ESC European Society of Cardiology

European Heart Journal (2026) **00**, 1–23
https://doi.org/10.1093/eurheartj/ehaf1059

SPECIAL ARTICLE
Ischaemic heart disease

Sex and gender differences in coronary pathophysiology and ischaemic heart disease

A Scientific Statement of the ESC Working Group on Coronary Pathophysiology & Microcirculation, the Association for Acute CardioVascular Care, and the European Association of Percutaneous Cardiovascular Interventions of the ESC

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Abstract

Ischaemic heart disease shows important differences between men and women, requiring an understanding of sex and gender dissimilarities to improve outcomes. This Scientific Statement provides an updated review of the current knowledge from risk factors to prognosis. It discusses the unequal impact of

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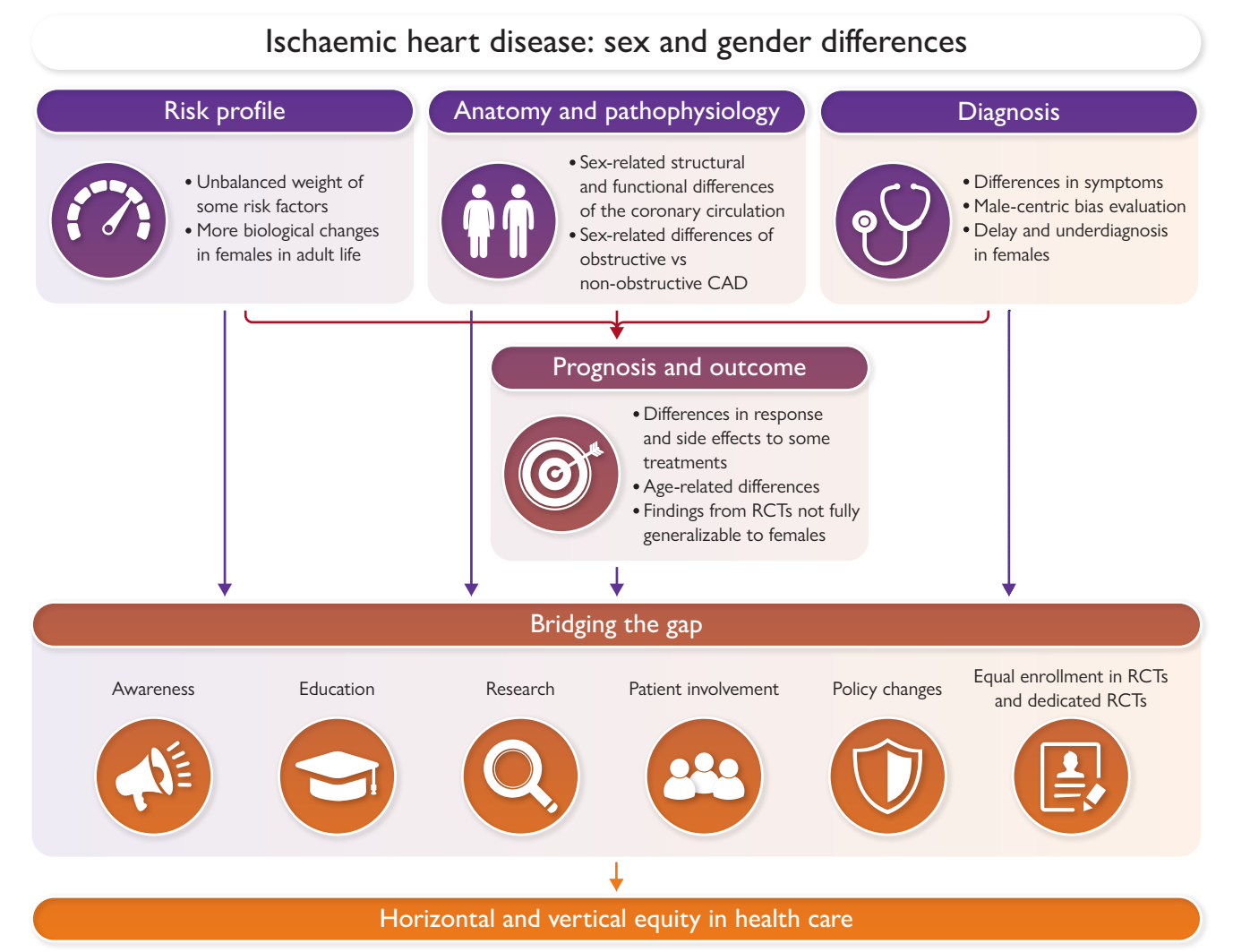
certain traditional risk factors between men and women, along with additional factors, such as hormonal changes and treatments (including those for transgender people and cancer), pregnancy-related complications, and autoimmune diseases, which contribute to the sex-specific risk profiles. Moreover, it outlines functional and structural sex differences in the pathophysiology (e.g. coronary atheroma plaques and burden, coronary dissection, vasospasm, and microvascular disease) with women being more prone to microvascular disease and endothelial dysfunction, while paradoxically experiencing less severe myocardial ischaemia at similar levels of coronary stenosis. The document further addresses the evaluation of diagnostic tools, which often have a male-centric bias, resulting in underdiagnosis in women who also tend to receive less guideline-recommended treatment. Additionally, women can have different responses and side effects to various preventive and therapeutic treatments, potentially contributing to the worse prognosis documented in acute coronary syndromes with obstructive coronary artery disease, particularly at a young age. Considering all these sex and gender differences and the low enrolment of women in randomized controlled trials, questions arise regarding the optimal treatment for women. Addressing sex differences requires conducting sex-specific research to close the knowledge gap. Overall, the Scientific Statement highlights all relevant sex- and gender-specific dissimilarities to advance clinical practice and identify directions for future research to improve guideline recommendations for equitable care.

