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Italian Association of Hospital Cardiologists Position Paper 'Gender discrepancy: time to implement gender-based clinical management'

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It has been well assessed that women have been widely under-represented in cardiovascular clinical trials. Moreover, a significant discrepancy in pharmacological and interventional strategies has been reported. Therefore, poor outcomes and more significant mortality have been shown in many diseases. Pharmacokinetic and pharmacodynamic differences in drug metabolism have also been described so that effectiveness could be different according to sex. However, awareness about the gender gap remains too scarce. Consequently, gender-specific guidelines are lacking, and the need for a sex-specific approach has become more evident in the last few years. This paper aims to evaluate different therapeutic approaches to managing the most common women's diseases.

Introduction

Cardiovascular diseases (CVDs) represent the leading cause of mortality worldwide in both sexes.[1] The purpose of guidelines is to provide evidence-based recommendations for the prevention and treatment of CVD by boards, working groups, and committees with international representativeness aimed at ensuring a plurality of perspectives regardless of race, ethnicity, and gender. In recent years, there has been increased inclusion of women among the authors of consensus documents and guidelines, although female representation remains consistently lower than that of males.[2] Moreover, in randomized clinical trials (RCTs), women are numerically inferior to men, sometimes even in contradiction with epidemiology. The reduced percentage of women in enrolled patient populations results in many disadvantages, as data on women are numerically inferior to those relating to their male counterparts.

It is important to emphasize that, despite the widely acknowledged gender differences in the field of CVD, the perception persists in the collective imagination that women have some sort of protection from CVD. In reality, already from pre-menopause, the protection provided by sex hormones drastically decreases, making women even more vulnerable compared to men. In this regard, scientific societies have made considerable efforts to recognize the importance of CVD in women.[1,2]

In light of these considerations, it would be desirable to revise the current cardiology guidelines to take into account gender differences, especially regarding the different pharmacokinetics and dosing aspects of the main molecules used in the cardiovascular (CV) field. The purpose of this document is to highlight how differentiated clinical and therapeutic pathways based on gender could play an important role in improving the treatment and prevention of CVD.

Menopause

Menopause is a normal ageing phenomenon in women and consists of a gradual transition from the reproductive to the non-reproductive phase of life; it is defined as the permanent cessation of menstruation and the diagnosis is made retrospectively after menstruation is absent for 12 months.[3] Most women enter menopause at the median age of around 50 years, while menopause before the age of 40 years is defined as premature. As a result of the increasing life expectancy, many women spend at least one-third of their life in the post-menopausal stage.[3-5] It represents a primary ovarian failure where there is a depletion of ovarian follicles, the primary source of oestrogens.[5] Exposure to endogenous oestrogens during the reproductive years provides young women with protection against CVD, whereas the female cardiovascular risk increases significantly around 10 years after the time of the menopausal transition, superimposing the effect of ageing.[6,7] The changing hormonal milieu, with the rapid loss of ovarian oestrogens and progesterone and the circulating androgens, may induce also sub-clinical (activation of the renin–angiotensin system and of the sympathetic nervous system, presence of coronary artery calcium, reduced compliance of the large arteries, alterations in rheological properties of plasma and platelet function) and overt changes in the cardiovascular system[8-10] Additionally, complex interactions between oxidative stress and levels of L-arginine and ADMA may also

influence endothelial dysfunction in menopause.[11] The arterial actions of oestrogens, but also part of that of androgens through their aromatization into oestrogens, are mediated by the oestrogen receptors (ER)α and ERβ. Oestrogen receptors belong to the nuclear receptor family and act by transcriptional regulation in the nucleus, but also exert non-genomic/extranuclear actions.[12] Besides the decline of oestrogens at menopause, abnormalities in the expression and/or function of ERs could contribute to the failure in protecting arteries during ageing.

Menopause, besides, is an important cardiovascular risk factor, favouring a constellation of risk factors, such as an increase in fat mass with visceral obesity, Type 2 diabetes, atherogenic dyslipidaemia, dysregulation in glucose homeostasis, non-alcoholic fatty liver disease, metabolic syndrome, and arterial hypertension.[13,14] In particular, women with vasomotor symptoms during menopause seem to have an unfavourable cardiometabolic profile.[6] Post-menopausal oestrogen deficiency may also have an overall negative effect on the reaction to stress[7] Independent of ageing, menopausal status is associated with elevations in serum total cholesterol, LDL-cholesterol, apolipoproteins, lipoprotein(a) and triglycerides, and decreases in HDL cholesterol.[13,14]

Emerging research also suggests that after menopause there is a loss of functional HDL cardioprotective properties.[14] Hypertension is more common in younger men than women, but this trend is inverted at approximately 60 years of age; thereafter, hypertension is more common in women.[15] The influence of menopause *per se* on blood pressure remains uncertain. Oestrogens influence the vascular system by inducing vasodilatation, inhibiting vascular remodelling processes, and modulating the renin-angiotensin-aldosterone system (RAAS) and the sympathetic system[16]

However, changes in the prevalence of hypertension in post-menopausal women might be due to ageing and not oestrogen deficiency.[17] Post-menopausal women are particularly affected by obesity and have higher rates of severe obesity when compared to their male counterparts. Obesity is linked to hormonal, lifestyle, and environmental changes that occur during the menopausal transition.[18]

Cardiovascular diseases account for at least one-third of all deaths in women and half of deaths in women over 50 years.[10] Indeed, the incidence of stroke and myocardial infarction (MI) is lower in females than in males, but only up to menopause, when, especially after 65 years of age, the differences disappear[19]; women develop CVD when they are about 10 years older than men.[20] However, an independent association of menopause *per se* with increased risk of CVD events has only been proven for early-onset menopause (<45 years).[20] In the EPIC-CVD,[21] post-menopausal women were not at higher CVD risk compared with pre-menopausal women, but earlier menopause was linearly associated with higher CVD risk (HR 1.02, 95% confidence interval, CI, 1.01–1.03, *P* 0.001), as well as surgical menopause compared with those with natural menopause (HR 1.25, 95% CI 1.10–1.42, $P < 0.001$).[22] Also in a pooled data analysis from the Atherosclerosis Risk in Communities (ARIC) study, the Multi-Ethnic Study of Atherosclerosis, and the Jackson Heart Study early menopause was associated with an increased risk for CVD.[23] In the ARIC study, compared with women with later onset of menopause, those with early menopause had elevated heart failure risk (HR 1.20, 95% CI 1.01–1.43).[24] In the UK Biobank Cohort study, compared with women with natural menopause, women with natural menopause before 40 years (HR 2.38, 95% CI: 1.64, 3.45) or hysterectomy before 40 years (HR: 1.60, 95% CI 1.23, 2.07) had a higher risk of cardiovascular mortality. A comprehensive meta-analysis of 16 studies encompassing 321 233 adults unveiled a notable link between experiencing menopause at a younger age and an increased risk of all-cause mortality. However, this association did not extend to the risk of CV mortality.[25] However, in the Dutch HELIUS Study, the addition of early menopause to current eligibility criteria did not improve the detection of women at high CVD risk.[26] In the Reasons for Geographic and Racial Differences in Stroke, white women in natural menopause (HR 0.45; 95% CI 0.31, 0.66) and surgical menopause (HR 0.65; 95% CI, 0.42, 0.99) had a reduced hazard of non-fatal events, compared to white men.[27] We should also consider the reproductive life span (RLS), the period between onset of menarche and menopause. In the National Health and Nutrition Examination Survey, a longer duration of reproductive years was associated with a lower risk of CVD, compared with a shorter duration (RR 0.70, 95% CI 0.53–0.92).[28] Also in the Malmo Diet Cancer Study, a shorter RLS was associated with an increased CVD risk (HR 1.19, 95% CI 1.06–1.34, *P* 0.004) and with a higher mortality risk. The association remained significant when specifically controlling for a history of hysterectomy and/or oophorectomy.[29] Another Chinese study showed that the CVD risk was reduced by 3.8% for every 1-year increase in RLS.[30] A systematic review confirmed that a shorter RLS is associated with a higher risk of CVD events.[31] As regards surgical menopause, in the Korean Genome and Epidemiology Study survey, it was a strong predictor of CVD (HR 4.32, $P < 0.001$). In a systematic review and meta-analysis including 78 studies on 10 187 540 persons, the pooled relative risks of any stroke were 1.42 (95% CI, 1.34–1.50) after oophorectomy vs. no oophorectomy.[32]

Hormone replacement therapy (HRT) is acknowledged as the gold standard for the alleviation of the disabling vasomotor symptoms of menopause. Early HRT initiation confers a favourable effect on lipid profile,[33] with increased medium-to-large HDL particle count and decreased small-to-medium LDL particle.[34] It has not been clearly demonstrated, however, that HRT reduces blood pressure levels.[34] In the past, it has been hypothesized that the protective effect of oestrogens could translate into improved CVD outcomes, buffering adverse effects of menopause, but, unfortunately, some trials have not consistently shown cardiovascular benefit[35,36] and others, i.e. the Women's Health Initiative study in older post-menopausal women, described significant risks.[37] It is increasingly recognized that hormone therapy is inappropriate for older post-menopausal women no longer displaying menopausal symptoms,[37] and guidelines do not indicate HRT for primary or secondary cardiovascular prevention.[33] However, the magnitude and type of HRT-associated risks, including breast cancer, stroke, and venous thromboembolism, are rare (<10 events/10 000 women), not unique to HRT, and comparable with other

medications[38]; some variables, such as the type of HRT, the time of initiation according to age and/or time since menopause, underlying health of target tissue, and duration of therapy should be considered.[38] Meta-analyses of randomized trials show an increased risk of ischaemic stroke associated with the use of oral conjugated equine oestrogens, associated or not with medroxyprogesterone acetate, while the use of transdermal oestrogen therapy combined with progesterone seems safer,[39] since they do not increase triglyceride concentrations and are not associated with increased risk of venous thromboembolic events (oral oestrogens are contraindicated in women with a history of venous thromboembolism).[13] The risk of coronary heart disease (CHD) is not increased and appears to be significantly reduced when HRT is started <10 years after menopause or before the age of 60.[39] A population cohort in Reykjavik, Iceland, showed the lowest coronary artery calcium in those who started HRT within 5 years after menopause.[40] In contrast, in the Stockholm Heart Epidemiology Program neither the timing of hormone therapy initiation nor the duration of therapy is significantly associated with MI risk.[41] The current international guidelines recommend women with early menopause use HRT until the average age of menopause.[42] One should carefully consider these factors before starting HRT, which may still have a role in the prevention of CVD if given to the right woman and at the right time.[43] For women who may benefit from the associated vasomotor, genitourinary, and/or bone health properties of HRT, CVD risks should be taken into account prior to administration[44] with a multidisciplinary approach, adequately monitoring and treating risk factors such as hypertension and dyslipidaemia.[45]

Pharmacodynamic and pharmacokinetic differences in the elderly

Due to the ageing of populations, clinical practice is increasingly challenged by the associated variations in pharmacokinetics and pharmacodynamics. This condition is evidenced by the excess incidence of adverse drug reactions (ADRs) in older patients, which are found in up to 46% of hospitalized elderly.[46]

Pharmacokinetics

Ageing *per se* does not affect gastric acid secretion; however, 50 to 80% of older patients exhibit HP-related atrophic lesions, with ensuing impaired acid secretion.[47] Also, ageing is associated with delayed gastric emptying and small bowel transit.[47] Noticeably, studies on middle-aged subjects indicated delayed gastric emptying in women as compared with men.[48] Eventually, bicarbonate secretion is reduced in older women, but not men.[49] The combined effect of such alterations is often unpredictable.[50] For instance, absorption of dabigatran should be hindered in advanced age because of increased gastric pH. Nevertheless, in older subjects, its area under the curve is increased by 40–60%, and Cmax by 25.

Serum proteins, particularly albumin, are reduced in advanced age. As unbound drug concentration is a major determinant of pharmacodynamic activity, the effect of drugs with high protein binding (such as warfarin, bound rate 98–99%) is enhanced; this phenomenon is not observed for agents with lower protein binding, such as flecainide (protein-bound fraction 40%).[51]

With ageing lean mass decreases, and total fat increases, particularly in older women. Thus, the concentration of hydrophilic agents, such as acetylsalicylic acid, digoxin, or direct oral anticoagulants is increased. Conversely, lipophilic agents accumulate in fat tissue. For instance, in long-term users, amiodarone concentrations are up to 266 times higher in fat than in plasma.[52]

Liver mass declines by 10–15% per decade in women, with 60% reduction in hepatic flow in both sexes. However, hepatic metabolism is substantially unaffected by age.[47]

Several cytochromes decrease with ageing, while CYP3A activity is substantially higher in older women than in men.[53] The effects of such modifications are still uncertain. Hepatic expression of *P* glycoprotein is 2.4-fold lower in women, yet its activity at the blood-brain barrier declines in men but not in women. This might account for the increased risk of confusion by cardiovascular drugs, including Class IC anti-arrhythmics.

