stimulation • Elastin production increase
Blood Pressure	Increased	Decreased
sympathetic nervous system and renin-angiotensin-aldosterone system activity	Increased	Decreased
Arterial stiffness	Increased	Decreased

plasma low-density lipoprotein (LDL) cholesterol concentration and rapidly progressing vascular disease, particularly premature coronary artery disease (CAD). The aortic valve may also be affected. Heterozygous FH affects one per 200–500 births (according to the race and ethnic origin). The plasma total cholesterol concentration is usually more than 290 mg/dL. The triglycerides (TG) concentration is normal or moderately elevated.

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 in 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.[12]

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, the mutations of which may lead to the clinical manifestation of FH.[13,14]

In rare cases (1:250,000–600,000 births), a child may inherit the abnormal gene from each parent (homozygous FH). In these patients, the plasma total cholesterol concentration may be >600 mg/dL, and in some cases, the concentrations more than 1000 mg/dL or even 1500 mg/dL were reported. Clinically evident atherosclerosis (i.e., MI, the 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 guidelines.[12,14]

2.3. Diabetes mellitus and metabolic syndrome

Metabolic syndrome (MetS) is defined as a constellation of 3 out of 5 CV risk factors, which include: a) Increased waist circumference with specific cutoffs based on the population and sex, b) Elevated TG >150 mg/dL (1.7 mmol/L), c) Reduced high-density lipoprotein (HDL) cholesterol <40 mg/dL (1.0 mmol/L) in male subjects and <50 mg/dL (1.3 mmol/L) in female subjects, d) BP >130/85 mm Hg, and e) Elevated fasting glucose >100 mg/dL. Other CV risk factors such as age, sex, family history, smoking, and levels of LDL cholesterol are not included in the definition. MetS is associated with increased CV mortality and the development of type 2 DM and some data suggest that it is more common in women.[15,16] Also, sparse data suggest that pre- and postmenopausal women who are breast cancer survivors or women with polycystic ovary syndrome have a high risk of developing MetS.[17,18]

Screening to identify and treat DM and MetS in women throughout the different phases in their life is mandatory because it can potentially decrease their long-term morbidity and mortality (See Table 2).

2.4. Smoking in women

Smoking is an important cardiac risk factor for the development of CVD in both women and men.[19] 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-segment elevation myocardial infarction (STEMI), has continuously increased between the years 1995 and 2010. The cardioprotective 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.[20,21]

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 should be discussed unless contraindicated.

3. Nontraditional risk factors for CVD in women

Autoimmune rheumatic diseases (ARDs) affect 8% of the population and 78% of patients are women.[22] Gender differences are the result of various causes, including sex hormones, microchimerism, genes on X or Y chromosomes, X chromosome inactivation, and environmental factors.[23] Estrogens can directly increase the incidence of ARDs in women by elevating autoantibodies and amplifying T- and B-cell responses.[24] 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.[25] Female predominance is observed in rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue diseases, and dermatomyositis/polymyositis. In some types of systemic vasculitis, there is a female preponderance as in Takayasu vasculitis, while in others, as in Kawasaki disease a male preponderance exists.

There is a female predominance in autoimmune rheumatic disease with CV implications. Thus, patients with ARDs should be evaluated by the cardiologist also. QRISK3 algorithm that has been developed by the UK National Health Service and includes nontraditional risk factors is useful in calculating 10 years risk of heart attack and stroke.[26]

3.1. Coronary artery disease (CAD) in women

Atherosclerosis in women shows a delayed occurrence as compared to men. There are anatomic differences between men and women that are related to pitfall alterations in diagnostic performance of cardiac imaging modalities. Furthermore, the

Table 2
Therapy in women with Metabolic Syndrome (MetS).[14]

Recommendation	Class	Level
The 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 the 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 min a week of moderate aerobic physical activity (30 min for 5 days/week) or 75 min a week of vigorous aerobic physical activity (15 min for 5 days/week) or a combination is recommended	I	A
Body weight control is indicated to avoid obesity (BMI >30 kg/m^2, or waist circumference >88 cm in women) and aim for healthy BMI (about 20−25 kg/m^2) 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 the intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended.	I	B
Following the Mediterranean diet on MetS is useful.	IIα	B
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 and 5.6 mmol/L (135-499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 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	B
In women with MetS and concomitant increase in the LDL cholesterol management based on the recently published guidelines is recommended with statins, ezetimibe, and PCSK 9 inhibitors if necessary tailored on the individual CV risk assessment.	I/IIb	A/B/C
Hypertension in women with MetS should be treated according to the published guidelines, which recommend initial therapy with either a CCB, renin angiotensin system inhibitor, or thiazide diuretic.	I	A
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.	III	C
In women with gestational hypertension, preexisting hypertension (can be the component of the MetS) superimposed by gestational hypertension, or with hypertension and subclinical organ damage or symptoms, the initiation of drug treatment is recommended when SBP is > 140 mmHg or DBP >90 mmHg. In all other cases, the initiation of drug treatment is recommended when SBP is >150 mmHg or DBP is >95 mmHg.	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.	II	A

MetS = metabolic syndrome; BMI = body mass index; LDL-C = low density lipoprotein; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; CKD = chronic kidney disease; SBP = systolic blood pressure; DBP = diastolic blood pressure; CCB = calcium channel blockers; ACE = angiotensin converting enzyme; and ARBs = angiotensin receptor blockers.

clinical presentation of symptoms may differ between genders, making women more vulnerable for delayed diagnosis and therapeutic approach.[27] Women should undergo careful investigation, as clinical symptoms might be atypical. The diagnostic accuracy of the exercise ECG is even lower in women than in men, which is in part related to functional impairment, precluding some women from achieving an adequate workload. Stress echocardiography with exercise or dobutamine stress is an accurate, noninvasive technique for the detection of obstructive CAD and risk among women with suspected CAD[28] (See Tables 3 and 4).

4. Nonatherogenic CAD in women

4.1. Myocardial bridging

Myocardial bridging is a congenital benign abnormality in which a segment of an epicardial coronary artery runs deep and for

Table 3
Anatomic differences between men and women are related to alterations in the diagnostic performance of cardiac imaging modalities.[27]

Anatomic differences in women	Imaging implications
LV size	Reduced accuracy of radionuclide MPI
Diameter of coronary arteries	CTCA: Inaccessibility to coronary segments particularly mid and distal segments
Increased chest wall attenuation due to breast tissue	Radionuclide MPI: attenuation artifacts at LAD territory The application of gating and attenuation correction techniques And the 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 nonionizing imaging modalities Use IV contrast when necessary
Sex-based differences in presentation and pathogenesis of CAD	
Higher mortality from CAD in women despite decreased severity of CAD	ETT: Reduced exercise capacity in older women may fail to identify CAD
Older age at presentation and atypical symptoms	Cardiac imaging may be delayed
Potential role of microvascular disease in the pathogenesis of CAD	Noninvasive quantification of MBF and CFR may identify microvascular disease

LV = left ventricle; MPI = magnetic resonance imaging; LAD = left anterior descending coronary artery; ETT = exercise test tolerance; IV = intravenously; ECG = electrocardiogram; CAD = coronary artery disease; MBF = myocardial blood flow; and CFR = coronary flow reserve.

