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CURRENT OPINION
Disease management

Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes

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Introduction

In the vast majority of cardiovascular diseases (CVDs), there are well-described differences between women and men in epidemiology, pathophysiology, clinical manifestations, effects of therapy, and outcomes.[1–3] These differences arise on one hand from biological differences among women and men, which are called sex differences. They are due to differences in gene expression from the sex chromosomes and subsequent differences in sexual hormones leading to differences in gene expression and function in the CV system, e.g. in vascular function and NO signalling, in myocardial remodelling under stress, or metabolism of drugs by sex-specific cytochrome expression. Sex differences are frequently reproducible in animal models. In contrast, gender differences are unique to the human. They arise from sociocultural processes, such as different behaviours of women and men; exposure to specific influences of the environment; different forms of nutrition, lifestyle, or stress; or attitudes towards treatments and prevention. These are equally important for CVDs. Both sex and gender (S&G) influence human development (*Figure 1*). Since it is almost impossible to distinguish properly between effects of S&G in the medical field, the EUGenMed writing group decided to discuss both of them together and to use the term S&G for all medical relevant differences between women and men in the present review.

In its current research framework programme 'Horizon 2020', the EU calls for the inclusion of the gender dimension into biomedical research since 'it helps improve the scientific quality and societal relevance of the produced knowledge, technology and/or innovation' (http://ec.europa.eu/programmes/horizon2020/en/h2020-section/promoting-gender-equality-research-and-innovation). The US National Institutes of Health and medicine regulating agencies, such as the European Medicines Agency or the US Food and Drug Administration (FDA), ask for information on potential sex differences for all new drugs and require prespecifications for testing sex effects in drug studies. In 2001, the US government published the results of a retrospective assessment of the drugs withdrawn by the FDA between 1997 and 2000 due to adverse effects, and discovered that these drugs posed greater health risks to women than men.[4] Inclusion of information about S&G is becoming a primary focus of the ongoing debate about the improvement of scientific validity and reproducibility, with the eventual goal to improve translation.[5] It is also a major aspect in optimizing daily patient care.[6,7] Even so a number of efforts have been made to obtain gender-specific data on

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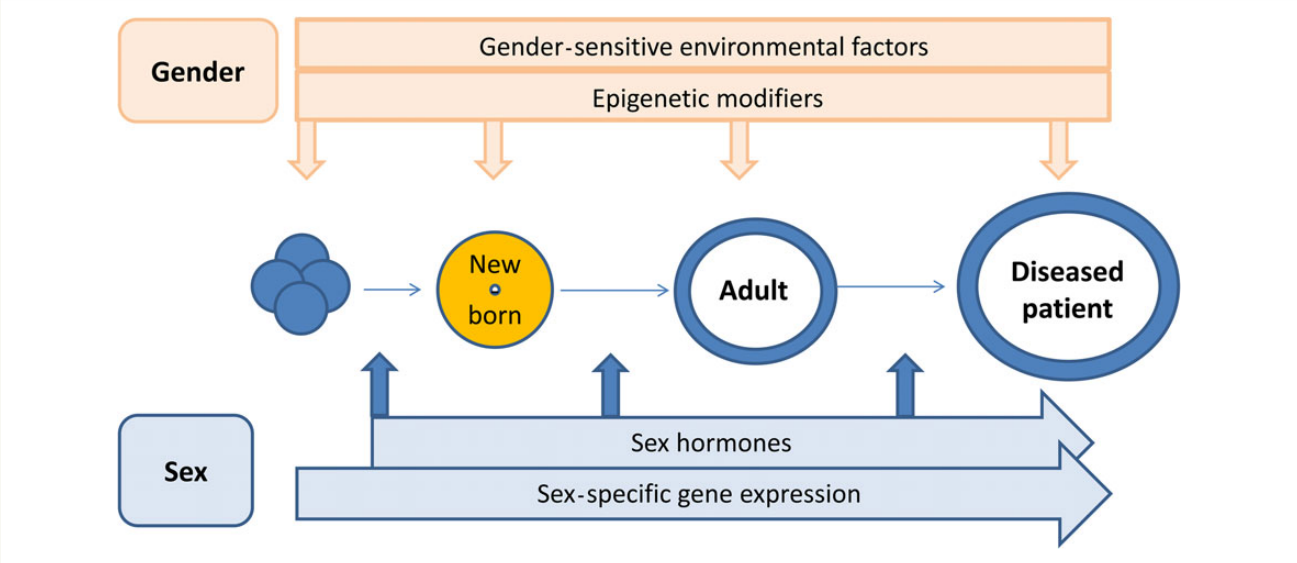

Figure 1 Interaction between sex and gender during lifetime: societal conditions (upper) as well as biological facts (lower) affect germ cells, the newborn, the adult, and the development of disease in women and men.

cardiovascular risk, as in the score project, S&G differences are still frequently missing in current CVD textbooks or guidelines.[8]

There is a lot of published knowledge on S&G differences, but the awareness is low. This may be due to the fact that existing knowledge is dispersed and not presented in a coherent manner. The present review aims to close the gap in knowledge transfer on S&G in major CVDs by reviewing the existing data that are relevant for patient treatment and identifying areas with a need for future studies. It focuses on issues that are both evidence based and meaningful to daily practice and have the potential to be included in future guidelines.

Methods

The present materials have been gathered within the interdisciplinary EU-funded project EUGenMed (FP 7, www.eugenmed.eu/) by a group of experts specifically charged to develop a roadmap for the inclusion of gender aspects in European biomedical and health research. This position paper is part of this road map. The selection of covered topic, CVD, is based on the result of the EUGenMed process as described in the project outline and in the report of the kick-off conference held in April 2014 in Brussels, which is available at the project homepage (www.eugenmed.eu/). In particular, the experts decided to use CVD as an exemplary field to document that S&G differences are important for diagnosis, treatment, and research, recognizing that other fields—such as neurology, oncology, or others—deserve the same effort.

Legitimation of the writing group has been achieved by selecting this group of experts from a large set of European stakeholders in gender medicine at the EUGenMed kick-off conference in April 2014 in an open, transparent process as predefined in the EUGenMed project outline. Experts were invited to a workshop 1 on 'Gender aspects in clinical research and pharmacology', held in Berlin, 30 November to 2 December 2014 and developed together the present paper.