Graphical Abstract



CAD, coronary artery disease, RCT, randomized controlled trial

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Sex and gender differences in ischaemic heart disease. The figure shows differences between men and women in terms of risk profile, pathophysiology, and diagnosis, which ultimately result in sex/gender differences in prognosis and outcome. To achieve horizontal and vertical equity in health care, several actions need to be taken. CAD: coronary artery disease; RCT: randomized controlled trial.

Keywords Sex differences • Women • Female • Risk factors • Microvascular disease • Coronary atherosclerosis • Acute coronary syndrome • Prognosis

Introduction

Many clinical manifestations of ischaemic heart disease (IHD) differ between men and women, with marked variations in prevalence, presentation, and outcomes. Cardiovascular (CV) disease accounted for 1.7 million deaths in the European Union in 2021, with IHD responsible for 34% of these deaths and an annual care cost of approximately €77 billion.[1] Mortality is about twice as high in men as in women.[2] However, when IHD mortality is normalized to prevalence, data consistently show that across most countries, women have persistently higher age-standardized mortality rates than men, indicating that although fewer women develop IHD, they are at greater risk of dying from IHD within the same age group as men.[2] Despite significant progress having been made in raising awareness of women's health, the recognition of how sex and gender impact CV clinical care is often lacking. Evidence from basic and clinical research indicates that sex and gender may significantly influence the pathophysiology and phenotype of IHD, but many unresolved aspects still exist.

Sex refers to biological aspects (e.g. genetics, hormones, anatomy), while *gender* encompasses sociocultural roles, behaviours, and identities shaped by societal norms.[3] In IHD, sometimes the interplay between sex and gender is complex. Although referrals for women are based on sex at birth, biological factors may interact with gender behaviours influencing CV health, making it difficult to attribute male-female differences to one factor alone[4] (further detail in Supplementary data online, *Supplementary Material, Section S1*).

This Scientific Statement of the ESC Working Group on Coronary Pathophysiology and Microcirculation, the Association for Acute CardioVascular Care and the European Association of Percutaneous Cardiovascular Interventions of the ESC provides a comprehensive update and critical review of the evidence for sex- and gender-specific differences in IHD, raising awareness of the still existing gaps with regard to risk factors (RFs), pathophysiology, presentation and response to treatment, and proposes directions for further research. Indeed, this state-of-the-art review aims to highlight and call for research to address current gaps in sex- and gender-related differences in diagnosis and treatment of IHD, to improve outcomes in women (*Graphical Abstract*).

Sex and gender in the risk profile

CV disease is the leading cause of death worldwide, driven by modifiable RFs in both sexes. Environmental and social factors, especially in low- and middle-income countries, worsen the burden and the outcome, particularly on women.[5] Prevention efforts remain uneven globally.[6,7] As populations age and urbanize, and as unhealthy lifestyles spread, the burden of CV disease continues to rise, primarily in regions with limited resources.[7] Addressing sex and social disparities and enhancing prevention strategies are crucial to reducing this global health threat. This section highlights sex/gender differences in CV RFs in order to address their influence in men's and women's risk profiles.

Differences between men and women occur from the very beginning of the development of coronary artery disease (CAD), reflecting complex interactions between sex and RFs. The unbalanced weight of some RFs between the sexes (*Figure 1*), and the greater biological changes occurring in women in adult life and ageing (*Figure 2*), lead to differences in the risk profile between men and women within the same age group. In addition to traditional RF, other factors contribute to the risk profile, with some non-traditional RFs being more prevalent or unique to women. All this should be taken into consideration when determining each woman's CV risk profile.