Renal function declines with ageing at an increased rate in women; nevertheless, the rate of decline is extremely variable, and in several cases, no age-related reduction is observed.[54] The assessment of renal function from serum creatinine is concealed by decreased muscle mass in older women[55]; the use of cystatin C might overcome this limitation.[56]

Pharmacodynamics

Pharmacodynamics in older age is affected by changes in receptor expression and affinity, second messenger response and cellular and homeostatic regulation.[57]

The effects of similar concentrations at the site of action might change due to changes in drug-receptor interaction, post-receptor events, or homeostatic responses; frail subjects are often also due to organ damage.[58] For instance, PR or QT prolongation from anti-depressants, neuroleptics, or other CNS drugs is almost exclusively found in older subjects. Polypharmacy accounts for most ADRs in the elderly[59]; nevertheless, ageing *per se* is associated with common ADRs, such as hypokalaemia from intravenous furosemide, or delirium from antibiotics, anti-arrhythmics, or digoxin.[60] These reactions derive from variations in renal tubular secretion, intracellular free calcium levels, blood-brain barrier permeability, and post-synaptic choline content. Also, peripherial alpha-adrenergic secretion and receptor expression are reduced in advanced age, so orthostatic hypotension from calcium antagonists or alpha-adrenergic blockers is common. For the same reason, even though older patients are less sensitive to the cardiac effects of beta-blockers because of reduced expression of beta receptors, orthostatic hypotension is a frequent ADR of these agents.

To conclude, older women might be at increased risk of toxicity, mainly because of increased drug serum levels; nevertheless, data from specific studies are needed to clarify the pitfalls of drug therapy in this population.

Heart failure

Heart failure (HF) is a leading cause of hospitalization and death worldwide, and its incidence has been stable

over the years despite recent drug and device advancements.[61] It has been well recognized that several gender discrepancies exist affecting clinical features and prognosis, with major mortality in men, although women are more likely to have more hospitalizations.[62]

It has been shown that females are more likely to be older than men when HF occurs. Moreover, sex-specific risk factors, including early menopause, adverse pregnancy outcomes, and reproductive disorders, have been reported to have a role in the development of HF in women.[5] Anaemia, a common comorbidity in HF, has been shown to occur more commonly in women than men, especially during fertile age.[63]

Moreover, it has been shown that females are more likely to be affected by HF with preserved ejection fraction (HFpEF), differently from men who more frequently experienced HF with reduced ejection fraction (HFrEF).[64,65] HFpEF is more common in post-menopausal women,[66] suggesting the role of endogenous oestrogen.

Despite the more severe symptoms and the worse functional status occurring in women with HF, they seem to have a better prognosis and lower mortality compared to men.[67,68]

Moreover, women experienced some physiological changes during pregnancy related to the cardiovascular remodelling for the volume overload that could represent a sort of training for the heart, resulting in preventing or improving HF if it occurs.[69] Furthermore, hypertension and lung disease, more common in women, are classically described as risk factors for HFpEF, also explaining the strict association among sex, comorbidities, and HF aetiology.

Lastly, in consideration of the different clinical courses of the disease, it has been noted that HF in women appeared clinically more severe, with more symptoms and worse functional class, expressed by New York Heart Association (NYHA) III or IV.[70] Despite the severity of symptoms, women with HF have a better prognosis compared to males, and the female sex seems to be an independent predictor of lower mortality in HFpEF patients.[68] These data have also been confirmed when HFrEF has been considered, even in the case of ischaemic aetiology or advanced systolic dysfunction.[67]

Angiotensin-converting enzyme-I, ARB, beta-blockers in HF

Physiologically, sex hormones elicit distinct effects on adrenergic receptors and the angiotensin II receptor blockers (ARBs). Oestrogens and progesterone confer cardioprotective benefits by suppressing the cardiac expression of β1-adrenoceptors and attenuating β-adrenergic-mediated stimulation.[71,72] Regarding the RAAS, oestrogens elevate angiotensinogen and angiotensin II levels but concurrently decrease ACE (angiotensin-converting enzyme) activity and the expression of angiotensin II Type 1 receptors. Conversely, androgens exert an up-regulatory influence on the RAAS.[73–75] These effects partially contribute to the cardioprotective influence of oestrogen observed during the pre-menopausal phase with respect to cardiovascular diseases.

Sex-related differences affect the pharmacokinetics of ACE-I, ARBs, and beta-blockers, which have a decreased drug clearance in females than males due to a smaller volume distribution and reduced glomerular and hepatic filtration. Accordingly, after administering a similar dose, maximum plasma concentration may be up to 2.5 times higher in females than males.[76–78] Additionally, contraceptive therapy can affect metoprolol metabolism with further increases in plasma levels.[79] Thus, a greater reduction in heart rate and blood pressure and a significantly increased risk of bradycardia have been reported in women.[80]

Consequently, due to these different sex-related pharmacokinetic characteristics and sex hormones, females are more likely to experience side adverse effects, with a 1.5–1.7-fold higher incidence than in men.[78]

Due to the under-representation of women in randomized controlled trials (RCTs) and in observational registries, assessing drugs' effects on women is more challenging than on men.

RCTs (CONSENSUS, SAVE, SOLVD) suggested a reduction of mortality in males but not in females[81–83] (*Table 1*). Meta-analytic data, however, did not find differences between sex in treatment effect for ACE-I and ARBs.[84] These data have further been confirmed in a recent meta-analysis from 7 RCTs showing no difference in the ACE-I or ARB's treatment between sex in all-cause mortality and the combined outcome of mortality and HF hospitalization.[85] HF guidelines recommend up-titration of these drugs to the same target dose in both sexes. However, two post-doc analyses from the HEAAL[86] and ATLAS[87] studies have shown that a lower dosage in women was equally effective compared to higher dosages. The importance of dose-dependent differences between sexes is further highlighted by the BIOSTAT-CHF study,[88] showing that men achieved the greatest reduction in the risk of death or hospitalization for HF at 100% of the recommended dose of ACE-I or ARBs, while women the lowest risk of death or hospitalization for HF at 40–60% the guideline-recommended doses. The most relevant observation was that, in women, there was no further decrease in risk at higher dose levels.[88] In contrast, up-titration may significantly increase the risk of adverse events.

Beta-blockers have been associated with a better outcome in males than females in patients with hypertension[89] and coronary artery disease (CAD).[90] Controversy does exist in HFrEF, likely due to the under-representation of women.[91–93] However, a recent meta-analysis of 5 RCTs concerning the role of beta-blockers in HF patients, showed no gender difference in treatment effect between males and females for the outcome of all-cause mortality and the composite of death or HF hospitalization.[85] The same results have also been shown in a European observational registry, wherein beta-blockers had a comparable effect in both sexes in reducing all causes of death and HF hospitalization. Importantly, similar to ACE-I, women needed lower doses of beta-blockers than males (50–60% of the target doses) to achieve the same reduction of the outcomes.[88]

Diuretics and mineralocorticoid receptor antagonists

Loop diuretics are considered the mainstay of the treatment of volume overload in patients with HF and are recommended to reduce signs and symptoms of congestion.[94] It has been shown that women with HF are prescribed comparable diuretic treatment regimens to

Table 1 Studies on treatment with statins and ezetimibe for cardiovascular prevention in both genders

Reference	Year	Setting	Main findings
Hendrix *et al.*	2005	72 351 hypertensive patients from 262 primary care providers at 69 sites in the US Southeast	Women received fewer statin prescriptions than men (47.7% vs. 65.1%, $P \leq 0.0001$)
Koopman *et al.*	2013	Pharmo database (1 203 290 persons ≥25 years eligible for primary prevention, 84 621 persons hospitalized for an ACS, and 15 651 persons eligible for secondary prevention)	The proportion of women using lipid-lowering drugs in primary prevention was lower than men
Gupta *et al.*	2016	Large hospital database in India	Statin use was significantly lower in women (5.8%) than men (10.3%)
Ballo *et al.*	2016	2088 consecutive patients discharged from 5 local community hospitals with a definite diagnosis of HF	Women showed a lower statin prescription rate (25.7% vs. 35.3%, $P < 0.0001$) and a lower prevalence of adequate statin dose (32.6% vs. 42.3%, $P < 0.0001$) than men. Female gender was independently associated with a 24% lower probability of statin prescription and a 48% higher probability of inadequate statin dose
Wallach-Kildemoes *et al.*	2016	Cohort of Danish inhabitants ($n = 4\,424\,818$) followed in nationwide registries	Statin use was higher in men than women (37 and 33%, respectively). Particularly, it tended to be lower in women until ages of about 60. In asymptomatic individuals (hypercholesterolaemia, presumably only indication) aged 50+, dispensing was highest in women. The fraction of statin dispensing for primary prevention, independent of age, was highest among women, e.g. 60% vs. 45% at ages 55–64
Kulenovic *et al.*	2016	1399 consecutive patients without known cardiovascular disease or diabetes hospitalized with a first myocardial infarction in Denmark	Statin therapy had been initiated in 12% of women and 10% of men prior to MI. The estimated pre-treatment risk was much lower in women than men (median 3.8% vs. 9.2%). Lower risk women receive as much statins as higher risk men
Rodriguez *et al.*	2016	US administrative claims database between January 2008 and December 2012 for 76 414 patients with established ASCVD	50.3% of men and 32.0% of women were prescribed a pre-index statin ($P < 0.0001$). Women initially treated with LLT were significantly less likely to receive a prescription for a higher potency LLT
Gamboa *et al.*	2017	4288 adults ≥45 years of age with diabetes mellitus who had low-density lipoprotein cholesterol (LDL-C) > 100 mg/dL or were taking statins recruited for the Reasons for Geographic and Racial Differences in Stroke study from 2003 to 2007	After adjustment for healthcare utilization factors, statin use was lower for black males and white and black females compared with white males [prevalence ratios (95% CI): 0.96 (0.89–1.03), 0.86 (0.80–0.92), and 0.87 (0.81–0.93), respectively, $P < 0.001$]
Byrne *et al.*	2018	Cross-sectional analysis of cardiovascular risk and socio-demographic factors associated with statin utilization from The Irish Longitudinal Study on Ageing	No association between using statins and gender
Moreno-Arellano *et al.*	2018	Multi-centre cross-sectional survey among 1046 patients with dyslipidaemia receiving statin therapy from the Primary Health Care of Andalucía (Spain)	Women were less likely to be treated with a more potent statin than men (9.2% vs. 14.4%, $P = 0.009$), and they received lower doses (45 ± 59 mg/day vs. 56 ± 71 mg/day, $P = 0.004$) than men
Shen *et al.*	2019	US cross-sectional study using administrative claims data from Inovalon's Medical Outcomes Research for Effectiveness and Economics Registry (MORE2 Registry) for patients enrolled in commercial (39 322) and Medicare Advantage (261 898) healthcare	Female gender was associated with a lower likelihood of receiving a statin and/or ezetimibe prescription from a cardiologist for patients in both commercial plans (OR 0.69; 95% CL 0.65–0.74) and in Medicare Advantage plans (OR 0.78; 95% CL 0.76–0.79)
Gober *et al.*	2020	Retrospective chart review of inpatients with newly diagnosed PAD	The majority of those discharged without a statin were female (67%)
Sidebottom *et al.*	2020	Electronic health record data by a large health system	66.4% of statin eligible men were prescribed a statin compared to 57.4% of statin eligible women ($P <$ 0.001)
Mahtta *et al.*	2020	192 219 males and 3188 females with PAD and 331 352 males and 10 490 females with ICVD	Women with PAD had lower prescription rates of any statin (68.5% vs. 78.7%, OR 0.68, 95% CI 0.62–0.75),

Continued

Table 1 Continued

Reference	Year	Setting	Main findings
		seeking primary care in the VA healthcare system	compared with men. Similar disparities were seen in ICVD patients
Metser *et al.*	2021	Electronic health record data for patients with at least one primary care or cardiology visit at an urban, academic medical centre in New York City	Compared with those never prescribed statins, patients prescribed statins were less likely to be women, mainly driven by lower statin prescription rates for women with diabetes
Lee *et al.*	2021	Data from 24 hospitals involving 35 232 ACS patients (79.44% men and 20.56% women)	Women remained less likely to receive statins
Colvin *et al.*	2021	Data from 374 786 adults ≥ 66 years of age with Medicare fee-for-service coverage who had an MI, were not taking ezetimibe, and had very high-risk ASCVD	The aHRs for ezetimibe initiation comparing women to men was 1.11 (95% CI: 1.06–1.17)
Raeisi *et al.*	2022	Data collected from a single US centre	Clear disparity in statin prescription favouring males
Ahmed *et al.*	2022	Single-centre, cross-sectional study at a US family medicine clinic on patients with a documented diagnosis of diabetes	Females had higher rates of prescribed statin therapy and appropriate statin intensity therapy when compared to males ($P > 0.05$)

ACS, acute coronary syndromes; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HF, heart failure; aHRs, adjusted hazard ratios; ICVD, ischaemic cerebrovascular disease; LLT, lipid-lowering therapy; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease.

men, albeit at lower dosages, regardless of whether they exhibit preserved or reduced left ventricular ejection fraction (LVEF).[95,96] Gender-specific differences have been observed in pharmacokinetics for torasemide, which was shown to have a clearance one-third lower in women than in men, thus resulting in higher peak and mean plasma concentrations.[97] Similarly, animal studies showed that females have higher natriuretic, kaliuretic, and diuretic responses to furosemide.[98] These findings could partially explain the higher incidence of adverse drug events for diuretics among women.[99,100] Indeed, women hospitalized for acute decompensated HF are more likely to develop acute kidney injury despite receiving significantly less furosemide than men.[96] These data could warrant closer monitoring of renal function and potassium after treatment initiation.