The group decided to focus on four major CVD areas—ischaemic heart disease (IHD), heart failure (HF), hypertension, and valvular heart disease—that are common in European populations. The group also decided to use the current ESC guidelines as a starting point for the definition of state-of-the-art knowledge and practice. The subsequently defined goal was to highlight S&G differences in the selected disease areas that are supported by evidence-based research findings and are relevant for patient care and to identify relevant missing aspects to be addressed in future research. For this purpose, systematic searches of the literature were performed using databases like PubMed and the GenderMedDB (http://gendermeddb.charite.de/), an international database of S&G-specific literature funded by the German Ministry of Education and Research.

Ischaemic heart disease

Ischaemic heart disease is a common disease in all western societies. Ischaemic heart disease includes all damage due to ischaemia in the myocardium, regardless of whether the cause lies in the major coronary arteries, in the microcirculation, or in a supply/demand disbalance, whereas coronary artery disease (CAD) in general is understood as a diseases of the epicardial coronary arteries.[9]

Epidemiology

Ischaemic heart disease develops on average 7–10 years later in women compared with men in most western societies. However, most likely due to unfavourable lifestyle changes over the past decades, manifestations of IHD in younger women are increasing.[10,11] Acute coronary syndromes (ACS), ST-elevation myocardial infarction (STEMI), or NSTEMI (Non-STEMI) occurs three to four times more often in men than in women below age 60, but after 75 years, women represent the majority of patients. Recently, the number of ACS in relatively younger women has increased in France and Germany for yet unknown reasons.[10,11]

Sex differences in risk factors for IHD have recently been discussed.[12] Premenopausal women have less often hypertension

and lower lipid levels than similarly aged men, whereas this reverses at older age. Diabetes emerged as a major risk factor that worsens the CAD outcome more in women than in men.[13] This applies not only to type 2 diabetes but also to young women with gestational diabetes or type 1 diabetes.[14,15] More comorbidities including obesity and inflammation as well as more unfavourable changes in coagulation and endothelial function may contribute to greater cardiometabolic risk factor load in diabetic women.[16] Women more often than men show isolated impaired glucose tolerance (IGT) that has a prevalence of up to 40% in elderly Europeans and already associates with higher cardiovascular risk. Detection of this prediabetic state and initiation of preventive measures are recommended.[17] Measurement of fasting plasma glucose and HbA1c combined or an oral glucose tolerance test (OGTT) to detect prevalent diabetes or IGT is recommended in all patients with CAD, but performance of OGTTs appears particularly important in women.

Depression and various forms of sustained mental stress (anxiety, anger, marital conflicts, work stress, etc.) have been acknowledged as aetiological and prognostic risk factors for CAD.[12] They increase the risk to develop CAD to similar degree in women and men. However, the prevalence is significantly higher in women, particularly in younger women, and this leads to a greater contribution to worse outcomes.[18,19] Multiple factors account for the impact of mental stress on increased risk for CAD—among them accumulation of behavioural risk factors and impairments in psychophysiological pathways with autonomic, endocrine, and inflammatory involvement in the first line. In the past, caution was warranted concerning psychological treatment options as several trials have shown that women with CAD and depression responded adversely to standardized depression interventions. However, emerging data now suggest that stress reduction programmes are safe and effective for women and men.[20,21]

Clinical manifestations and pathophysiology

Acute coronary syndromes, STEMI, or NSTEMI without epicardial CAD or structural heart disease occur more frequently in women than in men.[9] In particular, younger women with ACS may present with open coronary arteries, with plaque erosions with distal embolization rather than plaque rupture with thrombus formation.[22,23] In NSTEMI women, it was recently demonstrated that coronary artery plaque area was associated with myocardial ischaemia independent of presence of coronary stenosis.[24] Not unfrequently, angina or ACS in women may be due to coronary microvascular disease, also called microvascular angina.[25,26] Women have more frequently components of pathological vasoreactivity, such as spasm and endothelial dysfunction (*Figure 2*).[27,28] An underdiagnosed cause of ACS is spontaneous coronary artery dissection (sCAD), which occurs predominantly in women, mostly between 45 and 60 years of age, preferentially in pregnancy or in the immediate postpartum period and may be caused by hormonal changes.[29] It may be related to fibromuscular dysplasia, inflammatory/immunologic diseases, and connective tissue diseases.[30] Estimated 8% of ACS in women but <1% in men are associated with the so-called Takotsubo syndrome (see below).[31,33]

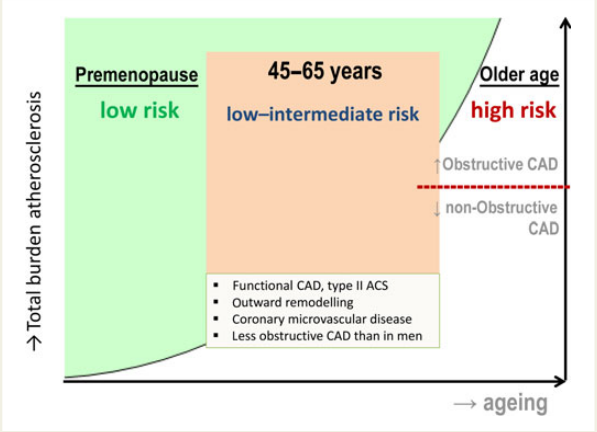

Figure 2 Development of ischaemic heart disease in women. The 'pink' zone reflects women at middle age, with a predominance of functional coronary artery disease and outward remodelling over obstructive CAD. CAD, coronary artery disease; ACS, acute coronary syndromes.

Diagnosis

In ACS, patient's delay before seeking medical help is longer in women.[34,35] The lower awareness that women may also have a significant risk to develop ACS among patients and healthcare providers is an important contributor to this delay. It has recently been postulated that a sex-specific threshold for troponin I may improve the diagnostic accuracy of this most important laboratory test for diagnosis of AMI.[36] With the use of high-sensitive troponins, the diagnosis of MI is more often established in women.[37] Other biomarkers are also found to be sex specific. Proneurotensin was recently related to incident CVD only in women.[38] This area needs further investigations (*Table 1*).