Traditional risk factors

The relationship among hypertension, hypercholesterolaemia, diabetes mellitus (DM), and smoking and clinical event rates is well established in both women and men. In fact, 85%–90% of patients with acute coronary syndromes (ACS) have at least one traditional RF.[8–10] and the absence of traditional RF has been observed in only 7.5%–13.8% of women vs 8.6%–16.1% of men.[9,11,12] However, until recently, it was unclear whether the presence of traditional RFs correlated with the extent of atherosclerosis and mortality, especially in women. Recent studies in patients with ACS demonstrate that cigarette smoking and DM disproportionally increase the risk of obstructive CAD in women, and that women with obstructive CAD and ACS have an excess risk of 30-day mortality (about 75% higher) compared with men.[9,13] These observations underscore the urgent need to develop prevention strategies tailored to women at a higher level than those existing in men. Intense efforts to reduce smoking and increase screening for prediabetes mellitus, combined with stricter follow-up of women with a history of gestational DM, have great potential to reduce the sex gap in CAD mortality between women and men. Sex and gender differences in the prevalence of traditional RFs and their association with CAD are summarized in *Table 1*[9,14,15] and discussed in more detail in the online Supplementary data online, *Supplementary Material (Section S2)*.

Non-traditional risk factors

Beyond traditional RFs, other factors contribute to sex differences in the risk of major coronary events. These include genetic predisposition and ethnicity, behavioural and environmental factors, such as physical inactivity, marital status, income, education, and air pollution (see online Supplementary data online, *Supplementary Information Section S2* for more details). In addition, comorbidities (such as obesity, mental disorders, and autoimmune diseases), and treatments (especially those related to oncological diseases) may influence the risk profile (*Figure 1*).

Obesity

Obesity is more frequent in women than in men.[16] Its prevalence increases with age and varies by race and ethnicity, with the highest rates among Black and Hispanic women.[17] Obesity is closely related to metabolic syndrome, hypertension, dyslipidaemia, and DM,[18] resulting in a three-fold higher risk of fatal CAD in obese diabetic women compared to non-diabetic women.[19] Abdominal obesity in post-menopausal women is associated with obstructive CAD and with pro-inflammatory and pro-coagulant factors such as C-reactive protein (CRP) and fibrinogen.[20] Additionally, in women but not in men, body mass index, pericardial, subcutaneous, and intraperitoneal fat are associated with low myocardial perfusion.[21,22] Intermuscular adiposity is associated with coronary microvascular dysfunction (CMD) and adverse outcomes, but sex differences have not been investigated.[23] Data on the relationship between obesity and the outcome of acute myocardial infarction (AMI) are inconclusive regarding sex-related differences.[24,25]

Psychological disorders

Depression increases the risk of CV disease by 1.7 times and is twice as common in women as in men.[26] This is attributable to biological, behavioural, and social gender-differences, such as experiencing physical or psychological abuse, which is more prevalent in women (15%–71% across countries).[27] Psychological distress is a strong predictor of