Table 4
Recommendations for diagnostic work up for ischemic heart disease in women.[28]

Diagnostic work up for IHD in women	Class	Level
ECG exercise test (ETT) could be the initial diagnostic test in symptomatic women with suspected CAD and intermediate risk and good exercise capacity (>5 METS)	I	C
Stress imaging should be reserved for symptomatic women with resting ST abnormalities and unable to exercise adequately	I	B
Stress imaging, SPECT, and PET should be the second modality of choice when ETT is indeterminate or abnormal	I	B
Stress echo is comparable between sexes, while its diagnostic performance is better than exercise ECG	I	B
Stress echo is the preferred imaging modality for pregnant women because it does not use radiation	I	C
PET MPI showed improved sensitivity and specificity with lower radiation doses in women over SPECT MPI	IIa	B
Coronary CT angiography may be reasonable in symptomatic women at an intermediate risk of CAD, including those with equivocal stress test results	IIb	B
Coronary CT angiography may be reasonable in symptomatic women of low risk for CAD	IIb	B
In the female 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	B
Cardiac MRI can offer a quantitative assessment of MBF, which may help in the diagnosis of microvascular disease or it can help in the noninvasive identification of significant coronary lesions	IIb	B

IHD = ischemic heart disease; ECG = electrocardiogram; SPECT = single photon emission computed tomography; PET = positron emission tomography; MPI = magnetic resonance imaging; CT = computed tomography; MRI = magnetic resonance images; MBF = myocardial blood flow; and CAD = coronary artery disease.

varying lengths through the myocardial fibers. Myocardial bridging remains clinically silent, being an incidental finding on angiography or autopsy, in most cases. However, stable angina, acute coronary syndrome (ACS), ventricular rupture, life-threatening arrhythmia, hypertrophic cardiomyopathy (HCM), apical ballooning syndrome, or sudden death have been described as rare clinical consequences of myocardial bridging without a clear pathophysiological explanation.[29] There does not seem to be sex or age difference in the prevalence of myocardial bridging.

In cases with clinical symptoms of CVD and no clear pathophysiological explanation, the myocardial bridging should be excluded.

4.2. Anomalous aortic origin of a coronary artery

The true prevalence of anomalous aortic origin of a coronary artery (AAOCA) in both adults and children, although difficult to ascertain, is estimated between 0.1% and 1.0%. This rate ranges from 0.3% to 5.6% in studies of patients undergoing coronary angiography, and in approximately 1% of routine autopsy.[30] The risk of sudden death among individuals with AAOCA is reported as low throughout literature, which is between 0.0001% and 0.35%. There has been no documented difference between the male and female sex. Interestingly, about 26% of AAOCA involve aortic root abnormality (such as bicuspid aortic valve), at least asymmetry of the

Table 5
Proposed Approach for the Diagnosis of Coronary Microvascular Dysfunction (CMD) in Women with Ischemia With No Obstructive Coronary Artery Disease (MINOCA).[33]

- Presentation of a woman with signs and symptoms of MINOCA
- Exclusion of secondary CMD causes
- If CMD is not confirmed, consider epicardial coronary vasospasm, microvascular coronary vasospasm, heightened cardiac nociception, or myocardial bridge.
- Myocardial disorders (e.g., hypertrophic, restrictive, and dilated cardiomyopathies), valvular heart disease (e.g., severe aortic stenosis), and high-output states (e.g., 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 (e.g., carvedilol), calcium channel blockers (e.g., diltiazem) and ranalozine
- If angina not improved, consider in women with persistent symptoms who are inappropriate for invasive testing or noninvasive testing
  - Pharmacological stress, cardiac, and positron emission tomography
  - Pharmacological, cardiac, and magnetic resonance imaging
  - Pharmacological transthoracic, Doppler, echocardiography, and coronary flow

If CMD not confirmed, consider reserve assessment through 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, and response to intracoronary acetylcholine.

aortic sinuses. Despite the very low risk of sudden death, the consensus statement in the Guidelines for the Management of Adults with Congenital Heart Disease supports that all cases of left coronary artery (AAOLCA) and the symptomatic patients with right coronary artery (AAORCA) should undergo surgical treatment.[30]

For symptomatic AAOCA and for all cases of AAOLCA, surgical intervention is recommended. In asymptomatic AAORCA, therapy is tailored toward an assumed risk profile. No significant sex difference has been observed.

4.3. Coronary artery embolism

Coronary artery embolism is a nonatherosclerotic cause of ACS ranging from 3% to 13% according to angiographic or autopsy studies.[31,32] Coronary artery embolism is classified into direct, paradoxical, iatrogenic, and hypercoagulability-related embolism. The embolic tissue may consist of blood products valvular material, infected vegetation, or even neoplastic cells. Coronary or surgical intervention and atrial fibrillation (AF) are the most frequent causes of coronary artery embolism.

Patients with ACS due to coronary artery embolism as compared to those without are presenting higher all-cause and cardiac mortality during 5-year follow-up and, therefore, require close follow-up.

4.4. Nonobstructive coronary arteries (MINOCA)

Women have a high prevalence of MI with nonobstructive coronary arteries (MINOCA), which varies from 6% to 30% and tends to affect young women[33,34] (See Table 5).

4.5. Coronary Artery Dissection

Spontaneous coronary artery dissection (SCAD) is a rare condition, accounting only 1%–4% of overall ACS cases.[35] SCAD healing is observed in the majority of the patients (70–97%) by one month.

Table 6
Recommendations for the management of spontaneous coronary artery dissection (SCAD).[29]

Treatment	
Nonpregnancy-associated SCAD	Pregnancy-associated SCAD
Acute phase	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	• Conservative management if feasible • Largely the same management as in nonpregnancy SCAD
Post-SCAD therapy[a]	Post-SCAD therapy[a]
• 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)	• Following conservative therapy - Low-dose aspirin use is safe during pregnancy and breastfeeding - Clopidogrel is not recommended - Labetalol is preferable (3) - ACE inhibitors/ARBs not recommended 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.

ACE = angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARBs = angiotensin receptor blockers; CABG = coronary artery bypass grafting; and PCI = percutaneous coronary intervention.

[a] Expert opinions, no evidence-based approach.

However, 5%–10% of medically managed patients may develop recurrent MI related to the extension of dissection during hospitalization; while there is a high risk of the extension of the dissection during percutaneous coronary intervention (PCI).