The interpretation of non-invasive diagnostic testing is less reliable in women compared with men, especially in the age group below 60 years when the prevalence of obstructive CAD is still relatively low.[39] Non-specific electrocardiogram (ECG) changes at rest and a lower exercise capacity contribute to the lower sensitivity and specificity of non-invasive exercise testing in women.[40,41] As most exercise testing scores have been developed from populations that were composed primarily of men, only few scores have been designed especially for women.[42,43] The current ESC guidelines advise stress imaging techniques (e.g. SPECT, stress echocardiography) when available as first test of choice, with a preference for non-radiation diagnostics in younger women (*Table 2*).[39,44]

In the Swedish coronary angiography and angioplasty register (SCAAR), almost 80% of women with stable angina symptoms below age 60 had no visible coronary obstructions at angiography, compared with 40% of men.[45] Thus, primary diagnostic strategies in women searching for the classical 'male' pattern of obstructive CAD may be suboptimal, increasing the risk for procedural complications and leave vascular dysfunction or coronary microvessel disease in symptomatic women underdiagnosed.[46] In 2014, the American Heart Association launched evidence-based gender-specific guidelines for non-invasive testing that promote

Table 1 Key sex and gender differences and recommendations for studies

	Key S&G differences	Key references for S&G	Recommendations for S&G sensitive studies
IHD	Distribution and impact of traditional risk factors for IHD (diabetes and stress), changing age distribution in patients with ACS	10–12,18,19	Mechanistic studies to understand greater relative increase in risk for IHD with diabetes for women; studies to analyse emerging changes in risk factor profiles; effect of stress reduction interventions
	Prevalence of CMD, sCAD, and Takotsubo (TTC) in women and men	9,23,29,31–33	Studies on mechanisms of vascular dysfunction in CMD; role of S&G differences in inflammation process in IHD; role of oestrogens in sCAD and TTC
	Sensitivity of diagnostic procedures of IHD	40–43	Identify optimal sex-, gender-, and age-sensitive strategies for the diagnosis of CMD
	Predictive value of hsTNI levels for MI and novel biomarkers (e.g. neurotensin) for IHD	36–38	Study whether the use of sex-specific diagnostic thresholds in hsTNI assays improves diagnosis of MI; study the contribution of neurotension to IHD prediction in women and men
	Outcomes after ACS and CABG	55–57	Prospective gender-sensitive outcome studies, focusing on gender-dependent risk factors
HF	Risk factors for HFpEF and prevalence of HFpEF	86,87	Test whether inflammation is a sex-specific and hormone-dependent risk factor in HFpEF; likewise for hyperglycaemia
	Ventricular remodelling in HFpEF	85,87,90	Test in valid cohort whether ventricular remodeling in women and men with HFpEF differs and whether this depends on risk factor profiles
	Patients with Takotsubo are characterized by low sex hormones and abnormal stress response	31–33	Test whether a decline in sex hormones leads to altered vascular function and altered stress response in male and female Takotsubo patients
	Response to CRT	97,99,164	Confirm S&G difference in outcome after CRT in prospective studies. Analyse mechanisms by MRT: more favorable remodeling or less fibrosis?
	Referral for cardiac transplantation	104	International multicentre prospective study on referral for heart transplantation, organ allocation, and survival
Hypertension	Ventricular adaptation to hypertension and patterns of regression	110	Study sex differences in myocardial remodelling and functional recovery under different drug therapies
AS	Myocardial adaptation and outcome after AV surgery	121,122,129,130,133	Study type of long-term remodelling after AS and its impact on postoperative (3 years) MACE and survival in women and men, and underlying mechanisms
	Myocardial adaptation and outcome after TAVI	130–132,135	Mechanistic study: why do women tolerate TAVI better than men? Impact of LVH type and of fibrosis (MRT)
MR	Atrial and LV diameters at comparable degrees of valvular dysfunction	137,140,141	Compare atrial and LV diameters, regurgitation fraction, and ventricular function in women and men with MR
	Outcome in MV surgery for MR	141	Test impact of sex-specific cut-off values for LV diameters on outcome after surgery in MR
Pharmacology	Serious adverse events due to drug interactions; outcomes under digitalis therapy for HF	145,151	Study whether numbers and causes of emergency hospitalizations for adverse drug effects differ in women and men; test sex differences in digitalis effects

The suggested key facts, key references, and studies represent examples for worthwhile investigations on S&G differences. They do not claim to offer a comprehensive spectrum. CABG, coronary artery bypass surgery. ACS, Acute Coronary Syndrome; AS, Aortic Stenosis; AV, atrio-ventricular; CABG, Coronary Artery Bypass Graft Surgery; CMD, Coronary Microvascular Dysfunction; CRT, Cardiac Resynchronization Therapy; HF, Heart Failure; HFpEF, Heart failure with preserved ejection fraction; hsTnI, high-sensitive Troponin I; IHD, Ischemic Heart Disease; LV, Left Ventricular; LVH, Left Ventricular Hypertrophy; MACE, Major Adverse Cardiovascular Events; MI, myocardial infarction; MRT, Magnetic Resonance Tomography; MV, Mitral Valve; sCAD, Spontaneous Coronary Artery Dissection; TAVI, Transcatheter Aortic Valve Replacement; TTC, Takotsubo Cardiomyopathy.

selective functional and anatomic testing with non-invasive imaging techniques in women at intermediate risk.[39] These are helpful to avoid the still too large number of unnecessary and inconclusive angiograms in this patient population. Women at low IHD risk most often require no testing. Women at low–intermediate or intermediate IHD risk who can exercise adequately should be

Table 2 Indications to stress testing/imaging or coronary computed tomography angiography in women with ischaemic symptoms

	Exercise status		ECG interpretable		Pretest probability of IHD		
Test	Able	Unable	Yes	No	Low	Intermediate	High
Exercise ECG	×		×			×	
Exercise MPI	×			×		×	×
Exercise Echo	×			×		×	×
Pharmacological stress MPI		×	Any			×	×
Pharmacological stress echo		×	Any			×	×
Pharmacological stress CMR		×	Any			×	×
CCTA	Any		Any			(x)	×

CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; IHD, ischaemic heart disease; MPI, myocardial perfusion imaging.