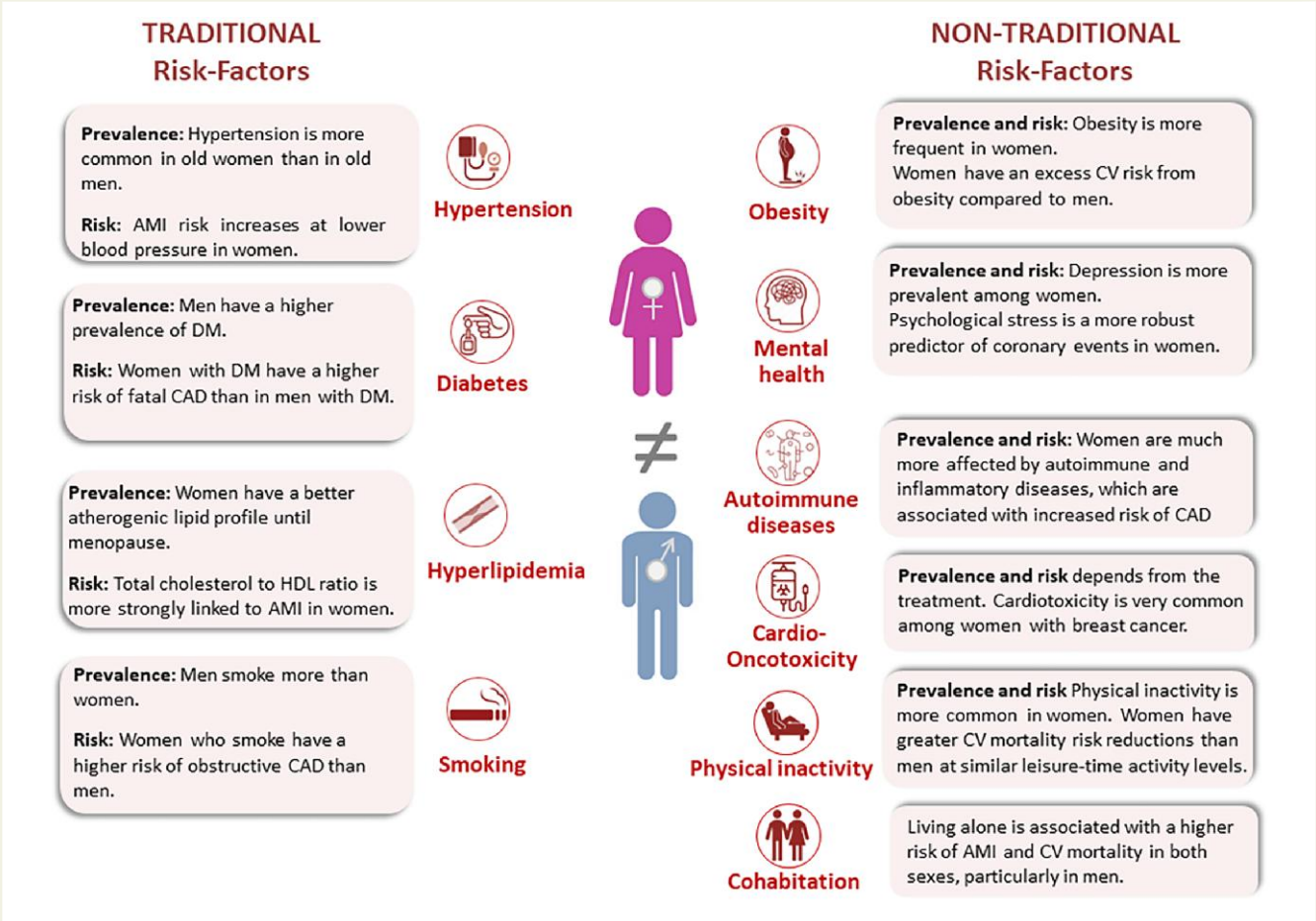

Figure 1 Sex and gender differences in traditional and non-traditional modifiable risk factors. AMI, acute myocardial infarction; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; DM, diabetes mellitus; HDLc, high-density lipoprotein cholesterol; HTN, hypertension; IHD, ischaemic heart disease; TC, total cholesterol

coronary events in women (less robust in men), placing them particularly at risk of stress-related AMI.[28]

Autoimmune diseases and inflammation

Autoimmune and inflammatory disorders are more common in women than in men and are associated with a high prevalence of coronary heart disease.[29] Oestrogens modulate the immune system by influencing the activity of various immune cells, including T and B cells, through oestrogen receptors expressed on these cells.[30] Depending on the stage of the menstrual cycle or pregnancy, different levels of oestrogen drive the immune response either towards or away from triggering autoimmunity. During periods of high oestrogen levels, such as pregnancy, the hormone promotes the development of regulatory T-cells, which dampen the immune response.[29] Conversely, low levels of oestrogen in post-menopausal women promote a pro-inflammatory state, favouring atherosclerosis and CV disease. Other mechanisms contributing to the higher prevalence of autoimmune diseases in women may relate to testosterone levels, X chromosome microchimerism, and sex differences in the microbiome.[31] A significant number of genes on the X chromosome are associated with immune regulation. In women, genes on the second X chromosome are normally inactivated. However, about 23% of X-linked genes escape this inactivation, including those involved in the regulation of the immune system response.[29]

Oncotoxicity

The influence of sex in the cardiotoxic effects of cancer treatments and the risk for IHD shows mixed results. Most studies indicate that female sex confers protection against anthracycline-induced cardiotoxicity, while female sex appears to be an RF for cardiotoxicity from immune checkpoint inhibitors.[32] Anthracyclines can cause progressive, irreversible damage to the coronary microcirculation, even at low doses and without contractile dysfunction, as shown in pig models.[33] Long-term IHD risk is found among breast cancer survivors treated with anthracyclines and/or trastuzumab,[34] with obesity further increasing the risk.[35] Vasospasm is the most frequent cardiotoxic effect of 5-fluorouracil, but studies on the prognostic role of sex are limited and show no differences.[36] Vascular endothelial growth factor inhibitors also cause myocardial ischaemia and vascular toxicity, but data do not show any sex difference.[37]

Radiation therapy for chest tumours (e.g. breast, lung, oesophageal, and lymphoma) increases IHD risk, depending on radiation dose, duration, tumour size, and patient age.[38] Women receiving radiation therapy for left breast cancer have an increased risk compared to those treated for right breast cancer.[39]

Female-specific cardiovascular risk factors

Premature menarche, age of menopause, hormonal contraceptives and hormone replacement therapy, polycystic ovary syndrome,