Female gender (>90%, 10%–35% of ACS in women <50 years), pregnancy (45% of ACS with 50% occurring in the postpartum period) and fibromuscular dysplasia are the most important risk factors for SCAD. There is 15%–35% risk of recurrence for the next 3 years. Avoidance of further pregnancy is advised, if the patient elects to attempt subsequent pregnancy, close monitoring is recommended (See Table 6).

4.6. Takotsubo syndrome in women

Takotsubo syndrome 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 postmenopausal women, although 5%–11% of cases have been reported in younger women <50 years.[36] Mortality rates are higher for men than women (8.4% vs. 3.6%, $p < 0.0001$), which is 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. The InterTAK diagnostic score was developed to assess the likelihood of Takotsubo syndrome on presentation and to distinguish between Takotsubo syndrome and non-ST-segment elevation MI (NSTEMI). It includes 7 parameters. Those are female sex, physical trigger, emotional trigger, neurological disorders, psychiatric disorders, non-ST elevation – except in lead avR, and QT prolongation. An increased score of 70 points increases the probability of the Takotsubo syndrome.[36]

4.7. Kounis syndrome

Kounis syndrome is a result of coronary artery spasm with/or plaque rupture or erosion in the course of an allergic reaction. The prevalence of Kounis syndrome is 3 times higher in men than women. A large number of etiological factors have been described, which are broadly categorized into drugs, environmental factors, food products, and various conditions. The release of inflammatory mediators such as histamine, cathepsin-D, chymase, tryptase, heparin lead to vasoconstriction, platelet activation, plaque rupture, plaque erosion, and thrombus destabilization and maturation, respectively.[37,38]

4.8. Coronary microvascular dysfunction causing cardiac ischemia in women

About two thirds of women with ischemia symptoms do not present obstructive CAD in cardiac catheterization. Those women may have been presented with symptoms of effort angina or dyspnea, electrocardiographic alterations and segmental hypokinesis at rest or during exercise at cardiac imaging. Although any negative findings of coronary angiography provoke relief; 1 out of 13 (1:13) of those women will express CV death and generally they experience high probability of hospitalization with symptoms of heart failure (HF) with preserved ejection fraction (HFpEF). This situation is due to coronary microvascular dysfunction, which are the small blood vessels in the heart, called the coronary microvasculature that carries most of the blood flow to the heart muscle, delivering oxygen.[39]

4.9. Hypercoagulable states

4.9.1. Idiopathic thrombocythemia

Idiopathic thrombocythemia is a rare blood clotting disorder that produces too many platelets and mainly affects women.[40] 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 idiopathic thrombocythemia can cause pregnancy complications, including spontaneous abortion, fetal growth retardation, premature delivery, and placental abruption. Pregnant patients may be treated with low-dose aspirin to reduce the risk complications.

4.9.2. Fibrinolysis disorders

Fibrinolysis disorders leading to 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. Recently, it was discovered that hyper-fibrinolytic disorders are associated with a high rate of obstetric complications such as miscarriage and preterm birth, particularly in a PAI-1-deficient patient.

4.9.3. Contraceptives drugs

Contraceptives are one of the most frequently used drugs by women. They could lead to activated protein C resistance, increased prothrombin levels, and decreased protein S levels, which produces a net prothrombotic effect. In women with inherited disorders of coagulation, the risk for vein thrombosis and pulmonary embolism due to contraceptive drugs increases 30- to 50-fold.[41]

4.9.4. Antiplatelets

Female patients demonstrate higher platelet reactivity on aspirin and clopidogrel therapy.

4.9.5. Primary prevention

Aspirin for primary prevention is associated with a higher risk reduction for ischemic stroke in female patients and for MI in male patients.[42]

4.9.6. Secondary prevention

There is no interaction between gender and efficacy of aspirin for secondary CV prevention.

There is a lack of evidence that aspirin can modify risk in women both in primary and secondary CV prevention, as presented in Table 7.

5. Heart failure in women

In women, HF with reduced ejection fraction (HFrEF) is a less common diagnosis as compared to the more prevalent HFpEF. In-hospital mortality remains equal in both women and men as they share the same risk factors – namely age, blood pressure, heart rate, and the history of chronic renal disease.[43] However, women presenting with HFrEF are more symptomatic than men, with lesser ability in self-care and daily activities, more evidence of congestion, reduced 6-min walk distance, higher LVEF, worse renal function, and overall a lower quality of life. At the same time, they have fewer hospitalizations and different frequency of comorbidities. The prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial showed reduced hospitalizations in the female subgroup treated with angiotensin receptor

Table 7
Suggested antiplatelet strategies for primary and secondary cardiovascular prevention in women.[42]

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). - Low-dose aspirin may be considered in women with a risk of >2 cardiovascular events/100 patients per year (i.e., 20% for 10 years) The bleeding risk increased by aspirin and the risk of cancer, particularly colon cancer, likely reduced by aspirin − along with patients' values and preferences should be considered. - low-dose aspirin may be considered among selected adult women <70 years old at higher cardiovascular risk, but not at increased bleeding risk - No convincing data for clopidogrel use
Specific settings	- Low-dose aspirin is indicated in women with type-1 diabetes and target-organ damage (the bleeding risk must be weighted) - 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) - Low-dose aspirin may be considered in postmenopausal women on hormone replacement therapy (the bleeding risk must be weighed) - Low-dose aspirin may be considered in pregnant women at a high-risk of early preeclampsia - Low-dose aspirin may be considered in women with breast cancer undergoing radiotherapy (the bleeding risk must be weighed)
Secondary prevention	
Women with CAD	- No gender-specific recommendations in patients with stable or unstable CAD
Women with noncardioembolic stroke/TIA	- Low-dose aspirin preferred; clopidogrel may be considered

CAD = coronary artery disease and TIA = transient ischemic attack.

Table 8
Pathophysiological mechanisms underlying the predominance of Heart Failure with preserved Ejection Fraction (HFpEF) in women.[46]

Pathophysiological mechanisms in HFpEF	What is particularly 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 or 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 an 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 Postmenopausal 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 estrogen serving a protective role Estrogen receptors play a role in ventricular remodeling Gene expression profiles differ in women; sex differences exist in the endothelin and nitric oxide systems, myocyte remodeling, 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 = Heart failure with preserve ejection fraction.

neprilysin inhibitor (ARNI). The device therapy [implantable cardioverter-defibrillator (ICD) and cardiac-resynchronization therapy defibrillator (CRT-D)] has been shown to decrease mortality in women with dilated cardiomyopathy (DCM) as seen in the sex-specific analysis of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial; perhaps due to an increased prevalence of left bundle branch block in female patients.[44,45] HFpEF is more common in women than men. As such, this constantly increasing elderly population of female HFpEF patients associated with adverse clinical outcomes, in combination with a lack of effective treatment, render HFpEF an important clinical and social problem.[46] However, there have not been enough studies to establish extensive knowledge about how HF manifests in women, the effects of various medications, and the impact of external factors, such as social inequalities and limited access to healthcare system, on the actual figures for HF in women (See Tables 8 and 9).