Table 3 Cardiac resynchronization therapy studies that allow comparison of effects in women and men and most important parameters, list of references, and key parameters

Trial	*N* women (proportion)	Treatment arms	NYHA class	LVEF	QRS	Primary endpoint	Gender difference in efficacy
COMPANION[96]	501 (33%)	Medical therapy vs. CRT vs. CRT-D	III–IV	≤35%	≥120 ms	Death or hospitalization for any cause	Similar efficacy of CRT and CRT-D in both sexes
CARE-HF[162]	216 (26%)	Medical therapy vs. CRT	III–IV	≤35%	≥120 ms	Death or hospitalization for major cardiovascular event	Similar efficacy of CRT in both sexes
REVERSE[163]	131 (21%)	CRT on vs. CRT off	I–II	≤40%	≥120 ms	HF (clinical composite endpoint)	Similar efficacy of CRT in both sexes
MADIT-CRT[97]	453 (25%)	CRT-D vs. ICD	I–II	≤30%	≥130 ms	Death or HF event	Significantly better efficacy of CRT-D in women than in men
RAFT[164]	308 (17%)	CRT-D vs. ICD	II–III	≤30%	≥120 ms or paced ≥200 ms	Death or hospitalization for HF	Borderline better efficacy of CRT-D in women than in men

CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; *N*, number of women enrolled.

referred to an Exercise Tolerance Test (ETT) first strategy. Coronary artery disease imaging is indicated for intermediate-risk or high-IHD-risk women with functional disability or an abnormal rest ECG. Diagnostic modalities for the assessment of coronary microvessel disease include measurement of coronary blood flow reserve by transthoracic echocardiography or positron emission tomography (PET)-CT perfusion or calculation of microcirculatory resistance indexes during coronary catheterization (coronary flow reserve).[25,47]

Women with recurrent chest pain syndromes and non-obstructive CAD need to be diagnosed and treated since they have a two-fold increased risk to develop obstructive CAD events in the next 5–8 years and have a four times higher risk for re-hospitalizations and recurrent angiograms than women without these symptoms.[48,49] Shaw *et al.* reported an expected consumption of nearly $750 000 of cardiovascular healthcare resources related to the burden of ongoing symptoms and medications.[176]

Treatment and outcomes

Treatment of stable CAD and ACS should be performed according to the current guidelines in both genders.[44] However, there is an ongoing debate whether outcomes are identical in women and men. In a large multicentre MI registry, female sex remained a strong independent predictor for re-hospitalization for ACS, but in other registries, the worse outcome in women was due to age and comorbidities.[50–52] Higher in-hospital mortality in women with ACS has been attributed to a longer patient's delay before admission, older age, a higher clustering of cardiovascular risk factors, lower use of invasive and medical treatment, and more bleeding complications after

interventions.[53] The risk for HF after MI in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) was higher in women than in men.[54] In younger women (<60 years) with STEMI, adjusted in-hospital mortality rates are nearly twice as high as in similarly aged men.[55,56] In non-STEMI (NSTEMI) patients, a recent collaborative meta-analysis of three studies indicated that routine invasive strategy may not be preferred over a selective invasive strategy in women, in contrast to men.[57]

It is now well accepted that women derive the same benefits from percutaneous coronary intervention (PCI) as men. Previously, worse prognosis was attributed to smaller luminal diameters of the coronary arteries, risk factor profiles, more comorbidities, and referral bias in women. The Belgian Working Group on Interventional Cardiology (BWGIC) registry analysed a large cohort of 130 985 PCI procedures in Belgium, from January 2006 to February 2011. Female gender remained an independent predictor of mortality after multivariable adjustment.[58] In most studies with second-generation drug-eluting stents, S&G differences in the long-term outcome after PCI are not supported further. However, female gender remains an independent predictor for peri-procedural myocardial infarctions and major bleedings after PCI, which are associated with increased short-term morbidity and mortality.[59,60] Due to the relative higher contribution of functional coronary abnormalities and a more diffuse pattern of atherosclerosis in female patients with CAD, residual symptoms of angina are often present after ACS or coronary interventions.[61,62]

Using the transradial access for coronary interventions reduces the incidence of peri-procedural bleeding complications and improves the clinical outcome.[63] Because of the smaller size of the radial artery and its higher spasm tendency, this approach is more challenging in women. Female gender is not only an independent predictor for transradial approach failure but also for local bleedings after transradial coronary interventions.[64,65] However, long-term clinical outcomes appear to be similar to men.[66]

The use of fractional flow reserve-guided PCI has improved outcomes.[67] Fractional flow reserve values are found to be higher in women after correction for visually assessed coronary anatomic severity. This may be caused by the more frequent microvascular disease in women.[68] It is currently discussed whether gender-specific guidelines in interpreting fractional flow reserve measurements are warranted.[68,69]

Women also had higher mortality after elective coronary artery bypass surgery.[70] Major risk factors for women's mortality were low physical function, respiratory dysfunction, renal failure, and old age.[71] A recent study identified a significantly higher prevalence of diastolic dysfunction among females presenting for elective cardiac surgery and reported that women had a prolonged hospital stay.[72] Women have poorer health-related quality of life than men after coronary surgery.[73] Depression is a significant predictor of worse outcomes in women and men.[74]

Therapeutic options for coronary microvascular dysfunction are less well investigated than those for epicardial CAD; the efficacy of anti-anginal medications for symptom reduction is relatively poor, and optimal treatment options are lacking.[44,75] The presence of detectable peripheral coronary flow abnormalities in patients with microvascular dysfunction is associated with impaired prognosis in both men and women.[76,77] Therefore, this syndrome urgently needs more research.

Heart failure and cardiomyopathies

Epidemiology

Heart failure is one of the major health threats of western societies and affects up to 10% of the elderly, in absolute numbers more women than men.[78] In most studies and registries, women survive better than men and HF in women frequently occurs in older age and with less ischaemic aetiology than in men.[79,80] Few studies determined the true incidence of HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) in women and men, but the available evidence suggests that the number of women with HFpEF is greater than the number of men, and HFrEF affects more men in Europe.[81] More HFrEF is due to MI in men longer life expectancy in women and greater prevalence of HFpEF in the older age groups may contribute to the higher prevalence of HFpEF in women. It is not clear how frequent a transition from HFpEF to HFrEF occurs in the population and if this is sex dependent. A transition from a hypertrophic to a dilated, hypocontractile phenotype has been described in detail in a case study of a women with hypertrophic cardiomyopathy (HCM).[82] More studies are needed here.