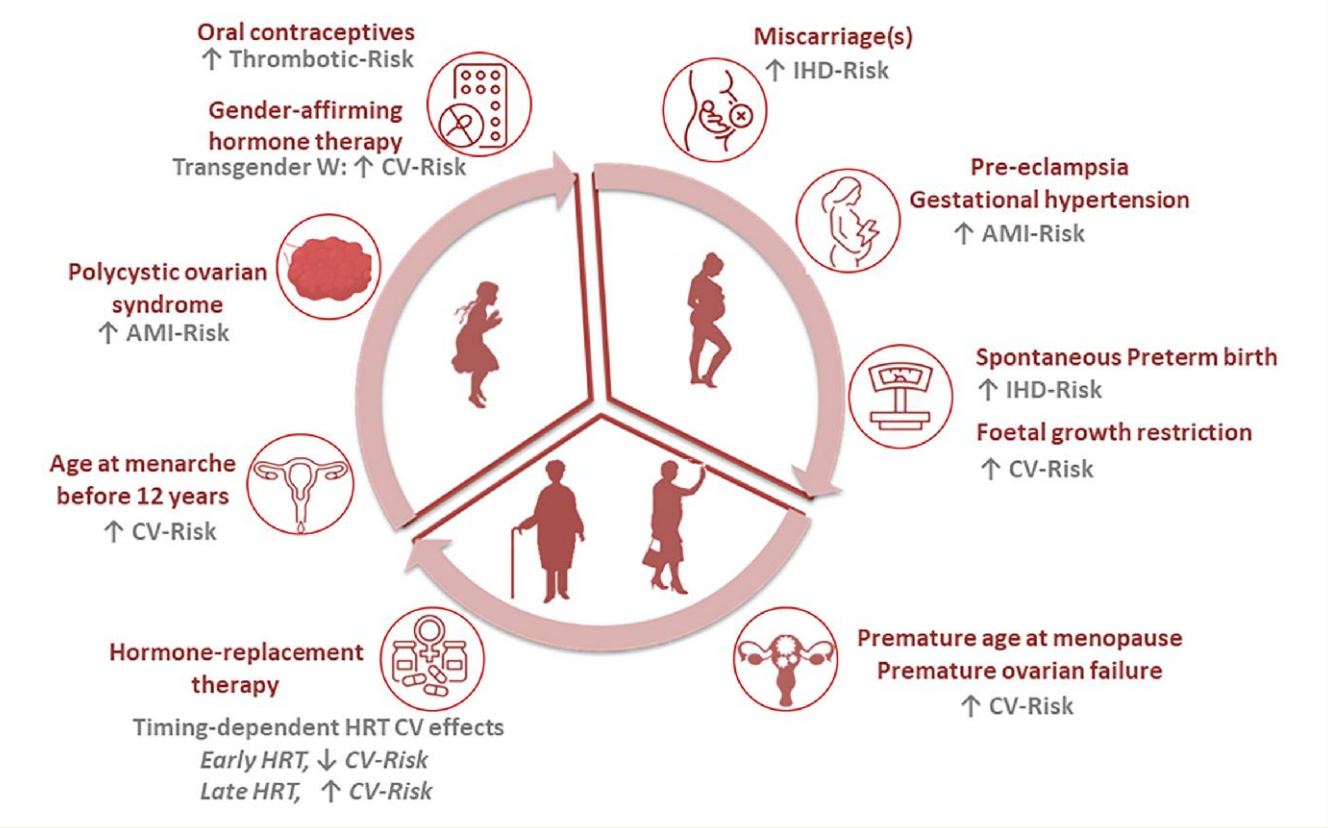

Figure 2 Female-specific risk factors for ischaemic heart disease. Menarche before the age of 12 years and polycystic ovarian syndrome are linked to an increased risk of future coronary artery disease. While oral contraceptive drugs have been associated with a higher risk of cardiovascular events, recent studies show inconclusive results. Oestrogens therapy in transgender women increases the risk of acute myocardial infarction compared to cisgender men. Pregnancy complications (miscarriage, spontaneous preterm delivery, foetal growth restriction, pre-eclampsia, and gestational hypertension) and premature menopause are related to an elevated risk of ischaemic heart disease. Hormone replacement therapy can have a detrimental effect on coronary artery disease risk when started in older women (> 10 years since menopause onset)

endometriosis, and pregnancy-related disorders (pre-eclampsia, gestational hypertension or diabetes, preterm birth, low birth weight, and foetal growth restriction) are all female-specific conditions associated with increased CV risk (*Figure 2*). Extended information on female-specific RFs and initiatives to improve women's risk awareness can be found in the online Supplementary data online, *Supplementary Material (Section S2)*.

Transgender and cardiovascular risk

Subjects undergoing gender-affirming hormone therapy (GAHT) constitute 0.6% of the general population.[40] In transgender women (assigned male at birth), treatments typically include oestrogen and androgen-lowering hormones, whereas transgender men (assigned female at birth) primarily utilize testosterone for masculinization.[40] Limited data exist on long-term CV effects of GAHT; however, recent evidence links GAHT to increased risk of hypertension and dyslipidaemia.[41] Additionally, feminizing hormones increase insulin resistance in transgender women, while testosterone enhances insulin sensitivity in transgender men.[42] Oestrogen therapy in transgender women is associated with the risk of CV events compared to cisgender men, while data on the effects of testosterone therapy in transgender men on CV or cerebrovascular disease risk compared to cisgender women are inconclusive.[41,43,44] A very large cross-sectional study found that the prevalence of AMI after adjusting for traditional RFs, age, and ethnicity was higher in transgender men than in cisgender women.[45] Conversely, the association was not confirmed in transgender women compared to cisgender men.[45] Mental health stressors and adverse health behaviours might also increase their CV risk.[46] The emerging trend of initiating GAHT before puberty could notably impact CV risk.