5.1. Cardiomyopathies in women

Cardiomyopathies (CMs) are a heterogeneous group of heart muscle diseases with a variety of specific phenotypes.[47] They are classified into HCM, DCM, arrhythmogenic right ventricular

Table 9
Emerging data on female-specific aspects of treatment in Heart Failure with preserved Ejection fraction (HFpEF).[43,44,46]

Nonpharmacological 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, the 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, which suggests a potential benefit for women with HFpEF
Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors)	In the EMPA-REG OUTCOME(R) trial, the treatment of high-risk type 2 DM 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 women may derive benefit at a higher EF than do men

Based on Tibrewala 2019 and McMurray 2019.
HFpEF = Heart failure with preserve ejection fraction; HF = Heart failure; EF = ejection fraction; and DM = diabetes mellitus.

cardiomyopathy (ARVC), and unclassified CMs, *for more details see main text [in press]* (See Table 10).

6. Cardio-oncology

CVD and cancer are the two main causes of death in both sexes. In women, the most common cancer diagnosis is invasive breast cancer with one out of 8 carrying an increased lifelong risk to develop, while the 5-year survival rate of the disease exceeds 90%.[48] 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 when compared with women without breast cancer. Furthermore, women with breast cancer have an adjusted 77% higher risk of death from CVD than women without breast cancer.[49,50] Strategies for screening and the detection of cardiotoxicity include cardiac imaging [echocardiography, nuclear imaging,

Table 10
Female Hypertrophic cardiomyopathy patients' characteristics.[47]

- Lower disease prevalence (2:1 predominance in males)
- Diagnosis made because of the onset of symptoms
- Older at the time of diagnosis
- More symptomatic on diagnosis
- Greater risk of heart failure and worse outcome
- Left ventricle outflow tract obstruction 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 as compared to younger female and male patients.
- Pregnancy: Absolute maternal mortality is low and confined to women at particularly high risk.

Table 11
Baseline risk factors for cardiotoxicity.[48]

Current myocardial disease	Demographic and other CV risk factors
Heart failure (with either preserved or reduced ejection fraction) • Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide) Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, and myocardial ischemia 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)	• Age (pediatric population; >50 years for trastuzumab; >65 years for anthracyclines) • Family history of premature CV disease (<50 years) Arterial hypertension Diabetes mellitus Hypercholesterolemia
Previous cardiotoxic cancer treatment	**Lifestyle risk factors**
Prior anthracycline use • Prior radiotherapy to chest or mediastinum	Smoking High alcohol intake Obesity Sedentary habit

LV = left ventricle; LVH = left ventricular hypertrophy; AF = atrial fibrillation; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; CAD = coronary artery disease; VHD = valvular heart disease; CV = cardiovascular; and LVEF = left ventricular ejection fraction.

Table 12
Proposed diagnostic tools for the detection of cardiotoxicity.[49,50]

Technique	Diagnostic criteria	Advantages	Major limitations
Echocardiography: - 3D-based LVEF - 2D Simpson's LVEF – GLS	LVEF: >10% GLS: >15% decrease: cardio toxicity.	Wide availability, lack of radiation, and the assessment of hemodynamics	• Interobserver variability • Image quality • GLS: intervendor variability and technical requirements.
Nuclear cardiac imaging (MUGA)	>10 percentage points decrease with LVEF: <50%: cardio toxicity	• Reproducibility	• Cumulative radiation exposure • Limited structural and functional information on other cardiac structures
Cardiac magnetic resonance	Typically used if other techniques are nondiagnostic or if estimated LVEF is borderline	• Accuracy and reproducibility • Detection of diffuse myocardial fibrosis	• Limited availability • Patient's adaptation (claustrophobia, breath hold, and long acquisition times)
Cardiac biomarkers: - Troponin I – High-sensitivity Troponin I - BNP - NT-proBNP	A rise identifies patients receiving anthracyclines who may benefit from ACE-Is	• Accuracy • reproducibility • Wide availability • High-sensitivity • May guide therapy	• Variations with different assays • Role for routine surveillance not clearly established • Insufficient evidence to establish the significance of subtle rises

cardiac magnetic resonance (CMR)], and biomarkers (troponin and natriuretic peptides). The choice of modalities depends upon local expertise and availability, and several important principles should be considered: The same imaging modality and/or biomarker assay should be used for continued screening throughout the treatment pathway. Modalities and tests with the best reproducibility, high quality radiation-free imaging and others that provide additional relevant clinical information are preferred (e.g., right ventricular function, pulmonary pressures, valvular function, and pericardial evaluation. The precise timing and frequency of imaging and/or biomarker sampling will depend upon the specific cancer treatment, total cumulative dose of cardiotoxic chemotherapy, delivery protocol and duration, and the patient's baseline CV risk.

Several circulating biomarkers [troponin I and B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP)] have been identified as useful for the early detection of myocardial dysfunction and overt HF related to cancer therapies. Although cancer treatment, chemotherapy, and radiotherapy, has been associated with accelerated atherosclerosis, there are several other factors that can explain this association.

Assessment of CAD should be based on the history, age, and gender of the patient, considering the use of chemotherapy drugs as a risk factor for CAD. Primary prevention of cardiotoxicity is still in the research domain, secondary prevention has already entered clinical practice guidelines despite persistent unresolved questions (See Tables 11 and 12).

7. Arrhythmia in women

The incidence of certain clinical arrhythmias undoubtably varies between men and women. Clinical and experimental observations suggest that true differences in electrophysiological variables exist between them and this is a sex hormones' effect through differences in the expression of ion channel subunits and channel

Table 13
Sex differences in cardiac arrhythmias.[52]

Type of Arrhythmia	Men	Women
Supra ventricular Tachycardia	Higher prevalence of WPW/AVRT Less robust AVN slow pathway conduction	Higher prevalence of AVNRT/AT Frequency/symptoms associated with menstrual cycle
Atrial Fibrillation	Higher choice of rhythm control strategy Lower ablation complications Lower risk of proarrhythmia due to antiarrhythmics	Lower rate of referrals to arrhythmia specialist Higher mortality Higher thromboembolic risk
Idiopathic ventricular tachycardia	Higher prevalence of Fascicular VT	Higher prevalence of RVOT VT Frequency/symptoms associated with menstrual cycle
Ventricular tachycardia in structural heart disease	Higher prevalence of CAD Inclusion of the majority of patients in RCTs Higher incidence of inappropriate ICD shocks	Underrepresented in major ICD therapy studies Underrepresented in major VT ablation studies Less likely to receive an ICD
Cardiac channelopathies	Shorter adjusted QT Higher childhood risk for the incidence of VT in LQTS Higher risk of cardiac events in Brugada syndrome	Higher adult risk for the incidence of VT in LQTS Lower prevalence of early repolarization syndrome
Sudden cardiac death bradycardia	Higher incidence of ventricular fibrillation Higher incidence of atrioventricular node dysfunction	Higher incidence of pulseless electrical activity Higher incidence of sinus node dysfunction Women on average present at an older age than men

SVT: supraventricular tachycardia, VT: ventricular tachycardia, and AF: atrial fibrillation.