Dilated cardiomyopathy (DCM) and HCM are slightly more common in men compared with women, even though the autosomal underlying gene defects appear to be distributed equally among women and men.[83,84] It has been hypothesized that women are better protected against ventricular dilatation and systolic dysfunction than men.[85]

In contrast to HCM and DCM, the so-called Takotsubo cardiomyopathy (TTC) is a rare disease affecting predominantly women, ~70–90% women in most registries.[31,33] The latter manifests as an ACS or acute HF, often preceded by acute massive psychological or physical stress. The patients frequently recover with normalized EF. However, mortality is 8% and recurrence is estimated 5%.

Clinical manifestations and pathophysiology

Sex differences were found in clinical characteristics and outcomes in elderly patients with HFpEF.[86] Ventricular remodelling under stress is also different. Combined effects of obesity and hypertension led to greater concentric hypertrophy in postmenopausal women, whereas in men, eccentric hypertrophy dominated.[87] The ventricular adaptation in HF should be considered in the context of normal physiology where women do have higher heart rates at rest and under exercise and, at different levels of stress, react with lower sympathetic response, greater vasodilation, and increased peripheral oxygen extraction, whereas men tend to use more the starling mechanism, increase stroke volume and blood pressures.[88] Smaller stroke volumes in women than in men were found in normal persons.[89] Women with HFpEF had smaller and stiffer hearts than men in a small single centre study.[85] Corroborating these findings, women with HF in the large Paramount trial had higher indexed left ventricular wall thicknesses and worse diastolic function than men.[90] Underlying mechanisms are not yet clear. A greater activation of profibrotic or proinflammatory pathways in men may contribute, as well as intrinsic sex differences in myocardial Ca handling or energy metabolism.[85,91] Paradigmatic changes in cardiac function in women and men are presented in *Figure 3*.

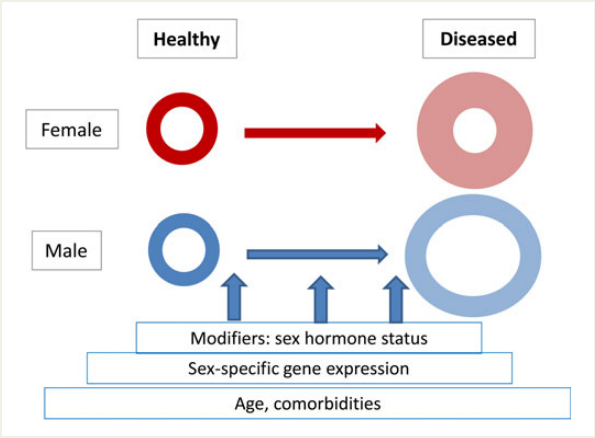

Figure 3 Cardiac remodelling in women and men. Circles symbolize cross sections through a prototypic left ventricle in females (upper part, red) and in males (lower part, blue). The arrows symbolize the transition from a healthy to a diseased state. Female hearts are smaller in the healthy state. Following stress, e.g. exercise or pressure overload, females develop more frequently concentric hypertrophy with smaller internal cavity and relatively larger wall thickness than males, whereas males in general develop more readily eccentric hypertrophy, increased stroke volume, and dilatation.

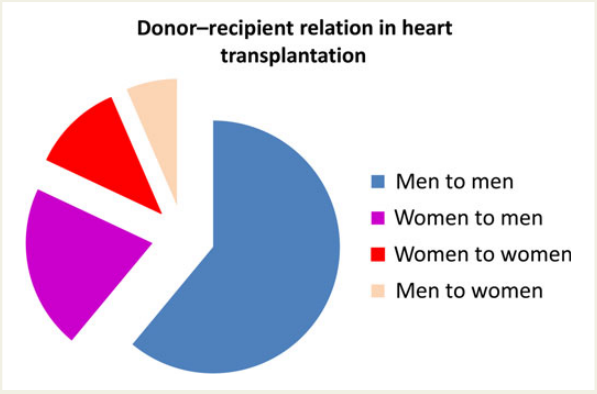

Figure 4 Donor–recipient relations in heart transplantation: fewer women than men undergo heart transplantation and women are more frequently donors than recipients. Example from a large German transplant centre, Deutsches Herzzentrum Berlin, based on 1263 cases from 1985 to 2012.

Oestrogen reduces catecholamine-induced vasoconstriction, promotes vasodilation, and may increase β2-adrenergic receptor responses.[88] A decrease in oestrogen levels may increase the sensitivity of the heart to circulating catecholamines. This is discussed as a contributing mechanism in HFpEF and in Takotsubo cardiomyopathy.

Major clinical manifestations in HF are not different in women and men.[80] Women exhibit a worse quality of life after diagnosis of HF and exhibit more frequently depression.[74,92] Because of the high prevalence of depression in women with HF, systematic screening may be considered.

In some but not all studies, women with HF had a lower prevalence of atrial fibrillation than men, which may be due to smaller left atrial size.[93] Since women with atrial fibrillation have a higher risk for stroke than men, for yet unknown reasons, female sex is included as an independent risk factor in the CHA_2DS_2-VASC score.[80]

Diagnosis

Guideline-based diagnosis and therapy in HF does not differ between women and men. However, diagnosis was less frequently based on objective diagnostic tests in women.[94] In the Euro Heart Survey, echocardiography was used less frequently in women.[81,95] Physicians should be informed about this potential bias in order to reduce it.

Treatment and outcomes

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) improves survival and quality of life in patients with HF and conduction delay.[96,97] Women are poorly represented in clinical trials (20% of enrollees) that result in a selection bias in current guidelines.[98] In some studies, women experienced more benefit than men from resynchronization therapy (*Table 3*). Women but not men had a benefit independently of the QRS duration and baseline characteristics.[97,99] A recent FDA meta-analysis of three major clinical trials with mild HF confirmed that the indication for CRT in women seems to be at a shorter QRS duration.[100,101] Results from the Swedish Heart Failure Registry showed that CRT was equally underutilized in both genders and QRS prolongation was not more harmful in women than in men.[102]

Ventricular assist device

Registry analysis of the International Society of Heart and Lung Transplantation (ISHLT) repeatedly showed a severe survival deficit in women after device implantation. This was frequently attributed to differences in disease states and types of devices used. Analysis of 139 patients (including 24 women) before (115/24) and after (24/24) propensity matching all treated with HeartMate II und HeartWare allowed for a comparison of women and men independent of device type.[103] This study indicated a survival benefit for men in the overall sample, whereas no difference was found in the matched patient group. Analysis of clinical data showed that women were referred in more severe disease state what explains survival disadvantages before and the disappearance after adjustment.