Sex differences in the pathophysiology of ischaemic heart disease

Sex differences in coronary circulation and autonomic function, along with their interaction with RFs, may lead to sex-specific coronary pathophysiology, ultimately contributing to differences in the clinical presentation of IHD.

The biological mechanisms by which sex influences the pathophysiology of IHD are complex (*Table 2*) and not yet fully understood. Much of the current knowledge derives from studies that, while primarily associative, consistently report recurring patterns, involving anatomical and functional differences in the vessels and heart between men and women, interacting with hormonal status and risk profile (*Figure 3*).

Table 1 Sex differences in traditional modifiable risk factors[9,14,15]

Hypertension
• *There is a sex-dimorphic course of BP across the lifespan:*
• *In men, BP gently increases with age.*
• *In women, BP gently increases with age until the 4th decade, after which it increases steeply and continuous to rise, surpassing men in the prevalence of HTN by the 6th decade.*
• *HTN is the most common RF in both sexes.*
• *HTN is more prevalent in women than in men with ACS, especially in young women.*
• *HTN is associated with risk of AMI, more in older women than in older men.*
• *In women, the risk of AMI increases with BP values lower than in men, starting from SBP thresholds of 110 mmHg, after adjusting for other RFs.*
Type 2 Diabetes Mellitus
• *Men have a higher DM prevalence than women.*
• *Women at the time of DM diagnosis have a more severe DM, especially at younger age.*
• *DM significantly increases the risk for fatal AMI, more in women than in men.*
Hyperlipidaemia
• *Until menopause, women have a less atherogenic lipid profile than men.*
• *In population studies, high cholesterol is a major factor for risk of AMI among women.*
Smoking
• *Smoking is associated to obstructive CAD more in women than men.*

Extended information to this Table is given Supplementary data online, *Supplementary Section S2.1*.
ACS, acute coronary syndrome; AMI, acute myocardial infarction; BP, blood pressure; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; RFs, risk factors; SBP, systolic blood pressure.

Sex differences in the coronary circulation

Anatomic features and myocardial perfusion

Epicardial coronary arteries and the heart in women are generally smaller than those in men, even when adjusted for body surface area.[47] However, myocardial perfusion corrected for the size of the perfusion territory is comparable between sexes. Healthy women exhibit higher myocardial perfusion at rest,[47,54–56] along with greater myocardial extracellular volume and myocardial blood volume,[47] suggesting higher capillary density.

The higher myocardial blood flow in women is likely due to a higher myocardial oxygen consumption,[57,58] likely related to a slightly higher heart rate,[59] in conjunction with a lower oxygen-carrying capacity of the blood, due to a lower haematocrit.[47]

Extended mechanistic information is reported in the Supplementary data online, *Supplementary File (Section S4)*.

Autonomic regulation

Despite a higher resting heart rate, women have greater vagal control over the heart and a lower sympathetic component compared to men.[59–61] But, during acute stress, women show a greater shift towards sympathetic dominance than men.[62] A blunted net sympathetic response to stress independently from CV RFs and myocardial perfusion predicted adverse CV outcomes over long term in women but not in men, indicating that autonomic dysregulation during stress may be a stronger predictor of CV risk in women and suggesting sex-specific pathways to CV disease.[62] Local skin cooling decreases heart rate in men by increasing vagal and decreasing sympathetic activity. In women, it increases both vagal and sympathetic contributions without significantly changing heart rate.[60] Regarding sympathetic tone, men tend to display a vasoconstrictor effect mediated by sympathetic α-adrenoceptors and/or increased parasympathetic component, whereas women exhibit a predominant coronary vasodilator effect mediated by sympathetic β-adrenoceptors.[63] This is consistent with findings in animal models, which show higher mRNA levels of β1- and β3-adrenoceptors in the female vasculature.[64]

Endothelial function

Women generally exhibit better endothelial function until the menopause, mainly due to the beneficial effect of endothelial oestrogen receptor activation on nitric oxide (NO) production by endothelial NO synthase.[48,65] In contrast, androgen-receptor-dependent signalling in women leads to reduced NO availability and impaired vasodilatation. In men, both oestrogens and androgens increase NO availability and vasodilatation.[48] Additional sex differences influencing endothelial function include activity of the renin-angiotensin system and endothelin-1.[48] Furthermore, women have lower expression of soluble epoxide hydrolase,[66,67] which metabolizes epoxyeicosatrienoic acids acting as endothelium-derived hyperpolarizing factors in the heart and kidney.[68] In women, but not in men, CAD is associated with impaired sublingual microvascular glycocalyx barrier function.[69] Recently, poor protective microvascular glycocalyx barrier function has been associated with increased levels of fibrinogen, factor IX, and factor VIII, linking sublingual microcirculatory health to procoagulant status in women but not in men.[70]

Sex differences in functional and structural causes of ischaemic heart disease

In vivo and *ex vivo* studies have reported many sex differences in the causes of IHD (*Figure 4*).