No sex-related differences in outcomes have been reported for mineralocorticoid receptor antagonists (MRAs) in HFrEF.[101,102]

In HFpEF, in a secondary analysis of the TOPCAT-Americas, treatment with spironolactone was associated with a lower risk of all-cause mortality in females but not in males[103] suggesting that differences in the biological activity of spironolactone in the kidney and the myocardium could account for a sex-specific benefit.[104,105]

However, a meta-analysis using individual patient data from three large RCTs (RALES, EMPHASIS-HF, and TOPCAT) representing the full spectrum of LVEF did not confirm the previous evidence on sex-related differences in treatment response to MRA in patients with HFpEF.[106] In this analysis, MRA treatment led to similar risk reductions of cardiovascular death/HF hospitalization in women and males (31% vs. 29%), regardless of their NYHA class, LVEF, and other confounding factors. Indeed, there were significant differences in clinical features between sexes, with women being older, with poorer NYHA functional class, and more likely suffering from hypertension and worsening renal function. The treatment effect was consistent between men and women, even in three subgroups of patients at particularly high risk, such as the elderly, patients with diabetes, and those with a low eGFR. Notably, sex-related differences in the occurrence of MRA-associated side effects did not emerge in this meta-analysis, and there was no specific impact of sex on hyperkalaemia and worsening renal function.[106]

Angiotensin receptor neprilysin inhibitor

Sex differences in pathophysiologic mechanisms of HF, pharmacokinetics and pharmacodynamics of drugs may impact pharmacological treatment benefits in HF. Sacubitril–valsartan, a drug class known as angiotensin receptor neprilysin inhibitor (ARNI), has been tested in both HF with reduced and preserved ejection fraction (EF), in the PARADIGM-HF[107] trial and the Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction (PARAGON-HF)[108] trial, respectively. In the PARADIGM trial, of 8442 randomized, 1832 patients (21.7%) were females. The pre-specified subgroup analysis showed that ARNI reduced the primary endpoint (a composite of hospitalization for HF or cardiovascular death) regardless of patient sex (P for interaction = 0.63).[107] However, ARNI clinical benefits in women appeared due to a reduction in hospital admissions without a significant effect on cardiovascular mortality.

The PARAGON-HF trial, which included 4796 patients (51.7% women), showed a trend towards a lower rate of the primary endpoint (a composite of hospitalizations for worsening HF and cardiovascular mortality) among patients treated with ARNI compared to those treated with valsartan, without to achieve a statistically significant difference between the two treatments arms. The pre-specified analysis that assessed endpoints according to sex found a lower rate of the primary endpoint in women treated with sacubitril–valsartan compared with those treated with valsartan alone [0.73, 95% confidence interval (CI), 0.59–0.90] and no difference in the risk rate of the two treatment arms in men (1.03, 95% CI, 0.84–1.25;

P-interaction = 0.017). In more detail, ARNI reduced hospitalizations, but not cardiovascular mortality, in females more than males. This result is potentially relevant since HF with preserved ejection fraction (HFpEF) is the most common HF phenotype in women. A sex-related difference in treatment effect by HF phenotype, preserved vs. reduced EF, has also been reported with other drugs, such as mineralocorticoid receptor antagonists in TOPCAT.[109]

In the pre-specified analysis that combined data from the PARADIGM-HF trial, which included patients with EF ≤40%, and the PARAGON-HF trial, which included patients with EF ≥45%, ARNI clinical benefits were shown to vary by EF with benefits in women that seem to extend at higher EF.[110]

Of note, HFpEF is a clinical syndrome that may present with different clinical characteristics and have different prognoses. Since ARNI pharmacokinetics do not differ between females and males,[111] other possible mechanisms have been postulated to explain the different effects of ARNI in men and women. For example, there are sex-related differences in natriuretic peptides biology, with a reduction in circulating NP concentrations after menopause.[112] Indeed, in the PARAGON-HF trial, women, compared with men, were older (mean age 71.8 vs. 73.6 years, $P < 0.001$) and had lower NP levels [median value 1712 pg/mL vs. 1508 pg/mL, $P < 0.001$, in patients with atrial fibrillation (AF), and 575 pg/mL vs. 625, *P* 0.022, in patients without AF].[108] By increasing NP levels, ARNI may have a greater therapeutic effect in females than in males. However, available data do not provide enough information to definite the mechanistic basis for the PARAGON-HF results in women. Since the female population in HF clinical trials is often under-represented, to provide robust sex-specific data on treatment effects and test the efficacy of a tailored treatment based on sex, specific measures to increase women's enrolment in clinical trials should be implemented.

Sodium–glucose cotransporter-2

Sodium–glucose cotransporter-2 inhibitors have been shown to improve HF prognosis across the EF spectrum, first in patients with HF and reduced EF (HFrEF) with the Phase 3 trials Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF)[113] and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced).[114] These drugs were later shown to improve clinical outcomes in HF with preserved EF (HFpEF) in the EMPEROR-Preserved[115] and the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER)[116] trials. In all these trials, the risk of the primary outcome, which was a composite of cardiovascular death or hospitalization for HF, was lower in patients treated with gliflozin than in the placebo arm. For all trials, analyses on the efficacy and tolerability of gliflozins in men and women were performed.

Patient-level data from DAPA-HF and DELIVER trials, which included 11 007 patients (35% women) overall, were analyzed together.[117] This study showed that dapagliflozin had a similar impact on the primary and secondary endpoints (*P*-interaction = 0.77 and > 0.35, respectively) and had a similar safety profile in both men and women.

The EMPEROR-Reduced trial included 3730 patients (23.9% women). In this trial, the benefit of empagliflozin in terms of primary endpoint incidence reduction was consistent in the pre-specified analysis for sex [0.80 (0.68–0.93) and 0.59 (0.44–0.80) were the hazard ratio and CI in male and female subgroups, respectively].

A recent study evaluated the impact of sex on empagliflozin effects in the EMPEROR-Preserved trial, which enrolled 5988 patients (44.7% women). The study showed that empagliflozin reduces the rate of the primary outcome similarly in both sexes (*P*-interaction = 0.54), with a benefit consistent across EF groups. The benefits of secondary outcomes and physiological measures, such as blood pressure, haemoglobin, and natriuretic peptide levels, were also similar.

These findings support the use of gliflozins in patients with HFrEF and HFpEF regardless of sex.

Cardiac resynchronization therapy

The benefits of cardiac resynchronization therapy (CRT) on the outcomes of HF patients are well known.

However, the interpretation of the data regarding gender-specific CRT effects is masked by the absence of prospective, randomized controlled clinical trials comparing responses in male vs. female CRT patients.[118] Moreover, women were under-represented in the studies and are less than one-third of the total population.[119] The reasons for this discrepancy can be the higher rates of HFpEF, for which CRT is not indicated, but also higher procedural complications and higher refusal rates to CRT implant in women than in men.[120]

Despite these limitations, some observational studies (MADIT-CRT,[121] MIRACLE,[121] RAFT[122]) showed that women had a greater benefit from CRT than men. Also, a large English database with almost 44 000 patients (25% women) demonstrated that women lived longer and had less hospitalization for HF after CRT.[123]

There are multiple reasons for the sex difference in CRT-D outcomes related to the anatomy, electrical dyssynchrony, and aetiology of HF. Women had small ventricles with higher incidence of non-ischaemic cardiomyopathy and lower scar burden that could improve the response to CRT.[124] Still, the effective relation between these factors and sex discrepancies remains unclear.[125,126] Also, the role of the left bundle branch block is debated. A shorter QRS duration was observed in women with LBBB,[127] and for any given QRS duration, women have greater electrical desynchrony with a consequence of greater CRT benefit. The use of cut-off based on trials with a high prevalence of male patients could deny a life-saving therapy to women likely to benefit from CRT.[128]

Also, other biological factors, such as hormonal differences and disparities in the cardiac autonomic system, could play a role in these discrepancies. Further studies are needed to understand sex differences and develop new strategies to tailor CRT therapy in our female patients.

Heart transplantation

Heart transplant (HTx) is the treatment of choice for patients affected by end-stage heart disease who have symptoms requiring frequent hospitalizations despite maximal medical therapy.[94] Several studies have analyzed

the sex differences in the waiting list and in the outcomes after HTx, despite females being under-represented in most of the trials on advanced HF.[129] Effectively, despite women representing more than half of deaths due to HF, only a quarter of all would definitely have access to the HTx list.[130] Moreover, women have had fewer opportunities to take advantage of temporary and permanent mechanical circulatory support along the time,[131] receiving a left ventricular assist device (LVAD) therapy only in less than one-third of cases.[132]

The aim of this chapter is to analyze the available data focused on gender discrepancy in relation to three important checkpoints in advanced HF management:

- HTx waiting list;
- access to mechanical circulatory supports (MCS);
- post-HTx outcome.

Concerning the data on HTx waiting list, women arrived at HTx more frequently for dilated cardiomyopathy (61.7%); conversely, CHD is the first reason for HF leading to HTx for men (48%).[133] Different comorbidities affect the two sexes: men have more frequent diabetes mellitus, hypertension, and kidney disease, both before and after HTx.[133,134] Furthermore, it has been demonstrated that women listed for HTx have an increased risk of death compared to men during waiting time; thus, the female sex is associated with higher mortality as United Network for Organ Sharing Status 1A (HR 1.14, 95% CI 1.01–1.29) and 1B (HR 1.17, 95% CI 1.05–1.30) according to an American report presented at the Scientific Meeting of HF.[135] These data have been analyzed with the aim of adequately changing the allocation system, with the female recipients significantly younger than males (51 years old vs. 54 years old, respectively).[133-136]

In consideration of temporary or permanent supports, data demonstrated that women would have access to LVAD therapy only in a more advanced stage than men.[137] Effectively, as demonstrated by an analysis of the multi-centre PCHF-VAD registry including 13 European HF tertiary referral centres, only 19% of LVAD patients were women, despite a huge number of females with advanced HF already reported in previous studies, suggesting its under-utilization.[138] Moreover, female patients have access to LVAD when already in INTERMACS Profiles 1 or 2, thus in great delay for this kind of therapy.[138,139] This later referral could justify the higher rate of complications after LVAD implantation, such as significant arrhythmias, major bleeding, or episodes of right-ventricular failure in women with LVAD compared to men,[140] leading to a worse prognosis for the first one. For all these reasons, survival rates are lower in women than in men following LVAD implantation.[130] On the contrary, survival rates following HTx are similar between the two sexes when adjusted for donor and recipient characteristics.[141]

Lastly, in relation to the outcome after HTx, cardiac transplanted women are more frequently affected by allograft HF, and they suffer more episodes of antibody-mediated rejections despite a low percentage of them developing cardiac allograft vasculopathy or malignancies of any grade. This could be explained by some sex-related differences, as far as the higher anti-HLA antibodies frequently detected in women.[142] Anyway, the majority of studies available until now are focused on donor-recipient mismatch after HTx[136]; conversely, when sex-related differences are analyzed in the recipients, no difference emerged in survival and 1-year outcomes after HTx.[143]

In conclusion, women are under-represented in advanced HF therapies, such as left LVADs and HTx. However, the underlying reasons for this phenomenon remain uncertain, and it is unclear whether it stems from selection or referral biases or if certain sex-specific factors may be the primary contributing factors. Additional endeavours are warranted to address the gender-related obstacles in the context of HTx patients.

Spontaneous coronary artery dissection

Spontaneous coronary dissection (SCAD) is an important cause of non-obstructive ischaemic heart disease in young to middle-aged women without traditional cardiovascular risk factors, particularly during pregnancy or the peripartum period.[144] Women comprise 87–95% of all SCAD patients, with the mean age of presentation ranging from 44 to 53 years.[145] SCAD should, therefore, be considered in the differential diagnosis of acute coronary syndromes (ACS) in women. The higher prevalence of SCAD in female patients and the association with pregnancy advocate a pathophysiological role for female sex hormones. The exact nature of this relationship remains to be explained but may relate to sex-hormonal influences on vascular, smooth muscle, and/or the vessel microvasculature.

There are a large number of reported risk factors for SCAD other than female gender: fibromuscular dysplasia, arteriopathy, inflammatory diseases, connective tissue disorders, and emotional or physical stress.

In SCAD, spontaneous non-iatrogenic or trauma-related separation of the coronary wall occurs with the formation of a parietal haematoma within the tunica media that separates the intima from the vessel, resulting in compression of the true lumen and impairment of coronary blood flow.[146] Two mechanisms have been proposed to explain the pathophysiological process. There is an ‘inside-out’ hypothesis where an endothelial-intimal flap develops first, and then blood enters the sub-intimal space from the true lumen. More recently, intracoronary imaging techniques such as optical coherence tomography (OCT) seem instead to better support the ‘outside-in’ hypothesis where medial haemorrhage or rupture of the vasa vasorum within the tunica adventitia results in haemorrhage into the arterial wall and an intramural haematoma.

The gold standard for diagnosing SCAD is coronary angiography. The Yip-Saw angiographic classification divides it into three types.[147] In SCAD Type 1, the contrast penetrates the false lumen, giving a double-lumen appearance. Type 2 is the most common and presents as a long, smooth stenosis. SCAD Type 2 is divided into Type 2A, where the narrowed segment of the coronary artery is followed by segments of normal calibre, and Type 2B, where the stenosis continues to the end of the affected coronary artery. Type 3 mimics focal stenosis of atherosclerotic disease and requires intracoronary imaging to distinguish. OCT is the imaging technique to be preferred because it allows a direct view of the walls of the coronary arteries but carries a certain risk as it can cause the dissection to spread, worsening the patient’s clinical condition.