Heart transplantation

Fewer women than men undergo heart transplantation and men are more frequently recipients, whereas women are more frequently donors (*Figure 4*). In a data set of 698 consecutive patients with idiopathic non-ischaemic DCM referred for heart transplantation to the German Heart Institute, only 15.6% were women, suggesting a referral bias against women. Women were more frequently in New York Heart Association functional class III–IV than men, had lower exercise tolerance, respiratory efficiency, and kidney function. Women referred for transplantation also had significantly frequently less diabetes than men, even though women in HF populations have the same diabetes rate as men. Thus, women were referred at a more advanced disease state and relative contraindications such

as diabetes appear to be taken more seriously in women.[104] However, the low number of women in this study may limit conclusions. An international multicentre prospective study on referral for heart transplantation, organ allocation, and survival appears mandatory.

Hypertension

Epidemiology

In European countries and the USA, one in three adults presents with arterial hypertension based on current guideline definitions.[105,106] Noteworthy are the differences between women and men in younger age groups (18 and 29 years), showing only a prevalence of 1.3% in women vs. 8.5% in men and 7.3% in women vs. 15.8% in men in the group between 30 and 44 years.[105] In contrast, hypertension is more common in women than in men in the elderly population.

Clinical manifestations and pathophysiology

No sex differences in clinical manifestations of hypertension outside of pregnancy-related hypertension have been described. A number of S&G differences in the pathophysiology of hypertension have been reported, mainly related to S&G differences in the renin–angiotensin system and in the bradykinin and NO system. However, none of those have had consequences for medical therapy so far. Disturbances in sexual hormone production as they occur in the polycystic ovarian syndrome or during postmenopausal decline in oestrogen levels have been associated with hypertension in women.[107,108]

Diagnosis

In accordance to current guidelines, no differences between men and women have been documented regarding diagnostic approaches for hypertension.[109] Female sex stands among the factors associated with a higher prevalence of white coat hypertension, whereas male sex is related to increased prevalence of masked hypertension.[109]

Treatment and outcomes

Hypertensive left ventricular hypertrophy is more difficult to treat in women, and residual hypertrophy is more common than in men despite systematic antihypertensive treatment.[110] Hypertensive women sustain higher left ventricular ejection fraction and other measures of systolic function.[110] Nevertheless, women exhibit less regression under medical therapy and they have an estimated three-fold higher risk for developing congestive HF or stroke compared with men.[111,112] Hypertensive women develop more vascular and myocardial stiffness than men at old age, and more often have isolated systolic hypertension, reflecting aortic stiffness.[113] This is closely associated with their higher prevalence of strokes and HFpEF.[114]

Aortic valve stenosis

Epidemiology

Aortic stenosis (AS) is the most common valvular heart disease requiring valve replacement. In the European populations, the prevalence is up to 5% among subjects aged 70–79 years and up to 10% among subjects >80 years of age. Aortic stenosis due to a congenital bicuspid valve is three times more common among men than women,[115] while degenerative AS is more common among women with a women : men ratio of 1 : 0.76.[116]

Clinical manifestations and pathophysiology

In general, the clinical presentation of patients with AS does not differ between women and men. As a consequence of AS progression, leading to increasing pressure overload on the left ventricle, women develop more concentric hypertrophy with smaller internal cavity and relatively larger wall thickness than men.[117,118] Women, independently of left ventricular size, also preserve better ejection fraction and myocardial contractility than men during progression of AS.[119,120] Lower myocardial function was found in men compared with women with AS in the SEAS and in a smaller study.[117] This may be due to the greater amount of fibrosis that is found in male in comparison with female hearts of patients undergoing aortic valve surgery.[121,122] Men exhibit more excentric hypertrophy at aortic valve surgery and show less regression of myocardial hypertrophy than women after surgery. More longitudinal studies are needed to understand the sex differences in remodelling and their clinical consequences.

Diagnosis

The diagnostic strategy in AS does not differ between women and men. However, calcification measured by multidetector computer tomography (Agatston score) is more pronounced in men than in women independent of the severity of the AS.[123] Recently, sex-specific cut-off values for Agatston score identifying severe AS were documented.[124] In subjects with small body size, frequently women, indexation of the valve opening area for body surface area avoids overestimation of AS severity and is recommended in the current guidelines.[125] However, in patients with mild AS and a small aortic root dimension, the effective aortic valve area indexed for body surface area may overestimate the actual AS severity by 30% if not adjusted for post-stenotic pressure recovery. A small aortic root is particularly common among elderly women, and unnecessary surgery in these is avoided by proper indexation.[126]

Treatment and outcomes

It is well recognized that perioperative mortality and complications are higher in women than in men undergoing surgical aortic valve replacement.[125] For AS patients at high operative risk, transcatheter aortic valve implantation (TAVI) is an increasingly recognized therapeutic option.[127,128] Current data argue for an outcome benefit in women treated with TAVI,[129] especially, among patients suitable for transfemoral access. Whereas procedural device success rates are similar between women and men after TAVI, short- and mid-term survival is greater in women (*Figure 5*).[130–132] In TAVI patients with severe left ventricular hypertrophy in the PARTNER trial, postoperative hypertrophy regression was more pronounced in women and associated with a 50% reduction in new hospitalizations, particularly for HF.[133] Interestingly, outcome benefit in women is observed despite more procedure-related complications, such as major vascular complications (related to smaller vessel size), bleedings, or rarely occurring coronary obstructions.[131,132,134] It remains