Table 14
Classification and definitions of hypertensive disorders in pregnancy.[53,56]

Preexisting hypertension	Precedes pregnancy or develops before 20 weeks of gestation. It usually persists for more than 42 days postpartum and may be associated with proteinuria.
Gestational hypertension	Develops after 20 weeks of gestation and usually resolves within 42 days postpartum.
Antenatally unclassifiable hypertension	When BP is first recorded after 20 weeks of gestation and hypertension is diagnosed; reassessment is necessary after 42 days postpartum.
Preeclampsia	Gestational hypertension with significant proteinuria [>0.3 g/24 h or ACR (Albumin: Creatinine Ratio) > 30 mg/g]. 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 preeclampsia	Preeclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or hematological impairment.
Eclampsia	A convulsive (grand mal seizures) condition associated with preeclampsia.
HELLP syndrome	Hemolysis, elevated liver enzymes, and low platelet count.

function modulation. 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. AF incidence and prevalence increase with aging, and it is 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.

Symptoms of supraventricular arrhythmias in women are more likely to be attributed to panic, anxiety, or stress disorders than in men. Women are referred three times less frequently for catheter ablation. At the time of referral, they are significantly older, have more comorbidities, and are more sensitive to amiodarone side effects than men. Gender-related anatomical differences could theoretically affect procedure outcomes.[50,51] Oral anticoagulant (OAC) use is similar in AF patients, but women were less often prescribed OAC and were given aspirin more often than male counterparts. Anticoagulation with warfarin may be less controlled in female patients with AF (lower TTRs).[52]

- Right ventricular outflow tract-ventricular tachycardia is twice more common in females.
- Female patients are underrepresented in randomized controlled clinical trials and registries of patients undergoing catheter ablation for ventricular tachycardia with structural heart disease, particularly with CAD.
- Women with LQTS have an increased risk during the 9-month postpartum 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 when compared with men.
- 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.
- In retrospective and prospective analyses, women have a higher incidence of sinus node dysfunction and men a higher incidence of atrioventricular node dysfunction.

Sex differences are presented in Table 13.

Further studies are needed 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, female patients 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.

8. Pregnancy

Pregnancy is a stress test for the CV system, while it can be complicated by maternal disease in 1%–4% of cases. New data about the prevalence and incidence of pregnancy-related heart disease are limited from most parts of the world. Sudden adult death syndrome, peripartum cardiomyopathy (PPCM), aortic dissection, and MI were the most common causes of maternal death in the UK over the period 2006–2008. The knowledge of the risks associated with CVDs during pregnancy and their management in pregnant women who suffer from serious preexisting conditions is of pivotal importance for advising patients before pregnancy. Pregnancy is associated with a three- to fourfold increase in acute MI (AMI) risk when compared with age-matched nonpregnant women. Risk factors include smoking, maternal age, hypertension, diabetes, obesity, and dyslipidemia. Additional risk factors include (pre-) eclampsia, thrombophilia, transfusion, postpartum infection, cocaine use, multiparity, and postpartum hemorrhage. The majority of CAD has nonatherosclerotic mechanisms, including pregnancy-related spontaneous coronary artery dissection (43%), angiographically normal coronary arteries (18%), and coronary thrombosis (17%).[53]

8.1. 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.[53] Risk factors include known aortopathies, namely Marfan, vascular Ehlers-Danlos, and Turner syndromes (the risk of rupture 1%-10%), bicuspid aortic valve (the risk of rupture 1%), AH, and advanced age. The risk of dissection relates to aortic diameter.

8.2. Arterial hypertension

AH can complicate up to 10% of pregnancies and is responsible for up to 20% of maternal deaths.[54,55] Preeclampsia remains the major complication of AH during pregnancy. Major risk factors for developing AH in pregnancy are chronic kidney disease, autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome, type 1 or type 2 DM, and chronic AH. Moderate risk factors are considered as a pregnancy interval of more than 10 years, body mass index of $\geq$35 kg/m^2 at first visit, family history of pre-eclampsia, and multiple pregnancy. AH along with pregnancy-related hemodynamics coupled with a neurohormonal milieu, have been linked with spontaneous coronary artery dissection[56] (See Table 14).

Table 15
Recommendations on invasive treatment in stable coronary artery disease in elderly women.[58]

	CABG		PCI	
	Class	Level	Class	Level
One-vessel CAD without proximal LAD stenosis	IIb	C	I	C
One-vessel CAD with proximal LAD stenosis	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

Those recommendations are equal in both sexes.
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 single randomized clinical trials or large nonrandomized studies; and C, consensus of opinion of the experts and/or small studies, retrospective studies, and registries.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; and SYNTAX =Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

8.3. Cardiomyopathies and peripartum cardiomyopathy

The etiology of pregnancy-associated cardiomyopathy includes acquired and inherited diseases such as PPCM, toxic cardiomyopathies, HCM, DCM, Takotsubo cardiomyopathy, and storage diseases. Although rare, they may cause severe complications as HF and arrhythmias in pregnancy. Pregnancy is poorly tolerated in some women with preexisting dilated cardiomyopathy DCM, with the potential for significant deterioration in LV function. PPCM is an idiopathic disorder defined as HF occurring in women during the last month of pregnancy and up to 5 months postpartum. Novel data strengthen the implication of endothelial function in PPCM pathogenesis. Bromocriptine may have a role in the treatment of PPCM, although it may confer to increased thrombotic risk.

8.4. Valve disease in pregnancy

Valvular heart disease is often due to rheumatic heart disease. Usually asymptomatic patients with severe aortic stenosis tolerate pregnancy without major adverse events, while even asymptomatic patients with severe mitral stenosis should be counselled against pregnancy. 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, which results in the risk of going through pregnancy with a dysfunctional valve, and eventually in the inevitable need for reoperation.[52]

8.5. Congenital diseases in pregnancy

In most women with congenital heart disease, pregnancy is well tolerated. Maternal cardiac complications are present in about 10% of completed pregnancies and are more frequent in mothers with complex disease. Pregnancy should be discouraged in patients with advanced heart disease.[52]

9. Menopause

Postmenopausal status is identified as a risk factor for CVD. Endogenous estrogens maintain vasodilation, improve endothelial function, and contribute to BP control in premenopausal women. PMW lose the cardioprotective effects of estrogen and have an elevated risk of developing hypertension. Furthermore, the incidence of traditional CV risk factors such as obesity, dyslipidemia, DM, and MetS is increased in postmenopausal women. Weight maintenance, physical activity, and the management of CV risk factors if present are recommended. Hormone replacement therapy is not indicated and should never be prescribed for the prevention of CVD risk.[56]

Weight maintenance, physical activity, and the management of CV risk factors if presented are recommended. HRT is not indicated and should never be prescribed for the prevention of CVD risk.