Management differs from ACS due to atherosclerosis with a first-line conservative approach recommended over percutaneous coronary intervention (PCI). Indeed, the natural history of SCAD appears to be gradual spontaneous healing of the vessel wall within a few weeks in most cases. In contrast, PCI is associated with worse outcomes and high complication rates in this setting. PCI should be performed only in case of ongoing myocardial ischaemia, persistent ST elevation, haemodynamic instability, and refractory ventricular arrhythmias, particularly when left main or the proximal coronary arteries are involved.[144,148,149]

To date, there are no definite indications about medical therapy, and recommendations are based only on expert consensus.[144,148,149] Thrombolysis is contraindicated, and heparin use is discouraged. It is currently suggested single antiplatelet therapy in SCAD unless the patient receives coronary stenting and DAPT is indicated. Nevertheless, DAPT increases the bleeding risk and could theoretically determine the expansion of the intramuscular haematoma and extension of the dissection. Beta-blockers, ACE-I, or ARBs should be administered, whereas since SCAD is not due to atherosclerotic plaque statins, the prescription is controversial.

Takotsubo syndrome

Takotsubo syndrome (TTS) is an acute cardiac syndrome characterized by transient regional ventricular contractile dysfunction in the absence of culprit epicardial CAD that is frequently precipitated by acute emotional or physical stress.[150] Although the precise pathophysiologic mechanism underlying this syndrome remains unknown, enhanced sympathetic stimulation resulting in microvascular dysfunction and/or direct myocyte injury is believed to have a role in the syndrome's pathogenesis.[151] Takotsubo syndrome is not the benign condition it was previously considered to be. To date, it is well recognized that TTS has a heterogenous course with rates of in-hospital mortality reported in literature up to 15% in men and from 1 to 6% in women.[152]

Since its first description in the early 1990s, many case series of TTS described the marked preponderance of women, approximately 90% of cases with a mean age of 65–75 years.[153] The precise reason why older women are more affected remains unknown. It has been suggested that oestrogen depletion following menopause may play a role in the worsening of cardiac microvascular function and in putting post-menopausal women at particularly high risk of TTS during episodes of excessive sympathetic stimulation. However, data on the role of oestrogen in TTS remain conflicting.[154] Although men clearly are the minority of reported cases, from the earliest literature evidence, men seemed to be more affected at younger ages, presented more physiological triggers, and more compromised clinical status at admission.[155] An analysis of age-related variation in TTS reported that the prevalence of male patients increased with decreasing age and was highest in younger patients.[156] These findings are in line with a prior study that suggested males are younger at the time of the index event.[157] Interestingly, the prevalence of cardiogenic shock (CS) and the need for intensive cardiac care treatment, including catecholamine use and non-invasive and invasive ventilation, was particularly high in younger TTS patients. Moreover, younger patients had a numerically higher in-hospital mortality.[156]

A recent analysis of 2492 patients included in the GEIST (German Italian Spanish Takotsubo) registry,[158] confirmed that 11% were men. Men with TTS were significantly younger and with a higher prevalence of comorbidity (diabetes, pulmonary disease, malignancies, smoking habit). A physical trigger was more commonly reported in men (55% vs. 32%, $P < 0.001$), whereas the emotional one was more common in women (39% vs. 19%; $P < 0.001$). Electrocardiogram findings and ballooning pattern were the same in both genders. Men with TTS more frequently presented with CS (19% vs. 8%; $P < 0.001$) and had higher in-hospital mortality (7% vs. 2%; $P < 0.001$). In multivariate analysis, the male sex is an independent predictor of in-hospital mortality, along with age, left ventricular EF, and CS. Male sex remains an independent predictor of long-term mortality.[158]

Hence, based on current observational evidence, it appears that men are less prone to developing TTS compared to women. However, when men do experience TTS, they tend to face more severe complications and a higher mortality rate, as illustrated in *Figure 1*. Gender differences in epidemiology and outcome of TTS may be due to the different susceptibility and the degree of sympathetic stimulation needed to cause the TTS: only mild sympathetic stimulation may need to precipitate TTS in highly susceptible individuals such as post-menopausal women, and strong noradrenergic stimulation may be necessary to precipitate TTS in men who have lower resting sympathetic tone and less microvascular dysfunction, resulting in larger myocardial involvement and a higher incidence of pump failure and mortality.[158] The reason why physical triggers were more frequently reported in male patients, whereas emotional triggers were more common in female patients, could be the consequence of different stress management strategies in men and women.

In patients with TTS presenting with CS, catecholamine, and inotropes should be avoided as they are considered to play a key role in TTS pathogenesis with a substantial risk for left ventricular outflow tract obstruction. In this setting, the use of MCS may represent a valid alternative. Recently a case series of 16 TS patients[159] supported with an Impella pVAD were identified (mean age, 61.8 ± 15.5 years; 87.5% women). Left ventricular ejection fraction at presentation was severely reduced (mean, 19.4 ± 8.3%). Prior to MCS, 13 patients (81.3%) were mechanically ventilated, 4 patients (25.0%) had been resuscitated, and the mean serum lactate was 4.7 ± 3.5 mmol/L. Thirteen patients (81.3%) survived to discharge, and all survivors experienced cardiac recovery with significant improvement of LVEF at discharge compared to baseline (20.4 ± 8.8 vs. 52.9 ± 12.0, $P < 0.001$).

In the absence of evidence-based treatments, patients with TTS continue to have an increased risk of complications, morbidity, and mortality. Sex differences in all these mechanisms remain to be explored. New clinical evidence is needed to guide clinical decision-making and improve the quality of life and outcomes for patients with TTS.

Cardiogenic shock

Cardiogenic shock is a life-threatening syndrome defined by clinical and haemodynamic criteria. The prevalence of CS complicating MI is higher among women than men

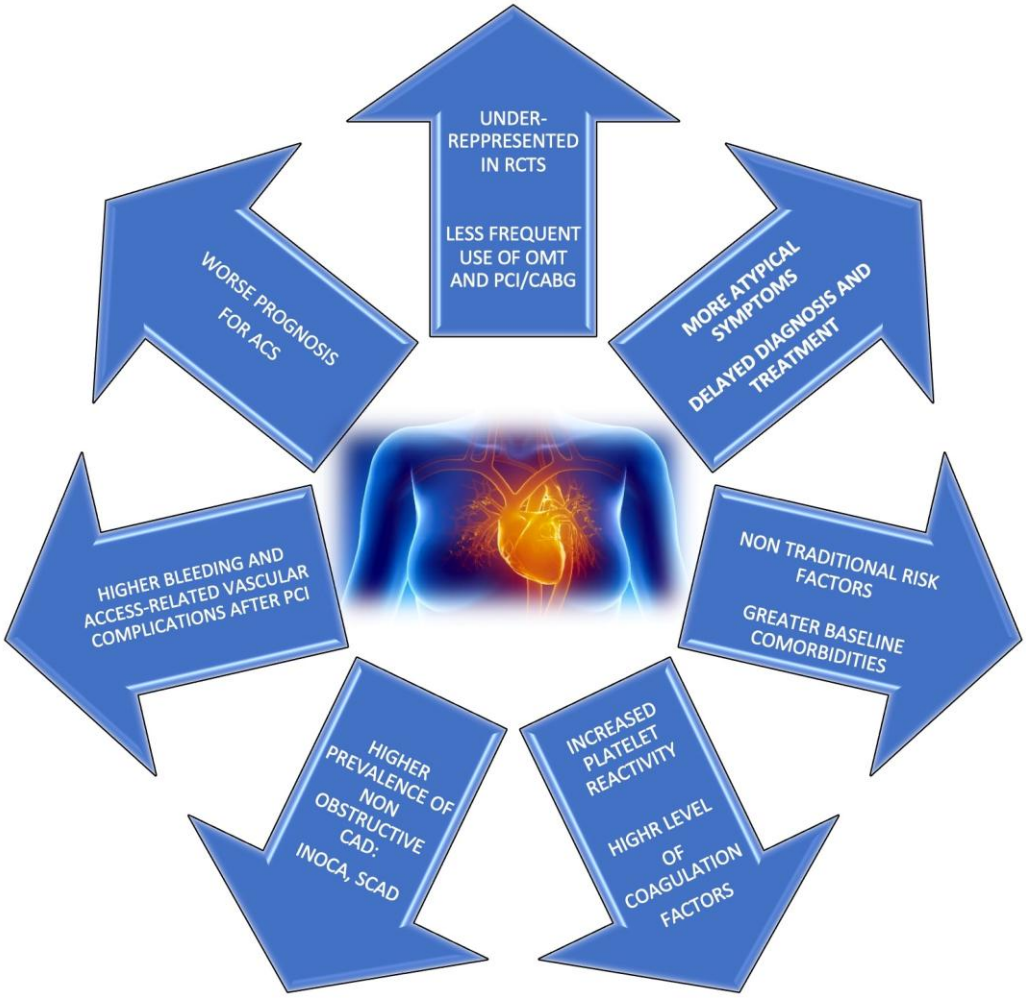

Figure 1 It has been shown that women are largely under-represented in randomized controlled trials (RCTs), leading to inadequate sex-specific analysis and misconceptions about cardiovascular risk in women. This under-representation has significant implications for understanding the effectiveness and safety of treatments in women with acute coronary syndrome (ACS) and other cardiovascular conditions. Optimal medical therapy (OMT) and invasive procedures (PCI/CABG) have been described. Studies have consistently shown that women with ACS are less likely to receive OMT and undergo invasive procedures such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) compared to men. The severity of ACS in women may be underestimated due to atypical symptoms and lower rates of obstructive coronary artery disease (CAD) on angiography. Moreover, women often experience delays in the diagnosis and treatment of ACS, which can result in missed opportunities for initiating OMT and recommending invasive procedures. Women with ACS may exhibit higher levels of certain coagulation factors than men. This difference in coagulation factor levels may contribute to variations in the pathophysiology, presentation, and outcomes of ACS between genders. Here's why women might have higher levels of coagulation factors. Higher levels of coagulation factors in women with ACS may contribute to a prothrombotic state, increasing the risk of thrombotic events such as myocardial infarction and stroke. Understanding these gender-specific differences in the coagulation system is essential for tailoring treatment strategies and improving outcomes in women with CAD. Women are more likely to have conditions such as Ischemia with No Obstructive Coronary Arteries (INOCA) and Spontaneous Coronary Artery Dissection (SCAD). These conditions may present symptoms similar to obstructive CAD but may not be detected by traditional angiography. This can lead to underdiagnosis, delays in treatment, and potentially poorer outcomes if not appropriately managed. CAD, coronary artery disease; INOCA, no obstructive coronary arteries; SCAD, spontaneous coronary artery dissection; ACS, acute coronary syndrome; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.

(11.6% vs. 8.3%, $P = 0.01$) but is still associated with a very high short-term mortality (≈50%).

In the clinical suspicion of CS, patient evaluation has to be fast and multiparametric to establish underlying aetiology and decide the appropriate timing of revascularization and therapy.[160]

The recent SCAI classification stratifies CS in five stages (A to E) from least to greatest severity: data regarding gender-associated differences are still insufficient.

The primary mechanism of acute myocardial infarction complicated by cardiogenic shock (AMI-CS) in women is LV failure, caused by mechanical complications such as ventricular septal or papillary muscle rupture (women 7.7% vs. men 3.5%, $P = 0.003$) and severe mitral regurgitation (women 11.4% vs. men 7.1%, $P = 0.014$).[161]

A large US nationwide analysis of AMI-CS patients (17 195, 37% women) showed that women received less guideline-recommended care and had worse in-hospital outcomes than men.[162]

In the CULPRIT SHOCK Trial, independent predictors for mortality in the AMI-CS female group within 30 days were

older age, no previous PCI, high levels of creatinine, and LAD as culprit vessel.[163]

Medical therapy in CS is based on catecholamines and inotropes/vasopressors with the aim of maintaining mean arterial pressure > 65 mmHg, 8–12 H_2O central VP, SvO_2 > 65%, and diuresis > 70 mL/h. These agents increase myocardial oxygen demand and cardiac afterload, hence the need to confine medical therapy at the shortest duration and the lowest dose, given the array of available mechanical circulatory supports (MCS).

The most common temporary MCS devices available are intra-aortic balloon pumps, micro-axial flow pumps (Impella, Abiomed Inc., MA, USA) and the extracorporeal membrane oxygenator (VA-ECMO).

IABP-SHOCK II trial demonstrated that IABP, compared to medical therapy before revascularization, did not reduce 30-day mortality. IABP is still largely used due to its wide availability, beneficial haemodynamic effects, smaller sheath size and ease of insertion. However, it provides only 0.5 L/min flow.

Impella is a percutaneous ventricular assist device (pVAD) based on a microaxial pump to move blood from the left ventricle to ascending aorta, using a constant axial flow. It can generate up to 5.5 L/min and provides significant unloading of left ventricle.

A recent systematic meta-analysis of six cohort studies comparing VA-ECMO to Impella in AMI-CS patients showed that Impella is associated with more reduction in short and medium term mortality and complication rates without statistical sex differences.[164]

Recent European data on 978 CS patients (295 women) showed that female patients were medically treated but less likely to undergo pLVAD support. A potential reason hypothesized might be physicians' reluctance to implant pLVAD, worried about higher complication risk in females due to their smaller body and thus vessel size, as pLVAD requires a large bore vessel access.[165]

Optimizing pLVAD, for example, by adjusting the inflow cannula design specifically for female patients might reduce device-associated complications.

Anyway, data are promising with the current generation devices.