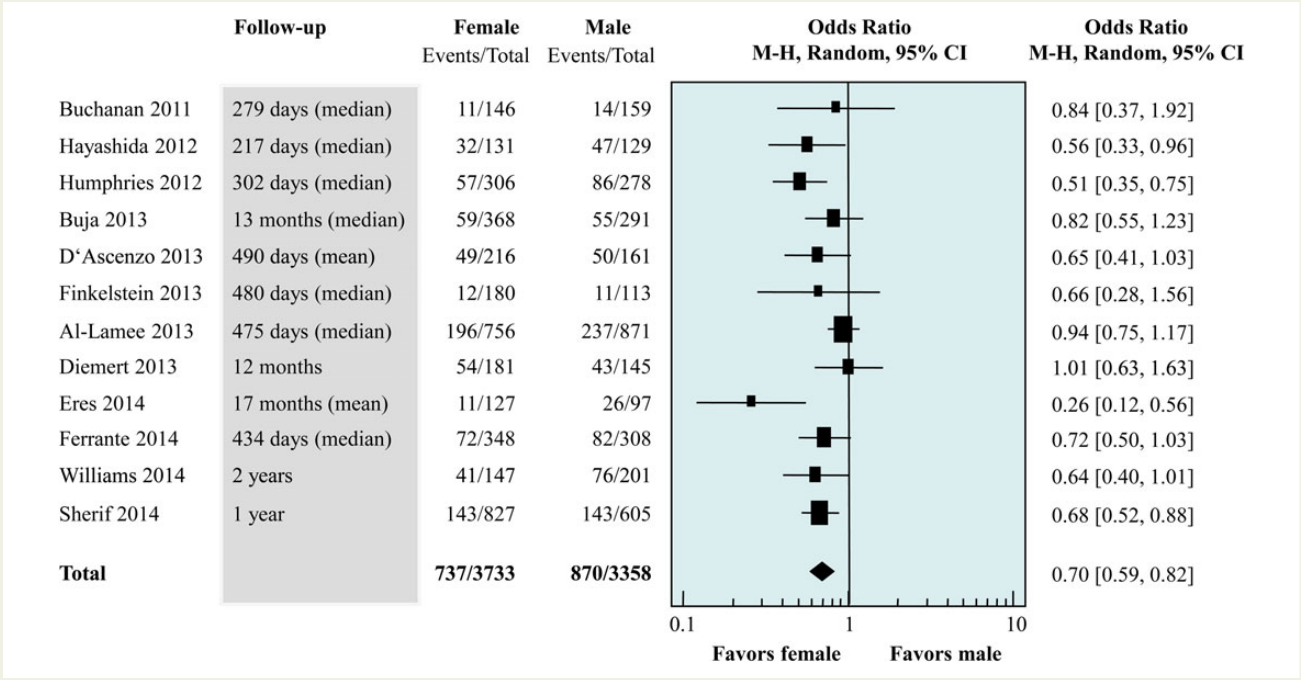

Figure 5 Gender differences in TAVI outcome. Metaanalysis of published trials with the end point total mortality during follow-up.[132]

to be elucidated whether this advantage is merely associated with differences in baseline characteristics or whether it reflects a better reversibility of myocardial hypertrophy in women.[135,136] Stroke rates are not different between genders.

Mitral valve prolapse and mitral regurgitation

Epidemiology

In general populations, mitral valve prolapse is found in 2.5–4% more frequently in women than in men, and more often involves the anterior or both leaflets, while men have more often posterior prolapse and flail leaflets.[137] The lifetime risk for need of mitral valve surgery is 4% in men and 1.5% in women with mitral valve prolapse.[138]

Diagnosis

Current guidelines do not include sex-specific recommendations for indications in mitral valve surgery.[125,139] For asymptomatic severe mitral regurgitation, an end-systolic left ventricular dimension >40 mm (>45 mm in European guidelines) and an ejection fraction <60% are criteria suggesting referral for surgical treatment.[125,139] Since women normally have smaller hearts and higher ejection fractions, these criteria may lead to underdiagnosis of asymptomatic severe mitral regurgitation in women, delayed surgical treatment, and lack of postoperative normalization of life expectancy.[140]

Treatment and outcomes

Among patients with severe regurgitation, women were 20% less likely than men to undergo mitral valve surgery in a retrospective study from the Mayo clinic.[137] This may be related to the smaller left ventricular and atrial dimensions in women, often not reaching the classic unadjusted dimensions used for surgical indication in severe mitral regurgitation.

From a review of >180 000 Medicare beneficiaries, women with mitral regurgitation undergoing mitral valve surgery had lower survival than men, independent of type of valve surgery (mitral repair or replacement, respectively).[141] The lower survival was attributed to higher preoperative risk, in particular HF, atrial fibrillation, and respiratory failure, reflecting a more longstanding and severe regurgitation at the time of referral for surgical treatment. The authors suggested a physician referral bias, but women seeking medical care at a later stage may also have contributed to a more advanced stage of illness before consultation with a physician.

Pharmacological therapy

Pharmacokinetics

Sex and gender differences in pharmacokinetics are caused by sex-specific oral bioavailability, amount and distribution of body fat, clearance, volume distribution, absorption, plasma protein binding, urinary excretion, and metabolism. A typical example of cardiac drugs showing overall systemic sex-specific differences in pharmacokinetics is β-blockers (for example metoprolol and propranolol).[142] A lower distribution volume for β-blockers in women, related to the difference in body dimension/composition, could potentially lead to the lower clearance rate of those drugs that is frequently observed in women.[143] Furthermore, the clearance of those β-blockers that are metabolized by the cytochrome P isoenzyme

Table 4 Sex differences in drug effects (adapted from Regitz-Zagrosek and Seeland[159])

Treatment	Sex-specific drug effects	References
Digitalis	Higher risk for death among women with HF compared with placebo Reduced distribution volume, lower drug elimination in women	146 165
Antiarrhythmics	Drug-induced Torsades de pointes (TdP) observed predominantly in women	166–170
Anticoagulants and ASA	Haemorrhage incidence increased in women Haematuria, haemoptysis, and intracranial bleeding incidence increased in men Higher benefit observed in women (Vitamin K antagonists, Fondaparinux) Increased bleeding risk observed in women (Bivalirudin)	171 172 173,174 175

ASA, Acetylsalicylic Acid.