9.1. Basic principles on menopausal hormone therapy

Menopausal hormone therapy should be part of a holistic therapeutic approach − if there are no contraindications that aim to maintain the health of PMW. Menopausal hormone therapy is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh CV and breast-cancer risk in symptomatic women before the age of 60 years or within 10 years after menopause. Despite the proven benefits, menopausal hormone therapy is not indicated for the primary prevention of chronic conditions (CAD, stroke, etc.) in PMW.[56,57]

9.2. CAD

CAD is the leading cause of morbidity and mortality in postmenopausal women. In general, CV mortality accounts for 40% of total women mortality, while breast cancer accounts for only 5%. The diagnosis of CAD in women can be challenging because of a higher rate of functional disorders and lower prevalence of obstructive CAD than in men. CAD risk factors vary by age and reproductive status. Several studies describe women presenting with less typical symptoms, including fatigue, sleep disturbance, shortness of breath, back pain, indigestion, weakness, nausea/vomiting, and weakness. After menopause, the prevalence of cardiac risk factors in women approaches that of men and concurrently increases the risk of CAD later in life. 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. Marital stress, in particular, has been implicated in the development of subsequent cardiac

events. Angina pectoris is the predominant initial and subsequent presentation of CAD in women, in contrast to MI and sudden death for men.[56–60]

In asymptomatic women, the use of risk-estimation systems such as SCORE is recommended. Only subjects at high-event risk should be considered for further noninvasive or invasive testing (for more details see main text [in press]). 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. Although CAD and valvular heart disease occur mostly in postmenopausal women, they may rarely affect premenopausal women (See Tables 15 and 16).

10. Valve disease in women

Mitral valve prolapse is more common in women, but they present with lesser degrees of mitral regurgitation. Higher incidence of increased leaflet thickness and anterior and bileaflet mitral valve prolapse is more predominant in women, whereas posterior leaflet prolapse, which is technically easier to repair is more common in men.

Women have a higher prevalence of mitral valve calcification, rheumatic mitral valve disease, and mixed regurgitation/stenosis.

Degenerative aortic stenosis is the most common cause of aortic stenosis secondary to progressive sclerosis and calcification. Women have demonstrated a higher prevalence of paradoxical low flow-low gradient aortic stenosis, which has been related to worse outcome as compared to high-gradient aortic stenosis. Surgical aortic valve replacement (SAVR) is less frequently chosen in women with severe symptomatic aortic stenosis than in men, which reflects the gender bias that results from 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 the transfemoral approach.[61]

The most common etiology of degenerative mitral regurgitation is mitral valve prolapse. Sex differences in mitral valve pathology have been described, which challenge women's candidacy for mitral valve repair. With regard to the percutaneous treatment of mitral regurgitation, MitraClip implantation has been demonstrated to be equally effective in both sexes (See Tables 17 and 18).

11. Cardiac surgery in women

Women who present for cardiac surgery are older, frailer, 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, hypertension, dyslipidemia, HF, cerebrovascular disease, and anemia. The diagnosis of CAD may be delayed in women as compared to men; while women exhibit worse operative mortality and long-term survival in many cardiosurgical procedures. In addition, women with CVD often experience a delay in diagnosis and treatment when compared with men, which may in

Table 16
Recommendations on invasive treatment in ACS in elderly women.[58]

	Class	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

Those recommendations are equal in both sexes.
Abbreviations: Class of recommendation I, is indicated/is recommended; Level of evidence A, data derived from multiple randomized clinical trials or meta-analyses; ACS = acute coronary syndromes; NSTEMI = non ST elevation myocardial infarction; STEMI = ST elevation myocardial infarction; PCI = percutaneous coronary intervention; and DES = drug-eluting stents.

Table 17
Sex-related differences in LV adaptation during AS progression.[61,62]

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; and LVRI: = LV remodeling index (= LV mass/LV end-diastolic volume).

Table 18
Calcium-score by multi-slice computed tomography.[61]

Quantitative data[a] that increase the likelihood of severe aortic stenosis in patients with AVA <1.0 cm^2 and mean gradient <40 mmHg in the presence of preserved ejection fraction		
	Men	Women
Severe AS very likely	≥3000	≥1600
Severe AS likely	≥2000	≥1200
Severe AS unlikely	<1600	<800

AVA = aortic valve area.
[a] Values are given in arbitrary units using the Agatston method for the quantification of valve calcification.

part, explain the more advanced coronary and/or valvular pathological conditions observed in women at the time of surgery.[61]

12. Women and peripheral artery disease (PAD)

Women are mostly asymptomatic, without an obvious reason, which often leads to delayed diagnosis. Sex-specific risk factors include the use of oral contraceptives, history of complications during pregnancy, such as intrauterine growth restriction, pre-eclampsia, and pregnancy-induced hypertension. In lower extremities, revascularization in women may be more prone to complications because of either open or endovascular revascularization; although endovascular intervention generally in female patients appears to be associated with better patency rates.[62]

13. CV involvement in autoimmune rheumatic diseases

ARDs affect 8% of the population and 78% of patients are women. Although ARDs affect several organs and tissues, their prognosis is mainly linked to CVD. CVD in ARDs is the result of various pathophysiological processes, including myo-pericarditis, atherosclerotic or inflammatory CAD and/or spasm, microvascular disease, valvular heart disease, and the effect of immunosuppressive medication. CVD in systemic lupus erythematosus includes myo-pericarditis, DCM, macro-micro- CAD, diastolic dysfunction, vasculitis or valvular disease and represents an important contributor to increased mortality. In systematic sclerosis, cardiac inflammation presenting either as myocarditis or as acute, diffuse, subendocardial vasculopathy leading to diffuse subendocardial fibrosis may also contribute to increased CVD mortality.[63]

14. Pulmonary hypertension

Pulmonary hypertension is classified into five groups based on the WHO classification system. It is a proliferative vasculopathy of the pulmonary arterioles characterized by vascular remodeling (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, which accounts for more than 50% of the cases. All these three conditions affect women disproportionately to men, in a fashion more than 2:1. The median age of patients at presentation is 50 years. In the early stage, most of the cases report exertional breathlessness. Diagnosis is suspected based on echocardiographic − Doppler findings after the exclusion of other cardiorespiratory conditions (chronic thromboembolic disease also included). Right heart catheterization is confirmatory (normal pulmonary capillary wedge pressure − PCWP and increased pulmonary vascular resistance).[64]

15. Congenital heart disease

Although published literature suggests that the prevalence of congenital heart disease is higher in women when compared with men in the adult population, aortic coarctation, and bicuspid aortic valve are more prevalent in male patients. Data from Mayo Clinic suggest that the ratio of isolated secundum atrial septal defect with the PH of women to men is 28/1. 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.[65]

16. Sex differences in COVID-19 Cardiovascular implications

Early reports demonstrated that when compared with women, male COVID-positive patients have more severe disease and a higher mortality. According to Global Health 5050, an organization that promotes gender 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 behaviors (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.[66] Thus, may explain sex differences in heart injury among patients infected with SARS-CoV-2.