The RECOVER III registry analyzed sex-based outcomes of 358 AMI-CS patients (82 women) receiving pLVAD pre-PCI: in-hospital adverse events were similar in women and men.

Women had better survival with pre-PCI pLVAD implantation without evidence of increased risk of access-related complications.[166]

The IMP-IT registry (Impella Mechanical Circulatory Support Device in Italy) showed that, among 406 patients, women with CS more frequently presented with other than ST-segment elevation MI aetiologies, including MI with non-obstructive CAD. Early pVAD support initiation pre-PCI was confirmed to be associated with reduced all-cause mortality.[167]

Myocardial revascularization

Cardiovascular disease (CVD) is the leading cause of death in women as well as in men both in Europe and worldwide. Although there was a decrease in the global age-adjusted prevalence of CVD in women between 1990 and 2010, the condition has been rising since 2010, particularly the annual incidence of MI hospitalizations in younger women has increased.[168–171]

Despite the fact that the guidelines for chronic CAD do not differ by sex, women with significant obstructive coronary disease less frequently receive guideline-recommended invasive treatment with PCI. Moreover, females treated with PCI tend to be older than males, with more cardiovascular risk factors.[172] Several studies show that females who undergo PCI for angina have worse short-term major adverse cardiovascular events (MACE) and all-cause mortality than males. However, this may, in part, relate to differences in baseline characteristics.[173–175]

An invasive strategy of early catheterization and revascularization improves the outcome of men with an NSTEMI when compared with a non-invasive approach. However, in women, the benefit of early invasive therapy appears to be more nuanced, as shown by a recent meta-analysis of contemporary trials.[176] Of note, a clear benefit in 6-month outcomes emerged when the subgroup of women with elevated troponin levels was examined. A subsequent meta-analysis of eight trials found that an early invasive strategy had a similar benefit in high-risk (troponin-positive) women as it did in men. Still, that benefit could not be shown for lower risk (troponin-negative) women.[177]

Women with ST-elevation myocardial infarction (STEMI) should be treated similarly to men. Women undergoing primary PCI have had higher rates of in-hospital and longer term mortality than men in both retrospective observational studies and subset analyses of randomized trials.[178,179]

A recent meta-analysis of 35 studies involving 18 555 women and 49 981 men with STEMI treated with primary PCI found that women had higher risk for in-hospital and 1-year mortality even after adjusting for baseline differences and comorbidities, demonstrating the need for further improvements in invasive management in female patients.[180]

Of note, both women and men have experienced improvements in mortality with the advent of modern, second-generation coronary drug-eluting stents.[181]

Lastly, data from DELTA registries show that in women undergoing coronary revascularization for unprotected left main CAD, coronary artery bypass grafting was associated with lower risk of death, MI, or cerebrovascular accidents. In contrast, no significant differences between coronary artery bypass grafting and PCI were observed in men.[182]

Women also have a greater risk of bleeding and peri-procedural complications. Despite the use of smaller sheaths and guiding catheters, their early removal and 'radial first' strategy for arterial access, in-hospital bleeding, and access-related vascular complications after PCI continue to be more frequent in women compared to their male counterparts. Although the increased bleeding risk in females remains a phenomenon not yet fully understood, the use of doses of anti-thrombotic drugs inappropriate for the body's surface area and renal function may partially explain it.[183] The incidence of contrast-induced nephropathy (CIN) after PCI is more frequent among women, partially due to the association with old age, diabetes, and hypertension, but also as an independent factor. Female gender is also a marker of <1-year survival after CIN in patients without pre-PCI chronic renal failure.[184] Moreover, despite a lower in-hospital survival rate, women were less likely to receive mechanical cardiac support such as IABP, Impella, or

ECMO, and the incidence of hospitalization for HF was higher among women during long-term follow-up, especially among patients who had undergone PCI.

Anti-thrombotic therapy

Compared to men, women have an increased platelet reactivity and a hypercoagulable state.[184-186] Moreover, there are several sex-related differences in pharmacodynamics and pharmacokinetics of anti-thrombotic drugs due at least in part to hormonal status but also to different drugs absorption, distribution, and elimination.[184-186]

Aspirin

Despite gender differences in response to aspirin,[187] two meta-analyses have demonstrated that the benefits and the risk of bleeding from aspirin in both primary and secondary prevention of cardiovascular disease were consistent across genders.[188,189]

P2Y12 inhibitors

Clopidogrel

The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial, evaluating the effects of clopidogrel in addition to aspirin in patients with ACS without ST-segment elevation, showed a smaller relative risk reduction in MACE in women compared with men.[190] Comparable results were found in the subgroup of patients who were scheduled to undergo PCI.[191] However, a subsequent meta-analysis of several clopidogrel trials, including about 80 000 patients, showed a similar efficacy and safety of clopidogrel in women and men.[192]

Prasugrel

In TRITON-TIMI 38 (trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Trombolysis in Myocardial Infarction 38) trial, prasugrel reduced MACE as compared with clopidogrel in ACS patients undergoing PCI, despite an increased risk of bleeding. No significant sex-treatment interaction was found despite a higher risk reduction of the primary endpoint with prasugrel in men as compared to women.[193] The TRILOGY ACS (the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial failed to demonstrate the superiority of prasugrel over clopidogrel for the reduction of ischaemic endpoints in medically managed ACS patients, with no significant heterogeneity observed between men and women.[194]

Ticagrelor

The PLATO (Platelet Inhibition and Patient Outcomes) trial showed that ticagrelor was associated with a significant reduction in MACE compared to clopidogrel in patients with ACS intended for an invasive or medical approach.[195] In this study, no significant sex difference has been observed in terms of both ischaemic or major bleeding events between genders.

Intravenous antiplatelet agents

In a pre-specified subgroup analysis of the CHAMPION PHOENIX trial, no differences were observed in MACE between sexes, but the incidence of bleedings with cangrelor was more frequent in females.[196]

Concerning glycoproteins IIb/IIIa inhibitors, two meta-analyses of RCTs demonstrated no significant sex-treatment interaction.[197,198]

Unfractionated heparin/low molecular weight heparin

It has been shown that women are more likely to reach higher activated partial thromboplastin time in response to unfractionated heparin (UFH).[199] On the other hand, a *post hoc* analysis of the TIMI 11A (Thrombolysis in Myocardial Infarction 11A) study showed that neither pharmacokinetics nor pharmacodynamics after enoxaparin administration in ACS patients are affected by sex.[200]

Fondaparinux

In the OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial, fondaparinux reduced major bleeding during long-term follow-up in ACS patients. Notably, women showed a higher reduction of major bleeding with fondaparinux, resulting in a trend for statistical interaction.[201] The risk of the composite endpoint (death, MI, refractory ischaemia, and major bleeding) was reduced in both sexes to a similar degree.

Although sex-based differences in thrombosis and platelet function, current evidence supports comparable benefits of anti-thrombotic therapy between genders. On the other hand, a higher incidence of bleeding has been consistently reported in women. Therefore, pharmacological strategies developed to minimize bleeding risk may be particularly suitable for women.

Dyslipidaemia

Statins and ezetimibe

A gender difference has been found in the achievement of target levels of low-density lipoprotein cholesterol (LDL-C).[202-204] In patients aged 60 years with ACS admitted to a tertiary hospital in Vietnam, i.e. the proportion of participants achieving LDL-C target after 3 months was 40.9% in women and 66.9% in men ($P < 0.001$, adjusted odds ratio, OR, 0.43, 95% CI 0.24-0.78).[204] In a multi-centre cross-sectional survey conducted among patients with dyslipidaemia receiving statin therapy in Spain, LDL-C levels were higher in women than in men (3.5 ± 1.2 mmol/L vs. 3.1 ± 1.0 mmol/L, $P < 0.0001$). Compliance with established goals for LDL-C (39.7% vs. 25.4%, $P < 0.0001$) was superior in men than in women.[203] In 4288 patients with diabetes mellitus with LDL-C >100 mg/dL or taking statins, recruited for the Reasons for Geographic and Racial Differences in Stroke study from 2003 to 2007, LDL-C control was lower for black males and white and black females than for white males [prevalence ratios (95% CI): 0.85 (0.79–0.93), 0.89 (0.82–0.96), and 0.73 (0.67–0.80), respectively, $P < 0.001$].[205]

In a meta-analysis, however, the odds of achieving LDL-C < 100 mg/dL was significantly greater for women vs. men.[202]

This can be due to variances in clinical practice. Women are less likely to receive statins (in particular at high intensity) and/or ezetimibe treatment.[206–214] Some recent data are, however, in contrast, namely in primary prevention.[138,212,215–217] Results of some recent studies on statin/ezetimibe treatment according to gender are shown in *Table 1*.

Adherence to statin/ezetimibe, side effects, and gender

Furthermore, disparities between women and men in medication adherence may influence statin efficacy in cardiovascular prevention.[218] In the VA healthcare system, women with peripheral artery disease (PAD) had lower statin adherence (PDC ≥ 0.8: 34.6% vs. 45.5%, OR 0.75, 95% CI 0.69–0.82) compared with men. Similar disparities were seen in ischaemic cerebrovascular disease (ICVD) patients.[219] Potential reasons for this gender difference can be observed both in intentional and unintentional non-adherence. Notable gender-specific contributing factors for statin non-adherence include decreased provider and patient awareness of cardiovascular risk and higher risk of statin intolerance among women, as well as competing demands associated with family caregiving responsibilities. The sex-dependent impact of adverse side effects is one of the reasons advocated for explaining the gender gap, but it is not evidence-proved. In the Understanding Statin Use in America and Gaps in Patient Education survey, a self-administered, Internet-based questionnaire,[220] more women reported switching or stopping a statin because of side effects compared with men. New or worsening muscle symptoms were reported in 31% of women compared with 26% of men ($P < 0.01$). The safety profile of subjects receiving ezetimibe plus statin was similar to that of patients receiving statin monotherapy and similar between the two sexes.[221] In a meta-analysis, women reported significantly more gallbladder-related, gastrointestinal-related, and allergic reaction or rash-related adverse events vs. men (no differences between statins and ezetimibe). Men reported significantly more creatine kinase elevations (no differences between treatments) and hepatitis-related adverse events vs. women (significantly more with ezetimibe + simvastatin vs. statin).[202]

Lipid-lowering effects of statin/ezetimibe and gender

The effect of statins in reducing cholesterol seems independent of gender. In the VOYAGER study, investigating 32 258 patients, all statins and doses gave significant dose-dependent reductions in LDL-C and non-HDL-C, and increases in HDL-C, in both genders. A 2.1% greater reduction in LDL-C was observed in women compared with men ($P < 0.0001$). However, men experienced a significantly greater increase in HDL-C than women.[222] In a recent meta-analysis,[223] statin therapy reduced after 12 months lipid values in both sexes. Adding ezetimibe to basal statin therapy further reduced total cholesterol, but it was significantly greater in males than in females.[224] In other studies, the enhanced lipid-altering effects of ezetimibe/simvastatin vs. those of simvastatin in patients with primary hypercholesterolaemia were consistent within genders.[225] A *post hoc* analysis of two multi-centre, 6-week, double-blind, randomized, parallel-group trials assessed gender effects on atorvastatin plus ezetimibe vs. up-titration of atorvastatin in hypercholesterolaemic patients. Although some variability existed, gender subgroups did not substantially differ from the entire patient population about lipid-altering findings.[226] In a 16-week, single-centre, prospective, randomized, open-label clinical trial involving 323 patients hospitalized for ACS, the response to atorvastatin and EZE combination was similar for both men and women.[227] In four randomized, double-blind, placebo-controlled, balanced parallel-group trials comparing the efficacy and safety of statin monotherapy vs. ezetimibe 10 mg plus statin, the beneficial effects of ezetimibe were comparable in women and men.[228] Among 18 144 patients in the IMPROVE-IT trial, at 12 months, the addition of ezetimibe to simvastatin significantly reduced LDL-C from baseline compared with simvastatin monotherapy in men and women equally (absolute reduction, 16.7 mg/dL in men and 16.4 mg/dL in women).[221] However, in a meta-analysis of 27 double-blind, active or placebo-controlled studies that randomized adult hypercholesterolaemic patients to statin or statin + ezetimibe, men treated with ezetimibe + statin experienced significantly greater changes in LDL-C ($P = 0.0066$), non-HDL-C, total cholesterol, triglycerides, HDL-C, apolipoprotein A-I (all $P < 0.0001$), and apolipoprotein B ($P = 0.0055$) compared with women.