Microvascular dysfunction

Myocardial ischaemia due to CMD may be of vascular origin, i.e. functional (endothelial or vascular smooth muscle dysfunction) and/or structural (inward remodelling or rarefaction), or extravascular (increased myocardial tissue pressure due to increased filling pressures or reduction in diastolic perfusion time).[71,72] The contribution of vascular and extravascular mechanisms of CMD to ischaemia and whether there are sex differences remains incompletely understood.[72] Patients without obstructive CAD and with CMD and high minimal microvascular resistance tend to have smaller epicardial vessels than those without CMD.[73] Nevertheless, CMD is more frequent in women than men, in part because of more frequent hormonal fluctuations (especially during menopause), autonomic dysfunction, and inflammatory responses, predisposing to endothelial dysfunction.[49]

The incidence of ACS without obstructive CAD is higher in women (3.6–27.8%) than men (1.6–22.2%).[71] Additionally, following primary percutaneous coronary intervention (PCI), women are more likely than men to experience the no-reflow phenomenon.[74] The mechanisms involved, though not fully understood, include myocardial oedema, micro-embolization, endothelial dysfunction, and/or rupture of capillaries with intramyocardial haemorrhage.[71,74] No sex difference was found in young adult minipigs between males and females (mimicking pre-menopausal state).[75] Pre-AMI CMD, which is more prevalent in women,[76] increases the risk of the no-reflow phenomenon.[74]

Table 2 Sex differences in coronary anatomy and pathophysiology of CAD[29,47–53]

	Women	Men
Vessel size and geometry	Smaller coronary artery size, even after correcting for body surface area.	Larger coronary artery lumens and greater vessel diameter.
Microvascular anatomy	Higher microvascular resistance	Generally better-preserved microvascular structure.
Plaque characteristics	More likely to have diffuse, non-obstructive plaque	More prone to focal, obstructive plaque and higher plaque burden
Coronary arterial remodelling	Positive (outward) remodelling is more common, but associated with more vulnerable plaque.	Negative (inward) remodelling is more common, often leading to luminal narrowing.
Endothelial function	Endothelial dysfunction is more prevalent and contributes to ischemia without obstructive CAD	Endothelial dysfunction tends to occur alongside obstructive CAD.
Microvascular dysfunction	More prevalent in women, even without obstructive CAD.	Less commonly diagnosed, often overshadowed by obstructive CAD.
Plaque rupture vs erosion	More prone to plaque erosion as a cause of acute coronary syndrome at young age.	Plaque rupture is the predominant cause of myocardial infarction at all ages.
Coronary artery spasm	Higher incidence of coronary artery spasm, contributing to ischemic symptoms.	Less common in Europe.
Hormonal influence	Estrogen offers protective effects pre-menopause but post-menopausal women lose this protection, increasing CAD risk.	Androgens have a more complex role, with potential pro-atherogenic effects.
Inflammation and immune response	Enhanced inflammatory and immune responses, contribute to increased vulnerability to microvascular dysfunction.	Generally lower inflammatory response compared to women.

CAD, coronary artery disease.