17. Conclusions

The diagnosis of CAD in women can be a challenge because of a higher rate of functional limitations and lower prevalence of obstructive CAD than in men. Women have less epicardial disease than men, which suggests that other mechanisms of ischemic heart disease 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 CAD. In pharmaceutical therapy, available data show different responses to antithrombotic therapy between male and female patients in both primary and secondary CV prevention. Additionally, women exhibit a higher prevalence of nonatherogenic CAD than men; while pregnancy and menopause promote alterations in CV function and physiology. Postmenopausal status is identified as a risk factor for CVD. Sex-specific patterns of cardiac and vascular aging play an important role; thus, differences between genders in patterns of age-related cardiac remodeling are associated with a relatively higher prevalence in women than in men of HFpEF. Similarly, gender variation in vascular structure and function changes with aging contribute to differences in the manifestation of CAD. Both hormonal and nonhormonal factors underlie gender differences in CV aging 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 the 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 CV risk factors, manifestation of CVD states, and response to therapies; in addition, it is crucial to promote diversity, health equity, and a broad range of perspectives in treating special needs for each gender, age category, demographic, and social status.[67]

Acknowledgments:

The first and the senior authors contributed equally to the concept and design of this consensus statement; all other authors are presented in alphabetical order.

References

1. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *Circulation*. 2011;123:1243–1262.
2. Gong IY, Tan NS, Ali SH, et al. Temporal trends of women enrollment in major cardiovascular randomized clinical trials. *Can J Cardiol*. 2019;35:653–660.