Treatment with statins/ezetimibe and outcomes

Another question is whether statin/ezetimibe treatment has the same impact on outcomes in both sexes. The small representation of women in clinical trials and the fewer rates of events due to the lower female baseline cardiovascular risk may have conditioned contradictory findings. Most studies evaluating the efficacy of statins have not been powered to compare efficacy between sexes specifically. Aside from a different pharmacological action, statins are not proven to be less effective or less safe in one gender compared to the other. Specifically, the benefits outweigh the disadvantages of statin therapy in women with a high risk, while their role in the primary prevention of cardiovascular disease remains controversial. Among female patients with PAD or ICVD, statin adherence was associated with lower odds of MI (OR 0.76, 95% CI 0.59–0.98), while use of any statin (OR 0.71, 95% CI 0.56–0.91) was associated with lower odds of death at 12 months.[219] In a prospective study conducted at a tertiary medical centre on older adults aged ≥80 years, the all-cause 3-year mortality rates were significantly lower only in women who had used statins compared with women who had not used statins (24.2% vs. 57.1%; RR 0.2; 95% CI 0.1–0.5; $P < 0.0001$). The 3-year cumulative survival rates were significantly higher in women who had used statins as part of primary as well as secondary cardiovascular prevention ($P < 0.0001$ and $P = 0.014$, respectively). A Cox regression analysis showed that statin therapy was independently associated with low 3-year cumulative mortality rates in women (HR 0.3; 95% CI 0.1–0.6; $P = 0.001$).[229] In 2088, consecutive patients discharged from 5 local community hospitals with a definite diagnosis of HF, statin prescription, and adequacy of dosing were associated with 35 and 44% decreases in the risk of 1-year mortality, respectively, irrespective of

gender. A nested case/control analysis confirmed that adequate statin dose was associated with 48% lower 1-year mortality, again without interaction with gender.[210] Finally, a recent large meta-analysis of both primary and secondary prevention with sex-specific outcomes on data from 22 trials of statin therapy vs. control ($n = 134\,537$) and five trials of more intensive vs. less intensive statin therapy ($n = 39\,612$) showed that the proportional reductions per 1.0 mmol/L reduction in LDL-C in major vascular events were similar in women (RR 0.84; 99% CI 0.78–0.91) and men (RR 0.78; 99% CI 0.75–0.81), both overall and among those at <10% predicted 5-year risk. Likewise, the proportional reductions in major coronary events, coronary revascularization and stroke did not differ by gender. Since there were similar proportional reductions in vascular mortality in women (RR 0.92; 99% CI 0.82–1.03) and men (RR 0.87; 99% CI 0.82–0.92) but no apparent effect on non-vascular deaths in either sex, all-cause mortality was reduced in both women (RR 0.91; 99% CI 0.84–0.99) and men (RR 0.90; 99% CI 0.86–0.95).[223]

In the IMPROVE-IT trial, women receiving ezetimibe/simvastatin had a 12% risk reduction over those receiving placebo/simvastatin for the primary composite end point (HR 0.88; 95% CI 0.79–0.99) compared with a 5% reduction for men (HR 0.95; 95% CI 0.90–1.01; $P = 0.26$ for interaction). When the total number of primary events was considered, women had an 18% reduction with the addition of ezetimibe (RR 95% CI 0.81; 0.71–0.94), and men had a 6% reduction (RR 0.94; 95% CI 0.87–1.02; $P = 0.08$ for interaction).[221]

In hypercholesterolaemic patients with co-existing polycystic ovary syndrome, simvastatin decreased serum levels of total testosterone (23%, $P < 0.001$), free testosterone (32%, $P < 0.001$), androstendione (20%, $P < 0.01$), and dehydroepiandrosterone sulphate (17%, $P < 0.05$), as well as tended to reduce the luteinizing hormone/follicle-stimulating hormone ratio (23%, $P = 0.095$), whereas ezetimibe only insignificantly reduced serum levels of free testosterone (14%, $P = 0.098$).[220]

Proprotein convertase subtilisin kexin Type 9

Proprotein convertase subtilisin/kexin Type 9 (PCSK9) is a key regulator of cholesterol metabolism and increases plasma LDL-C levels by triggering the degradation of LDL receptors. Proprotein convertase subtilisin kexin Type 9 also has direct atherosclerotic effects on the vascular wall and is associated with coronary plaque inflammation. Thus, high PCSK9 concentrations are associated with an increased risk of cardiovascular disease. Interestingly, emerging data show that women have higher circulating PCSK9 concentrations than men, suggesting that the potential roles of PCSK9 may have different impacts according to sex.[230] In a large European cohort of individuals ($n = 3673$, aged 54–79 years) free of cardiovascular diseases enrolled in seven centres of five European countries: Finland, France, Italy, the Netherlands, and Sweden, PCSK9 plasma level was higher in women than in men.[231] Another study among Thai subjects confirmed that PCSK9 concentrations were significantly higher in women than in men ($P = 0.002$).[232]

PCSK9 concentrations were also significantly higher in post-menopausal women than in pre-menopausal women ($P < 0.001$), and in post-menopausal women with metabolic syndrome than in pre-menopausal women without ($P < 0.001$).[232]

Circulating PCSK9 represents a valid pharmacological target for preventing cardiovascular events. New medications such as PCSK9 inhibitors have shown significant results in treating hyperlipidemia. Alirocumab and evolocumab were approved for lowering LDL levels in patients with familial hyperlipidemia and those with high atherosclerotic cardiovascular disease risk. These life-altering drugs are, however, still limited in use because of their difficulty in accessing, as public and private insurers have set up administrative obstacles (formulary exclusions and prior authorizations) to offset the high costs. By 2017, only two in five eligible patients were approved for PCSK9 inhibitors.[233] Thus, it is likely that women might be discriminated in PCSK9 inhibitors prescription. According to data from 374 786 adults ≥ 66 years of age with US Medicare fee-for-service coverage who had a MI between 2015 and 2018, were not taking ezetimibe or a PCSK9 inhibitor, and had[217] very high cardiovascular risk, overall, only 1433 (0.4%) beneficiaries initiated a PCSK9 inhibitor. Adjusted hazard ratios (aHRs) for PCSK9 inhibitor initiation comparing women to men were 1.11 (95% CI: 1.06–1.17) and 1.13 (95% CI: 1.01–1.25), respectively. This seems to indicate the lack of significant difference between genders for PCSK9 initiation. However, a systematic review including 20 articles demonstrated that women were less likely to receive the correct, clinically indicated therapy for hyperlipidemia.[234]

Multiple studies were performed on these drugs to illustrate their effectiveness in both genders. Available evidence indicates that women derive a similar benefit as men from secondary prevention pharmacological therapies with PCSK9 inhibitors.[235] In the FOURIER trial, the LDL-C reduction with evolocumab at four weeks was nominally greater in men than women, but the relative risk reductions in the primary endpoint and key secondary endpoint were similar in women [0.81 (0.69–0.95) and 0.74 (0.61–0.90), respectively] compared with men [0.86 (0.80–0.94) and 0.81 (0.73–0.90), respectively].[236] Consistently, the preliminary results of the ODYSSEY OUTCOMES trial comparing alirocumab with control (placebo/ezetimibe) showed that the relative risk reductions for the primary composite endpoint were broadly similar in women and men (9 and 17%, respectively).[237] Besides, from data pooled from 10 phase 3 ODYSSEY randomized trials ($n = 4983$), overall, 36.5 and 58.7% of women and men, respectively, achieved on-treatment LDL-C < 50 mg/dL. Each 39 mg/dL lower LDL-C was associated with a 33 and 22% lower risk of MACE in women ($P = 0.0209$) and men ($P = 0.0307$), respectively, with no significant between-sex difference.[238] In the real world, however, a multi-centre and retrospective study of 652 patients initiating treatment with any PCSK9 inhibitor in 18 different hospitals showed that on-treatment LDL-C was higher in women, and the mean LDL-C reduction was lower in women (47.4% vs. 56.9%; $P = 0.0002$) receiving evolocumab or alirocumab. The percentage of patients who achieved ≥50% LDL-C reduction was higher in men (71.36% vs. 57.62%; $P = 0.002$, OR: 0.31).[239]

As regards safety issues, in the FOURIER trial adverse events were more common in women but, with the exception of injection site reactions, there were no

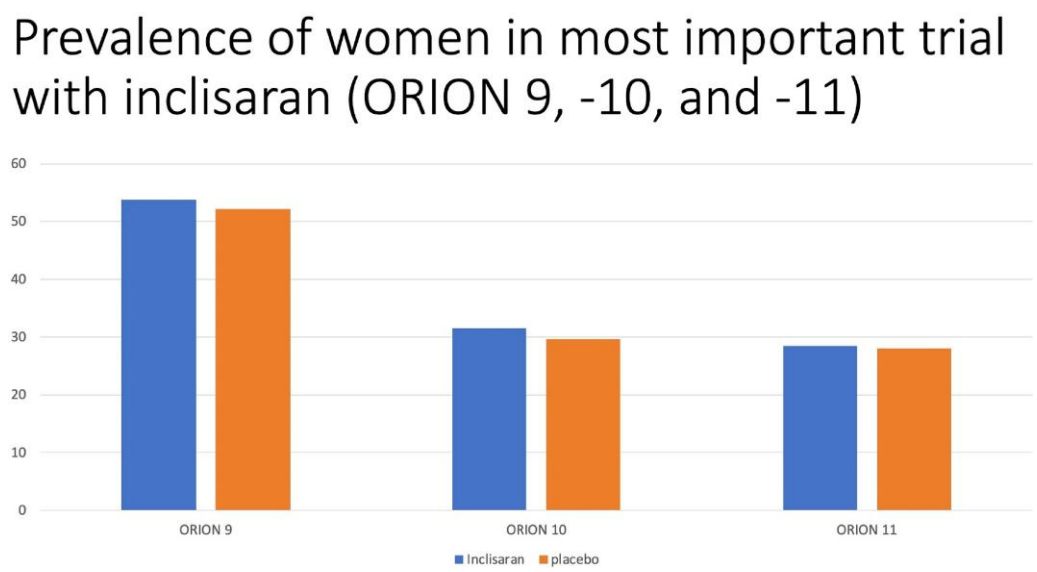

Figure 2 The figure represents the prevalence of females in the ORION 9, -10, and -11 studies.

important significant differences reported by those assigned evolocumab vs. placebo.[236] In ODISSEY trials, alirocumab was generally well tolerated in both sexes.[238]

Inclisiran

Inclisiran is a first-in-class small interfering RNA targeting the mRNA of PCSK9 specifically in the liver, owing to the conjugation with triantennary *N*-acetylgalactosamine.[240] The main advantage over conventional pharmacotherapy and anti-PCSK9 monoclonal antibodies is its favourable administration regimen, with a subcutaneous dosing schedule of once every six months after the initial and 3-month doses (0–90–180 days), which should lead to much better compliance.[241,242]

Clinical trials conducted so far have confirmed the tolerability and efficacy of inclisiran in long-term robust and durable reductions of PCSK9 and LDL-C level. Inclisaran has been studied in the ORION clinical development programme, consisting of some Phases 2 and 3 RCTs, some of which have been completed.[241]

ORION-1 was a Phase 2 trial assessing 6 different inclisiran dosing regimens vs. placebo, evaluating 501 participants with atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk and elevated LDL-C despite receiving maximally tolerated statin therapy received a single-dose (200, 300, or 500 mg) or 2-dose starting regimen (100, 200, or 300 mg on Days 1 and 90) of inclisiran or placebo.[243-245] Inclisiran was associated with marked declines in LDL-C.[243-245] This trial allowed us to establish that 300 mg on Day 1 and Day 90 and then every 180 days was the best dose regimen to be adopted. Inclisiran, besides had an adverse profile like that of placebo. Among ORION-1 participants, 35% were females.[246]

Participants with heterozygous familial hypercholesterolaemia (482 patients) [ORION-9 (Trial to Evaluate the Effect of Inclisiran Treatment on LDL-C in Subjects With Heterozygous Familial Hypercholesterolaemia)], ASCVD (n = 1561) [ORION-10 (Inclisiran for Participants With ASCVD and Elevated LDL-C)], or ASCVD and ASCVD risk equivalents (n = 1671) [ORION-11 (Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated LDL-C)] taking maximally tolerated statin therapy, with or without other LDL-C–lowering agents, were randomly assigned in a 1:1 ratio to receive either inclisiran or placebo.[247] A pooled analysis, involving ORION-9, -10 and -11 trials, showed the superiority of inclisiran vs. placebo, i.e. LDL-C was lowered at Day 510 by 50.7% (95% CI: 52.9–48.4%; $P < 0.0001$).[247] See *figure 2* shows the prevalence of women in these trials.

The results of the ORION-4 trial will provide definite evidence of the effects of Inclisiran on the reduction of major cardiovascular events (MACE). Awaiting these results, in a pre-specified exploratory endpoint of MACE including non-adjudicated CV death, cardiac arrest, non-fatal MI, and fatal and non-fatal stroke, among 3655 patients of ORION-9, -10 and -11 trials, over 18 months, 303 (8.3%) experienced MACE, including 74 (2.0%) fatal and non-fatal MIs, and 28 (0.8%) fatal and non-fatal strokes. Inclisiran significantly reduced composite MACE [OR (95% CI): 0.74 (0.58–0.94)], but not fatal and non-fatal MIs [OR (95% CI): 0.80 (0.50–1.27)] or fatal and non-fatal stroke [OR (95% CI): 0.86 (0.41–1.81)].[244]

These effects are consistent in different categories of patients, although published data focused specifically on women are lacking.[242] This drug should not be used in pregnancy and may not be safe in breastfeeding.

Bempedoic acid

Bempedoic acid (BA) is a first-in-class, small oral molecule, which reduces plasma LDL-cholesterol by inhibiting the enzyme adenosine triphosphate-citrate lyase (ACL).[248] Adenosine triphosphate-citrate lyase is involved in the cholesterol synthesis pathway by acting upstream of the hydroxy-methylglutaryl coenzyme A reductase. BA is administered orally once daily as a single dose of 180 mg. Bempedoic acid is a prodrug and

must be converted to the active bempedoyl-CoA by the enzyme very-long-chain acyl-CoA synthetase-1 (ACSVL1). ACSVL1 is expressed only in the hepatocytes; the activity of BA, therefore, is limited to the liver and, unlike statins, should not cause muscle-related adverse events.[249] Bempedoic acid is rapidly absorbed in the small intestine and has a half-life of 15–24 h. Food does not affect its oral bioavailability nor its pharmacokinetic properties by age, sex, race, or weight.