CYP2D6 is markedly higher in men, and increased plasma levels are associated with more adverse effects in women.[143,144]

Pharmacodynamics

Sex differences in drug effects are most commonly described for digitalis, antiarrhythmics, and anticoagulants (*Table 4*), but sex differences do also exist for other drugs. Mortality under digitalis treatment was higher in women than in men in a *post hoc* analysis of the largest randomized prospective trial on digitalis in HF.[145] Underlying reasons are unclear but may be associated with higher blood concentrations in women due to hormonal factors or sex differences in renal function.[146] They may, however, also be related to sex differences in cardiac ion channel function. Testosterone and oestrogen affect several cardiac ion channels.[147,148] Women have a longer repolarization phase resulting in longer QT duration on the ECG. Therefore, female sex is a potential risk factor for fatal ventricular tachycardia type 'Torsade de Pointes', which can be induced by, for example, antiarrhythmic, antidepressive, and antiallergic medications.

The efficacy of aspirin in the primary prevention of MI and stroke differs in women and men, with greater protection from a first MI in men and from stroke in women. In primary prevention, there are reports that aspirin protects more against stroke in women and more against MI in men.[149] The reason is unclear. It could be a matter of prevalence of the diseases in women and men at different ages or an interaction of hormonal state with age-specific disease mechanisms. In secondary prevention, however, the effects of aspirin are the same in both sexes and at similar ages.

Sex and gender differences in cardiovascular drug safety

Sixty percentage of all patients admitted to the hospital for adverse drug events are women.[150–154] Predominantly women display dose-related adverse drug events[154] that may be due to the fact that risk factors for adverse drug events, such as polytherapy, aging, and depression, are more frequent in women than in men.[155] Furthermore, doses of drugs are frequently not well adapted to the smaller body size, higher body fat content, or hepatic metabolism in women, or lower kidney function in elderly women. As discussed, women with HF have a higher rate of adverse drug events than men especially with diuretics, anticoagulants, digoxin, and Angiotensin Converting Enzyme Inhibitors.[156] In conclusion, adverse drug events represent a source of greater health concern in women than in men and, therefore, need to be investigated further in more depth. Reducing the number and severity of adverse drug events in women should be a priority because decreasing the number of adverse drug events will increase the social and economic benefits of pharmacotherapy.[157] The US GAO report from 2006 describes that six drugs were withdrawn from market for adverse effects and that these posed greater health risks to women than men. A recent analysis suggests that costs for a new molecular entity to launch are in the mean $1.78 billion.[158] Thus, preventing some of the drug withdrawals by better targeting drugs and doses for women could have saved several billions.

Consequences, needs, and implementation

Consequences

We described a number of S&G differences in CVD (supplementary materials), but these differences are not well known in the medical community and therefore do not have major impact in medical practice so far. This lack of knowledge is costly. If coronary angiography is used as an early diagnostic procedure in women with angina like syndromes, that are at low or intermediate risk for developing CAD, far too many women will undergo this expensive and invasive procedure without a positive result.[45] In valvular heart disease, consideration of gender may be helpful to decide on most efficient treatment strategies, i.e. the use of TAVI or conventional surgery. The same may apply for decisions on resynchronization therapy that is less frequently used in women than in men but has a greater benefit in women and may help to prevent more expensive consequences of HF. In contrast, implanted defibrillators may be more efficient in men. Thus, gendered approaches may lead to a more specific and effective use of resources.[159]

Needs assessment

In order to include gender into decision algorithms, we still need more evidence-based data. This requires gender-sensitive study

strategies. Cardiovascular outcome trials must be designed with an adequate statistical power to obtain meaningful results for women and men. This is a challenge for study planning, since we must include knowledge on estimated event rates in specific population groups as well as knowledge on gender-specific risk factors for developing CVD and outcomes during the design process. We must use strategies like potentially oversampling one sex, pre-stratification, prospective planning for meta-analyses based on segregated patient data,[160] studying effect of interactions of risk factors with multilevel Cox regression models,[50] or plan intersectional designs for relevant covariates from the beginning[161] to avoid inefficient data gathering, i.e. accumulation of data that cannot be analysed by lack of power. Such studies may appear more costly at first glance; however, since they give much more answers than a gender-blind design, they will be more conclusive in the long run and reduce the economic and indirect costs of post-marketing withdrawal as discussed above. Withdrawal of drugs from market for adverse effects has to be estimated with $1.78 billion,[158] and six from eight drugs withdrawn from the market and included in the GAO report had more adverse effects in women than in men.

Implementation

The cardiology societies are at the forefront of implementing the new gender-sensitive findings into the research and healthcare strategies. They have already accumulated a large number of knowledge in S&G differences and they are in a position to communicate this at their congresses and to organize sessions on S&G issues. They are in charge of integrating new knowledge into guidelines. They are frequently involved in designing registries and clinical studies and it should be mandatory for them to assure that gender-sensitive data are collected and distributed. They can organize training courses that are badly needed because today's practitioners have not been trained in gender medicine. For active clinical and basic research, a number of tools have been developed that can facilitate gendered analysis (http://genderedinnovations.stanford.edu/). The willingness of the funding agencies is needed to include S&G into preclinical research and clinical studies. National Institutes of Health published on 9 June 2015 a notice announcing that sex has to be included into all animal research and human studies or it has to be justified why this is not the case (Notice Number: NOT-OD-15-102). Likewise, journal editors should require information on S&G or an explanation why it is not important in all studies submitted for publication. Neglecting S&G issues without proper reasoning and explanations prevents proper validation of research findings, limits reproducibility, and will not lead to high-quality results. Last, policy makers must be convinced that S&G issues improve the quality of biomedical research and health care and must also be willing to mandate S&G issues into research and medical practice.

In conclusion, more precise algorithms for gendered approaches may lead to a more specific and effective use of resources in CV therapy. For this purpose, more evidence-based clinical data are required. For successful implementation, the support of cardiology societies, active researchers, funding organizations, journal editors, and policy makers is needed.

Author's contributions

V.R.-Z. designed the study; V.R.-Z. handled funding and supervision; V.R.-Z., S.O.-P., E.B.-P., F.F., E.G., A.F.-L., A.M., A.K.-W., D.K., U.K., K.H.L., K.S.-G., and V.S. acquired the data; V.R.-Z. conceived and designed the research; V.R.-Z., S.O.-P., E.B.-P., F.F., E.G., A.F.-L., A.M., A.K.-W., D.K., U.K., K.H.L., K.S.-G., and V.S. drafted the manuscript; S.O.-P., E.B.-P., F.F., E.G., A.F.-L., A.M., A.K.-W., D.K., U.K., K.H.L., K.S.-G., and V.S. made critical revision of the manuscript for key intellectual content.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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