3. Scott PE, Unger EF, Jenkins MR, et al. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *J Am Coll Cardiol*. 2018;71:1960–1969.
4. Garcia M, Mulvagh SL, Merz CN, Buring JE, Manson JE. Cardiovascular disease in women: clinical perspectives. *Circ Res*. 2016;118:1273–1293.
5. Cho L, Davis M, Elgendy I, et al. Summary of updated recommendations for primary prevention of cardiovascular disease in women. *J Am Coll Cardiol*. 2020;75:2602–2618.
6. Kolovou GD, Kolovou V, Kostakou PM, Mavrogeni S. Body mass index, lipid metabolism and estrogens: their impact on coronary heart disease. *Curr Med Chem*. 2014;21:3455–3465.
7. Triantafyllidi H, Pavlidis G, Trivilou P, et al. The association of elevated HDL levels with carotid atherosclerosis in middle-aged women with untreated essential hypertension. *Angiology*. 2015;66:904–910.
8. Kouremenos N, Zacharopoulou IV, Triantafyllidi H, et al. Genes and genetic variations involved in the development of hypertension: focusing on a Greek patient cohort. *Hellenic J Cardiol*. 2014;55:9–16.
9. Williams B, Mancia G, Spiering W, et al. Practice guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens*. 2018;36:2284–2309.
10. Tadic M, Cuspidi C, Grassi G, Ivanovic B. Gender-specific therapeutic approach in arterial hypertension - Challenges ahead. *Pharmacol Res*. 2019;141:181–188.
11. Holt E, Joyce C, Dornelles A, et al. Sex differences in barriers to antihypertensive medication adherence: findings from the cohort study of medication adherence among older adults. *J Am Geriatr Soc*. 2013;61:558–564.
12. Allahyari A, Jernberg T, Lautsch D, et al. LDL-cholesterol target attainment according to the 2011 and 2016 ESC/EAS dyslipidaemia guidelines in patients with a recent myocardial infarction - nationwide cohort study, 2013-2017. *Eur Heart J Qual Care Clin Outcomes*. 2020. qcaa016.
13. Kolovou GD, Kolovou V, Papadopoulou A, Watts GF. MTP gene variants and response to lomitapide in patients with homozygous familial hypercholesterolemia. *J Atherosclerosis Thromb*. 2016;23:878–883.
14. Arnett DK, Blumenthal RS, Albert MA, et al. Guideline on the primary prevention of cardiovascular disease: a report of the ACC/AHA task force on clinical practice guidelines. *Circulation*. 2019;140:e596–e646.
15. Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol*. 2011;57:1299–1313.
16. Scuteri A, Laurent S, Cucca F, et al. Metabolic syndrome and arteries research (MARE) consortium. Metabolic syndrome across Europe: different clusters of risk factors. *Eur J Prev Cardiol*. 2015;4:486–491.
17. Zhu S, Zhang B, Jiang X, et al. Metabolic disturbances in non-obese women with polycystic ovary syndrome: a systematic review and meta-analysis. *Fertil Steril*. 2019;1:168–177.
18. Buch Kristian, Gunmalm Victoria, Andersson Michael, Schwarz Peter, Brøns Charlotte. Effect of chemotherapy and aromatase inhibitors in the adjuvant treatment of breast cancer on glucose and insulin metabolism—A systematic review. *Cancer Med*. 2019;1:238–245.
19. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet*. 2011;378:1297–1305.
20. Pomp ER, Rosendaal FR, Doggen CJ. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. *Am J Hematol*. 2008;83:97–102.
21. Bolego C, Poli A, Paoletti R. Smoking and gender. *Cardiovasc Res*. 2002;53:568–576.
22. Zandman-Goddard G, Peeva E, Shoenfeld Y. Gender and autoimmunity. *Autoimmun Rev*. 2007;6:366–372.
23. Kolovou G, Kolovou V, Koutelou M, Mavrogeni S. Atherosclerotic and non-atherosclerotic coronary heart disease in women. *Curr Med Chem*. 2015;22:3555–3564.
24. Mavrogeni S, Sfikakis PP, Dimitroulas T, Kolovou G, Kitas GD. Cardiac and muscular involvement in idiopathic inflammatory myopathies: noninvasive diagnostic assessment and the role of cardiovascular and skeletal magnetic resonance imaging. *Inflamm Allergy - Drug Targets*. 2014;13:206–216.
25. Mok MY, Lau CS. The burden and measurement of cardiovascular disease in SSc. *Nat Rev Rheumatol*. 2010;6:430–434.
26. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357:j2099.
27. Taylor DT, Kicska AG, Jacobs EJ, et al. Imaging of Heart Disease in Women. *Radiology*. 2017;282:34–53.
28. Knuuti J, Wijns W, Saraste A, et al. ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2019;41:407–477, 2020.
29. Tarantini G, Barioli A, Nai Fovino L, et al. Unmasking myocardial bridge-related ischemia by intracoronary functional evaluation. *Circ Cardiovasc Interv*. 2018;11, e006247.
30. Brothers JA, Frommelt MA, Jaquiss RDB, Myerburg RJ, Fraser Jr CD, Tweddell JS. Expert consensus guidelines: Anomalous aortic origin of a coronary artery. *J Thorac Cardiovasc Surg*. 2017;153:1440–1457.
31. Raphael CE, Heit JA, Reeder GS, et al. Coronary embolus. An underappreciated cause of acute coronary syndromes. *JACC Cardiovasc Interv*. 2018;11:172–180.
32. Shibata T, Kawakami S, Noguchi T, et al. Prevalence, clinical features, and prognosis of acute myocardial infarction attributable to coronary artery embolism. Clinical perspective. *Circulation*. 2015;132:241–250.
33. Tamis J, Jneid H, Reynolds H, et al. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease a scientific statement from the american heart association. *Circulation*. 2019;139:e891–e908.
34. Sharaf B, Wood T, Shaw L, et al. Adverse outcomes among women presenting with signs and symptoms of ischemia and no obstructive coronary artery disease: findings from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) angiographic core laboratory. *Am Heart J*. 2013;166:134–141.
35. Saw J, Starovoytov A, Humphries K, et al. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J*. 2019;40:1188–1197.
36. Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on Takotsubo syndrome (Part II): Diagnostic workup, outcome, and management. *Eur Heart J*. 2018;39:2047–2062.
37. Mavrogeni S, Mertzanos G, Grassos C, et al. Role of cardiovascular magnetic resonance in assessing patients with chest pain, increased troponin levels and normal coronary arteries. *Hellenic J Cardiol*. 2017;58:384–386.
38. Abdelghany M, Subedi R, Shah S, Kozman H. Kounis syndrome: A review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome. *Int J Cardiol*. 2017;247:14.
39. Wei J, Cheng S, Merz CNB. Coronary microvascular dysfunction causing cardiac ischemia in women. *J Am Med Assoc*. 2019. https://doi.org/10.1001/jama.2019.15736.
40. Barbui T, Thiele J, Passamonti F, et al. Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study. *J Clin Oncol*. 2011;29:3179–3184.
41. Kolovou G, Giannakopoulou V, Vasiliadis Y, Bilianou H. Effects of estrogens on atherogenesis. *Curr Vasc Pharmacol*. 2011;9:244–257.
42. Wenger N. Female-friendly focus: 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *Clin Cardiol*. 2019;42:706–709.
43. Adamo M, Lombardi CM, Metra M. May 2020 at a glance: ischaemic heart failure and sex-related differences. *Eur J Heart Fail*. 2020;22:761–762.
44. McMurray JJV, Jackson AM, Lam CSP, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. *Circulation*. 2020;141:338–351.
45. Arshad A, Moss AJ, Foster E, et al. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. *J Am Coll Cardiol*. 2011;57:813–820.
46. Dewan P, Rørth R, Raparelli V, et al. Sex-related differences in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2019;12, e006539.
47. Meyer W, van der Meer P, van Tintelen P, van den Berg M. Sex differences in cardiomyopathies. *Eur Heart J*. 2014;16:238–247.
48. Barish R, Lynce F, Unger K, Barac A. Management of cardiovascular disease in women with breast cancer. *Circulation*. 2019;139(8):1110–1120.
49. Ky B, Putt M, Sawaya H, et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. *J Am Coll Cardiol*. 2014;63:809–816.
50. Friberg J, Scharling H, Gadsboll N, et al. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). *Am J Cardiol*. 2004;94:889–894.
51. Tadros R, Ton AT, Fiset C, Nattel S. Sex differences in cardiac electrophysiology and clinical arrhythmias: epidemiology, therapeutics, and mechanisms. *Can J Cardiol*. 2014;30:783–792.
52. Linde C, Bongiorni MG, Birgersdotter-Green U, et al. Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart. *Rhythm Society Europace*. 2018;20, 1565-1565.
53. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. ESC Scientific Document Group, 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J*. 07 September 2018;39(34):3165–3241.
54. Faden MS, Bottega N, Benjamin A, et al. A nationwide evaluation of spontaneous coronary artery dissection in pregnancy and the puerperium. *Heart*. 2016;102:1974–1979.
55. Webster LM, Conti-Ramsden F, Seed PT, Webb AJ, Nelson-Piercy C, Chappell LC. Impact of antihypertensive treatment on maternal and perinatal outcomes in pregnancy complicated by chronic hypertension: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6, e005526.
56. Nanna MG, Hajduk AM, Krumholz HM, et al. Sex-Based differences in presentation, treatment, and complications among older adults hospitalized for acute myocardial infarction: the SILVER-AMI study. *Circ Cardiovasc Qual Outcomes*. 2019;12(10), e005691.
57. US Preventive Services Task Force, Grossman DC, Curry SJ, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US preventive services task force recommendation statement. *J Am Med Assoc*. 2017;318(22):2224–2233.

58. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: a scientific statement from the american heart association. *Circulation*. 2016;133(9):916–947.
59. Alam M, Bandeali SJ, Kayani WT, et al. Comparison by meta-analysis of mortality after isolated coronary artery bypass grafting in women versus men. *Am J Cardiol*. 2013;112(3):309–317.
60. Knuuti J, Wijns W, Antti Saraste A, et al. ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2019;00:1–71.
61. Nguyen V, Mathieu T, Melissopoulou M, et al. Sex differences in the progression of aortic stenosis and prognostic implication: The COFRASA-GENERAC study. *JACC Cardiovasc Imaging*. 2016;9:499–501.
62. Schramm K, Rochon P. Gender differences in peripheral vascular disease. *Semin Intervent Radiol*. 2018;35:9–16.
63. Mavrogeni S, Karabela G, Koutsogeorgopoulou L, et al. Pseudo-infarction pattern in diffuse systemic sclerosis. Evaluation using cardiovascular magnetic resonance. *Int J Cardiol*. 2016;214:465–468.
64. Lau EMT, Giannoulatou E, Celermajer DS, Humbert M. Epidemiology and treatment of pulmonary arterial hypertension. *Nat Rev Cardiol*. 2017;14(10):603–614.
65. Giannakoulas G, Vasiliadis K, Frogoudaki A, et al. CHALLENGE investigators. Adult congenital heart disease in Greece: Preliminary data from the CHALLENGE registry. *Int J Cardiol*. 2017;245:109–113.
66. Sharma G, Volgman AS, Michos ED. Sex differences in mortality from COVID-19 Pandemic: are men vulnerable and women protected? *JACC Case Rep*. 2020 May 4. https://doi.org/10.1016/j.jaccas.2020.04.027.
67. Legato M, Johnson P, Manson J. Consideration of sex differences in medicine to improve health care and patient outcomes. *J Am Med Assoc*. 2016;16:1865–1866.