The efficacy of BA has been tested in the wide clinical CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) programme, which enrolled 3621 patients with heterozygous familial hypercholesterolaemia and/or atherosclerotic cardiovascular diseases in 4 Phase III RCTs (CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity and CLEAR Tranquility). Overall, the LDL-C was reduced from baseline to week 12 by 17.8% (placebo corrected, 95% CI, −19.5% to −16.0%; $P < 0.001$) among individuals receiving a maximally tolerated statin and by 24.5% (placebo corrected, 95% CI, −27.8% to −21.1%; $P < 0.001$) among those with statin intolerance. The reduction in LDL-C levels with BA was sustained during long-term follow-up in both groups of patients. On the other hand, BA is very well tolerated with very few adverse events that did not differ when compared to placebo, except for a slight increase in serum uric acid levels (2.1% and 0.5% and $P = 0.001$), a greater incidence of gout (1.4% vs. 0.4%, $P = 0.008$)[250] and a higher risk of tendon rupture (0.5% vs. 0%). According to Mendelian randomization studies[251] and based on its pharmacokinetic and pharmacodynamic characteristics, BA is an excellent add-on therapy to all the current lipid-lowering treatments. Bempedoic acid reduced LDL-C by 38% (placebo corrected) when combined with ezetimibe[252] and by 60% (placebo corrected) together with ezetimibe and atorvastatin 20 mg.[252] Furthermore, BA lowered LDL-C by an additional 30.3% when added to a background PCSK9i therapy.[253] Finally, it is noteworthy that, according to the preliminary announcement, BA reduces the risk of major cardiovascular events in high-risk patients with statin intolerance during an expected median duration of 3.5 years in the Phase III CLEAR Outcomes trial.

So far, gender-related differences in BA efficacy/safety are scant. To identify potential clinical factors associated with enhanced LDL-C lowering with BA, a *post hoc* analysis from pooled data of the CLEAR Harmony, the CLEAR Wisdom, the CLEAR Serenity and the CLEAR Tranquility studies has been performed.[254] Patients randomized 2:1 to once daily BA 180 mg ($n = 2321$) or placebo ($n = 1167$) for 12–52 weeks were grouped based on percent change in LDL-C from baseline to week 12. Multiple logistic regression analyses identified several factors associated with increased rates of achieving ≥30% LDL-C reduction with BA. Among these, younger age, baseline LDL-C, non-statin use, history of diabetes, ezetimibe use, baseline body mass index, high-sensitivity C-reactive protein (hsCRP) level and female sex. In particular, being female was associated with the probability of achieving at least a 30% reduction in LDL-C of >60% compared to males (OR 1.643, 95% CI 1.365–1.978; $P < 0.0001$). After adjusting for covariates, female sex remained statistically associated ($P = 0.0096$) with an enhanced LDL-C lowering with BA compared to males. This result could be the consequence of the higher total atherogenic lipoprotein burden in middle-aged women compared to men, to the higher experiencing of statin intolerance or to the fact that women are less likely to be treated with any statin or guideline-recommended statin intensity than men. In other words, the particular benefit of BA in women was not related to the female sex *per se*, but because women are often under-treated or unable to tolerate statins and at higher risk for cardiovascular disease.

A deeper evaluation of the efficacy and safety of BA in women vs. men, using the same pooled data from the CLEAR programme, can be obtained from a previous communication at the 2020 American Heart Association Scientific Sessions.[254] According to the data presented, among the 3621 (2424 in the BA group and 1197 in the placebo) patients included in the analyses (separated by background statin and study length) 34.3% were women ($n = 1242$) with a higher proportion of women in the statin-intolerant pool (58.4%) compared with the ASCVD and HeFH on statins pool (29.4%). Baseline demographics were generally comparable between the sexes, while baseline lipid levels and hsCRP concentrations were slightly higher in women compared with men (*Table 1*). After 12 weeks of treatment, BA significantly lowered LDL-C in both sexes: the placebo-corrected difference was −21.2% (95% CI, −24.8 to −17.5; $P < 0.001$) and −17.4% (95% CI, −19.2 to −15.5; $P < 0.001$) in on-statin pool and −27.7% (95% CI, −32.1 to −23.2; $P < 0.001$) and −22.1% (95% CI, −26.9 to −17.2; $P > 0.001$) in statin-intolerant group, for women and men, respectively. The P per interaction values for treatment by sex subgroup resulted in significant ($P = 0.044$) for the on-statin pool or borderline significant ($P = 0.079$) in the statin-intolerant group, suggesting an enhanced response in females compared to males. As far as safety is concerned, common treatment-related adverse events occurred at similar rates in both sexes. There was a higher incidence of urinary tract infection (8.0% vs. 2.7% in BA group; 10.3% vs. 3.0% in placebo group), headache (4.1% vs. 2.1% in BA group; 4.8% vs. 2.2% in placebo group) and pain in extremity (4.2% vs. 2.6% in BA group; 2.9% vs. 1.6% in placebo group) in women compared to men both in BA and placebo groups, but rates of special adverse events, such as new onset diabetes/hyperglycemia, hepatic enzyme elevations, muscular disorders, CPK elevation neurocognitive disorders, renal disorders, uric acid elevations/gout, anaemia, were generally similar between the sexes, in both treatment arms and both in on-statin and in-statin intolerance pools. Women were slightly more likely to discontinue the study drug treatment compared to men, but the difference could not be attributed to any specific adverse events.

In conclusion, BA seems well tolerated in both sexes and marginally more effective in women compared to men. However, the reason remains unclear and will require further investigation in the real-world setting.

Atrial fibrillation

Several studies have been published on gender differences in the pathology and treatment of cardiovascular diseases.[255–257] However, there are only a few specific studies aimed at investigating gender differences and anti-arrhythmic drugs. A few studies, both in Western and Asian patients, showed that female AF patients are

usually older than male ones, and they often present more severe AF-related symptoms.[258] Nevertheless, they usually received more conservative treatments (e.g. female patients received less anti-arrhythmics, less cardioversion, and less radiofrequency catheter ablation).

Anti-arrhythmic medications remain a keystone treatment for cardiac arrhythmias. While the efficacy of Class I and Class III anti-arrhythmic drugs appear to be similar, the risk of adverse effects, most notably drug-induced pro-arrhythmic, is much higher for the latter.

A well-known meta-analysis of 93 articles[259] showed that women are more likely to develop torsade's de pointes (TDP) during the administration of anti-arrhythmic drugs that prolong cardiac repolarization (including drugs: quinidine, procainamide, disopyramide, amiodarone, sotalol, bepridil, and prenylamine). An important sub-analysis of the Rate Control vs. Electrical Cardioversion (RACE) study,[260] including 192 females out of 522 patients, showed that severe adverse effects of anti-arrhythmic drugs occur more frequently in women than men; however, as the numbers were small, this should be confirmed through larger trials. In this respect, it should be noted that a gender difference was not observed in the AFFIRM study,[261] nor in the 1330 patients enrolled in the Stroke Prevention in Atrial Fibrillation Study.[262,263]

One must also consider the different hormonal levels during the different phases of a woman's life.[264] Safety Phase I studies usually enrol young and healthy volunteers. This population has a rather different hormonal profile than the men and (post) menopausal women who often receive treatments for AF. A female patient could react variably to an anti-arrhythmic drug in different phases of her life based on hormonal levels. In case of a drastic change in hormonal profile (e.g. menopause), the patient should be re-evaluated.

A recent consensus document of the European Society of Cardiology gathers evidence from the available literature suggesting that Class IA and Class III anti-arrhythmic drugs present a higher risk of acquired long QT syndrome and, consequently, torsades de pointes. To avoid the risk of such a severe complication, the European Society recommended carefully monitoring the QT interval and potassium levels, especially in the first weeks after drug intake. The use of potassium antagonist drugs is dangerous, and they should be used with caution in all patients taking Class IA and Class III drugs. This is particularly crucial for women as they showed additional risk factors for TDP. In case of bradycardia-like symptoms, such as dizziness or newly onset palpitations, an ECG and/or 24-h Holter monitoring is recommended, as the risk of TDP is higher during bradycardia. An ECG monitoring should also be performed a few weeks after any dosage increment.

Class IA and Class III antiarrhythmic drugs-induced torsades de pointes is due to the inhibition of IKr encoded by the hERG gene.[265] Oestrogens are known to prolong the repolarization and, consequently, the QT interval, via the inhibition of IKr and enhancement of Ica, L channels. Therefore, they increase sensitivity to QTc prolongation from additional IKr-blocking agents. Moreover, they present a specific IKr and hERG-blocking action. *Table 1* reports gender differences for different anti-arrhythmic drugs. To the best of our knowledge, increased risk of TDP in female patients has not been reported for anti-arrhythmic drugs of IC class (e.g. propafenone and flecainide).

In order to provide meaningful gender-specific analyses, it is important that future studies reverse the trend of disparity between male and female-enrolled patients shown in previous trials.[266]

Ablation of AF

AF ablation is the first-line therapy for symptomatic AF patients who fail medical therapy.

Female patients are widely under-represented in RCTs of AF ablation: 29% of patient[267] in the ADVICE trial and 39% in the Fire and ICE trial[268] for paroxysmal AF, and only 19% in the STAR AF II[269] for persistent AF. Catheter ablation seems to be widely underused in the female gender, probably due to the reluctance of female patients to receive invasive treatment, fear of complications, and doubts about outcomes,[270] but the reasons are complex and may differ between countries.

Women underwent ablation less than men. The German Ablation Registry[271] stated that women represented only 33% of the cohort and presented more often paroxysmal than persistent/long-standing AF (72% vs. 28% in women, 61% vs. 39% in men). Furthermore, women referred for ablation were older than men and had less CAD and hypertension.

There is wide evidence that procedure times and energy application duration are shorter in women than in men[270] because of the smaller atrial volume and the thinner left atrial wall that could make transmural lesions easier to achieve.[272,273]

Most studies showed that female sex is a predictor of less favourable outcomes in paroxysmal and persistent AF ablation.[272-274] In the German Ablation Registry, women experienced higher AF recurrence rates and less beneficial outcomes in spite of more favourable prognostic factors (higher rates of paroxysmal AF and less reduced LV function).[272]

Women tend to have less favourable outcomes from pulmonary vein isolation, and these results probably reflect a higher prevalence of non-PV foci in women than in men.[275]

Possible explanations are the more advanced atrial substrate in older female patients enrolled in trials and the higher rates of complications compared to men. Probably for this reason, in case of AF recurrences, women were less inclined to undergo a second procedure.

Prior studies suggested that the female gender is a risk factor for complications of AF ablations (with OR varies from 1.39 to 1.48).[276-278]

Female patients are associated with the worst risk profile for complications as older age, higher rate of persistent AF, and longer duration of AF.

In particular, women tend to experience more bleeding, pericardial effusion, and vascular complications.[272] The cause may be the close location or overlap of groin vessel branches and smaller vessel size.[279,280] A smaller left atrium may also make intra-cardiac catheter movements difficult. In addition, sex-related differences in heparin pharmacokinetics should be evaluated, leading to higher ACT.[281]

For these reasons, a careful clinical evaluation[272] is mandatory before ablation in order to reduce the incidence of complications.

Female patients are widely under-represented in RCTs on AF ablation. The women represented only the minority of the AF ablation cohort, and catheter ablation seems to be widely underused in the female gender with paroxysmal and persistent AF. Although the procedure times and energy application duration are shorter in women than in men, female patients experienced higher AF recurrence rates and higher rates of complications.

Further studies are needed to understand the causes of these discrepancies. Meanwhile, new technologies, such as a smaller catheter with contact force, intra-cardiac echo, and echo-guided venous access, can help us to reduce this kind of complications.

Valvulopathies

The impact of sex on pathophysiology, clinical presentation, and outcomes in degenerative aortic stenosis (AS) still remains poorly defined.[282,283] In contrast with RCTs on CAD, which enrol only 25% of women, female patients are well represented in the transcatheter treatment of severe AS, both in national registries and clinical trials. A higher benefit with transfemoral aortic valve implantation (TAVI) compared with surgical treatment was apparent in women compared with men.[284]

The prevalence of symptomatic severe AS in patients over 75 years (4%) is similar in women, and in men. Notably, under-diagnosis and under-treatment of severe AS in women may be due to more common paradoxical low flow-low gradient disease in elderly females.[285]

Due to a low body surface area and smaller peripheral vessel diameter, women may experience a higher rate of bleeding complications after TAVI.[282] In the combined cohorts of the PARTNER (Placement of Aortic Transcatheter Valves) II SAPIEN 3 (S3) (Edwards Lifesciences) trial, female sex emerged as an independent predictor of major vascular complications, whereas 30-day mortality and stroke were similar in women and in men[286] A higher rate of vascular complications in female patients was demonstrated in two meta-analysis, which also showed a higher rate of stroke in women.[287,288]

The WIN-TAVI (Women's INternational Transcatheter Aortic Valve Implantation) registry was a multinational, prospective, observational registry of women undergoing TAVI for AS witch enrolled over 1000 women.[289] The primary endpoint was the Valve Academic Research Consortium (VARC)-2 early safety endpoint at 30 days (composite of mortality, stroke, major vascular complication, life-threatening bleeding, stage 2 or 3 acute kidney injury, coronary artery obstruction, or repeat procedure for valve-related dysfunction). The 30-day VARC-2 composite endpoint occurred in 14.0% with 3.4% all-cause mortality, 1.3% stroke, 7.7% major vascular complications, and 4.4% life-threatening bleeding. The impact of small valve size on clinical outcomes after TAVI in women was also evaluated at 1-year follow-up (Impact of Small Valve Size on 1-Year Outcomes After Transcatheter Aortic Valve Implantation in Women (from the WIN-TAVI Registry).[290] Women were stratified into small (≤23 mm) and non-small (>23 mm) valves, and no difference in terms of all-cause death, stroke, MI, hospitalization for valve-related symptoms or HF, or valve-related dysfunction at 1-year follow-up were found.

Data addressing the sex-related differences in transcatheter treatment of mitral regurgitation are limited. The randomized COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial demonstrated that selected patients with HF and moderate-to-severe or severe SMR treated with transcatheter mitral valve repair (TMVr) with the MitraClip (Abbott) and concomitant guideline-directed medical therapy (GDMT) had significantly lower rates of HFH and death at 2 years compared with GDMT alone.[291]

Among 614 patients (36.0% of females), women were younger and more frequently non-Caucasian, more frequently had non-ischaemic cardiomyopathy, and less frequently had histories of coronary artery disease, MI, previous coronary revascularization, atrial or ventricular arrhythmias, renal dysfunction, and hypercholesterolaemia.[292] Left ventricular end-systolic and end-diastolic volume indices were smaller in women compared with men at baseline, although the LVEF did not differ between sexes. Women had lower right-ventricular systolic pressures but more frequently had moderate-to-severe or severe tricuspid regurgitation. Number of MitraClip devices implanted and procedure duration were lower in women compared with men. Site-reported reduction MR was similar in both groups. The postprocedural duration of hospitalization was longer in women than men. TMVr with the MitraClip resulted in improved clinical outcomes compared with GDMT alone, irrespective of sex. However, the impact of TMVr in reducing HFH was less pronounced in women compared with men beyond the first year after treatment. The change in functional capacity from baseline to 1 year, as evaluated by 6MWD, was superior in MitraClip-treated patients compared with those treated with GDMT alone, irrespective of sex. Notably, in the MITRA-FR trial, only 32 women were randomized to the interventional arm.[293]

In a recent meta-analysis including 24 905 patients (45.6% women), women were older and had a lower prevalence of comorbidities, such as diabetes, chronic kidney disease, and CAD. There was no difference in procedural success and short-term mortality (i.e. up to 30 days) between women and men. Women had a higher incidence of peri-procedural bleeding and stroke. At a median follow-up of 12 months, there was no difference in mortality and HF hospitalizations.[294]

Cancer treatments and cardiovascular toxicity

Differences between men and women have been pointed out also in adverse drug responses to anti-cancer treatments.[295]

Anthracyclines represent the cornerstone for the treatment of many solid and haematological cancers; among patient-related risk factors for cardiac toxicity, female sex deserves special consideration together with age. For young girls who survived cancer in paediatric

age, cardiotoxicity risk is greater than male childhood cancer survivors when anthracyclines were delivered. Both decline in left ventricular function and congestive HF were more frequent in females than in men survivors of childhood cancer[296-298] even if these observations were not confirmed in a large cohort study.[299] Though post-menopausal women appear to be equally susceptible to cardiotoxicity as men, studies analyzing sex-related differences in cardiac side effects in the adult cancer population revealed that the male sex has an increased risk for cardiovascular events. These differences could be explained (at least in part) by the presence of pre-existing cardiac conditions.[300] There are not any good explanations for why cardiac toxicity from anthracyclines varies by gender. Some theories on the role of female hormones in oxidative stress and mitochondrial dysfunction have been put forth (both pathways are believed to be involved in the genesis of cardiac damage from doxorubicin).[301,302] Finally, it is impossible to rule out the possibility of pharmacokinetic variations between male and female patients.[303] The female sex appears so to be protective in adult fertile women but is associated with a risk for anthracycline cardiotoxicity in individuals with paediatric cancer. Cancer patients who are post-menopausal share the same risk for cardiac toxicity as elderly males.

The second main anti-cancer therapeutic category with a documented sex-related issue in cardiovascular toxicity is radiation-associated cardiac disease (RACD); RACD is an umbrella term that encompasses myocardial fibrosis with a probable evolution in myocardial dysfunction and congestive HF, pericarditis, valvular heart disease, conduction anomalies, and vascular disease including CAD.[304] After thoracic RT, CAD is the most common cardiotoxic phenotype, and this is the moment at which sex becomes a problem. In male patients with CAD, the epicardial coronary arteries are primarily affected, whereas in female individuals, the microvascular circulation is most affected. These variations will manifest also as the CAD phenotype of RACD.[305,306] Patients with lymphoma and those who have lung malignancies are the best candidates for studying sex-related changes in RACD. Breast cancer, a disease researched almost entirely in the female gender, cannot be reliably compared for cardiotoxicity between male and female patients. Male and female mice were subjected to localized radiotherapy in a recent pre-clinical study to examine the molecular underpinnings of sex-specific differences in toxicity; female mice displayed increased tolerance to radiotherapy, and this cardioprotective effect was shown to be oestrogen-dependent.[307] Unfortunately, in the clinical setting, very few compared RACD in male patients and female patients. In a meta-analysis on 13 975 patients, a 4-fold increased rate of cardiovascular events in women was observed following radiation therapy for Hodgkin lymphoma with modern techniques. There hasn't been a thorough justification for this disadvantage of female patients in RACD.

Sex and gender differences in cardiac toxicity for other anti-cancer drug classes are less clear. In particular, immunotherapy toxicity profiles for men and women seem to differ, but no firm conclusions can be made.[295] Female patients may be at higher risk of ICIs-related myocarditis, albeit this has not been proven consistently.[303,308]

In conclusion, while more data suggested that sex plays a role in predicting the side effects of anti-cancer treatments for anthracyclines and RACD, the sex relationship for all new anti-cancer drug classes (in particular immunotherapy) has yet to be fully explored.

Targeted therapeutic choices in cardiovascular rare and orphan disorders

The European Union defines a disease as rare if it affects fewer than 1 in 2000 people within the general population. In 2020, the Orphanet database contained information on 6172 unique rare diseases, 71.9% genetic and 69.9% exclusively paediatric onset.[309] Few rare diseases are preventable or curable, and most of them currently have no effective treatment and result in early death.[310]

Gender discrepancy for rare diseases starts early since women tend to be diagnosed later than men. As a result of delayed diagnosis, the uptake of appropriate treatment and care is also deferred. This often leads to a rapid progression of the disease, severely impacting the quality of life, socio-economic status, and mental health.[311]

Among the rare diseases affecting the heart, Fabry disease and, more recently amyloidosis could be specifically treated with a disease-modifying therapy.

Fabry disease is an X-linked rare disease due to the deficit of the enzyme alpha galactosidase A,[312] determining the reduced catabolism of neutral glycophingolipids in the lysosomes of different organ or tissue. In the heart, it results in an increase in left ventricular wall thickness and diastolic dysfunction. The X-linked nature of the disease leads to a different involvement in female patients, ranging from pauci-symptomatic to severely affected women, according to the skewed X-linked inactivation.[312]

It is now evident that up to 70% of heterozygous females may exhibit clinical manifestations, and Fabry disease cardiomyopathy has been described in up to 12% of females with late onset hypertrophic cardiomyopathy.[313]

In affected women, as in males, the severity of the disease increases with age.[314]

Enzyme replacement therapy and chaperone treatment aim to replace the deficient enzyme and to stabilize residual enzymatic activity if present. Most of the studies on the long-term efficacy of the treatments included women. Globally, it appears that disease-modifying treatments can stabilize the disease and prevent its progression either in men or in women. An important grey zone is related to the timing of starting treatment in women. It is actually recommended to initiate therapy as soon as clinical signs appear.[315] Further studies may clarify the benefit of early treatment also in females before the disease became clinically evident.

Cardiac amyloidosis is characterized by the deposition of amyloid fibrils in the heart, causing an increase in wall thickness. Amyloid proteins can be mostly immunoglobulin amyloid light chain (AL) or amyloid transthyretin (ATTR). A left ventricular wall thickness $\geq$12 mm plus at least one red flag should raise suspicion of cardiac amyloidosis.[316] As normal values of LV wall thickness are lower in women, the adoption or the same cut-off values for men and women could lead to under-diagnosis or delayed diagnosis in women[317] and justify the more frequent detection of the

disease in males. A recent study aimed to characterize sex differences among consecutive patients with non-hereditary and two prevalent forms of hereditary TTR amyloidosis diagnosed over a 20-year period did not demonstrate overall differences between sexes in either clinical phenotype when indexed or with respect to disease progression and prognosis.[318]

Data on the efficacy of the different 'd-modifying' treatments real world are still limited and mostly related to male patients.[319] Better diagnostic criteria for women and real-world results of treatment efficacy on females will increase our knowledge of this disease in women.

Cardiac rehabilitation

Several controlled studies and meta-analyses have found a survival benefit for patients receiving cardiac rehabilitation (CR) after ACS; most recent indications include patients with 'stable' anginal symptoms (or atypical symptoms such as dyspnoea), symptomatic patients >1 year after diagnosis or revascularization, and patients with angina and suspected vasospastic or microvascular disease. CR programmes should be available for all coronary artery and valve surgery patients. Patients who undergo transcatheter aortic valve implantation (TAVI) are also candidates for CR: patients are commonly very old, mainly women, frail, and with many comorbidities.

Multidisciplinary structured activities aimed at obtaining clinical stabilization, cardiovascular risk reduction, disability reduction, psychosocial and vocational support, and lifestyle behaviour change, including patients' adherence and self-management, constitute the core component of the programme. A key component of CR is an individually prescribed, supervised, centre-based exercise programme aimed to improve aerobic capacity, cardiometabolic risk factors, and psychological well-being.[320]

Despite the well-known benefits of CR, this therapy continues to be under-utilized, particularly for women. Therefore, efforts are needed to identify effective ways to promote and provide equal access to CR for all patients.[321] Sex-specific analyses, however, reveal that men and women achieve similar physical and mental health improvements after CR. Despite poor cardiovascular risk control, women receive less robust clinical interventions in the management of their CVD. Women who participate in CR demonstrate CVD risk factors, including physical inactivity, obesity, hypertension, diabetes mellitus, and poor mental health (depression, anxiety, and perceived stress). The association between CR participation and mortality was stronger in women than in men.[322] One contributing factor to the gender difference is a higher treatment potential in women, as women have a higher mortality compared to men. As CAD is a leading cause of death in women, greater emphasis needs to be placed on improving referral to and attendance at CR for women, thereby positively impacting their quality of care and further decreasing mortality.[323]

Initial assessment with a careful clinical history is a core component of CR: women often have other forms of heart disease diagnostic tests that are less sensitive than men, and some CVD risk factors are manifested differently. Preeclampsia, gestational diabetes, pregnancy-induced hypertension, small for gestational age infants, preterm births, and early or surgical menopause are not routinely documented as important data. Exercise prescription dose also deserves close attention because women might not have the same increases in cardiorespiratory fitness with CR as men. Social determinants of health and psychosocial issues are more predominant in women than men (e.g. depression, anxiety, low socio-economic status, intimate partner violence). Gender-tailoring education for women includes consideration of the mode and content of CR: where possible, education should be delivered in accordance with their preferences. However, delivery via multiple modes might be best.[324]

Pregnancy and puerperium

Regarding the management of therapy for pregnant women, it is well known that many medications can have teratogenic effects. A multidisciplinary approach is advisable for the treatment of cardiovascular pathologies during pregnancy, involving a pregnancy heart team (PHT) comprised of cardiologists, gynaecologists, obstetricians, anesthetists, nurses, and other specialists, according to their specific clinical expertise. Women with cardiovascular diseases or risk factors should be referred to such multidisciplinary teams to enhance care and treatment. The role of the PHT extends beyond the pregnancy period, being crucial both pre-conception and postpartum. Women directed to the PHT should receive adequate consultations regarding maternal and fetal risks before conception and should continue to be monitored postpartum for potential teratogenic effects of various medications.

Conclusions

Some physiological differences influencing pharmacotshowkinetics and pharmacodynamics of drugs do not translate into clinically significant variances, while others can markedly affect pharmacodynamic properties, yielding different therapeutic outcomes in women compared to men. Limited knowledge in this area, stemming from the under-representation of women in clinical trials, results in current guidelines lacking differentiation in dosage recommendations for major cardiovascular drugs. In reality, however, dosage titration considering gender should be evaluated. There are no additional benefits in titrating doses of β-blockers and ACE-I/ARBs in women with HFrEF. Moreover, it's essential not to overlook that women experience up to twice the rate of adverse drug events for HF medications compared to men. Serum concentrations of digoxin should be maintained below 0.9 ng/mL in women, as higher values have been associated with increased risk of death and worsening of HF in women compared to men. Adequate use of new therapeutic strategies for HF in females is also necessary. Greater awareness of the benefits of lipid-lowering therapy is crucial to promote its use, considering under-utilization in females, including those in secondary prevention. Lastly, antiplatelet and anticoagulant strategies in women should be appropriately employed.[325,326]

During pregnancy and the postpartum period, a multidisciplinary approach becomes fundamental. In this

regard, the PHT plays a crucial role in managing the care and treatment of pregnant and postpartum women to reduce maternal and foetal mortalities.

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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