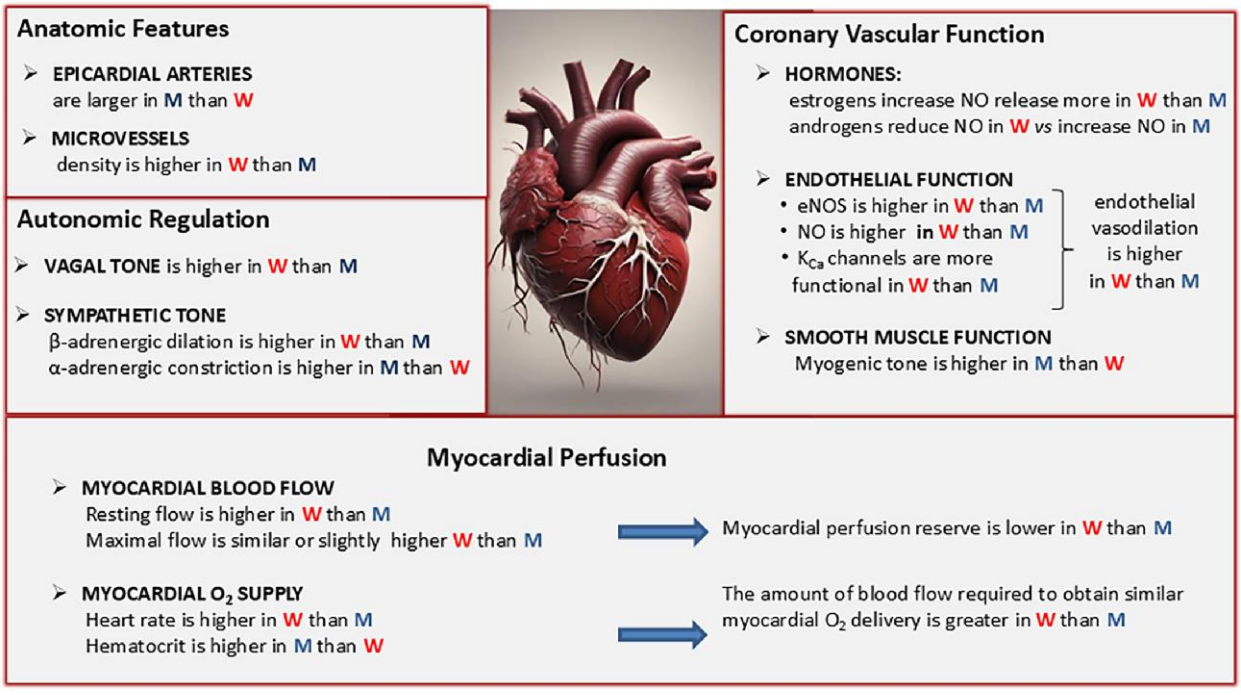

Figure 3 Sex differences in regulation of the coronary circulation. eNOS, endothelial nitric oxide synthase; M, men; NO, nitric oxide; W, women

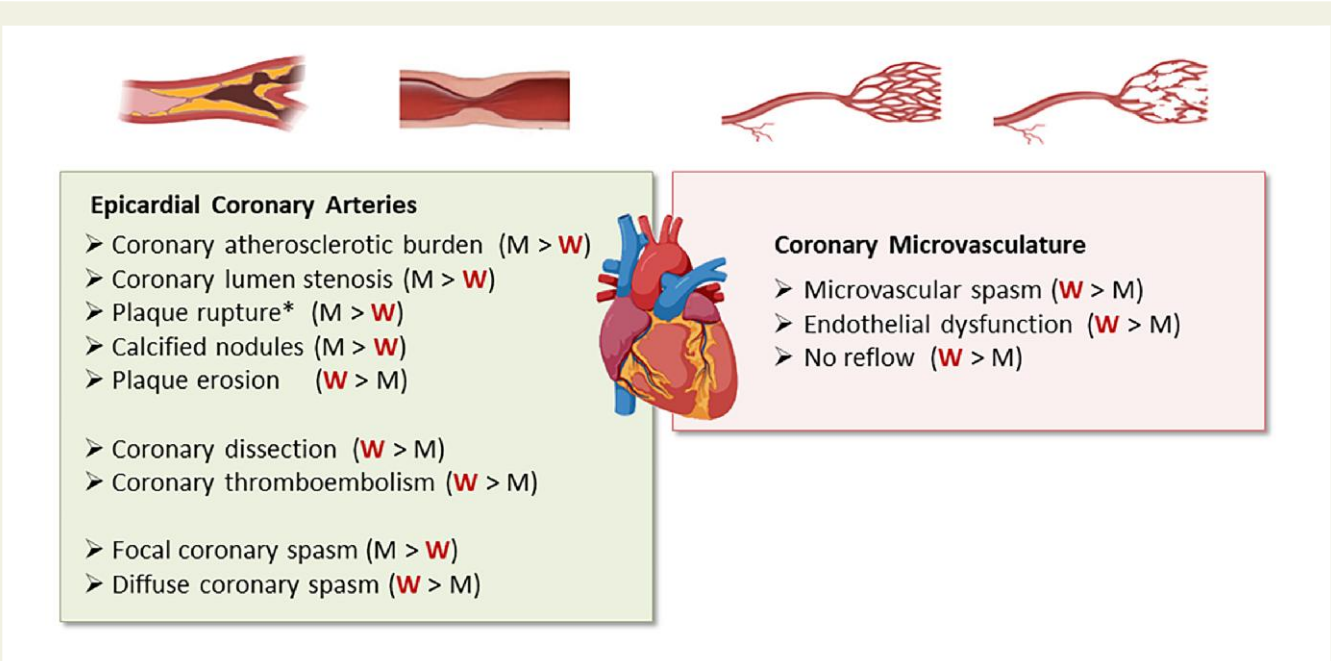

Figure 4 Sex differences in functional and structural causes of coronary syndromes with and without coronary atherosclerosis. M, men; W, women; * women before menopause

Coronary spasm and vasospastic angina

Coronary spasm was initially described as a focal epicardial coronary constriction in response to stimuli.[77] Further observations revealed that it can also occur as a diffuse epicardial constriction with possible microvascular involvement,[78,79] and that it can involve exclusively the coronary microcirculation[80] (extended information in Supplementary data online, *Supplementary File Section S3.4*). Investigations on sex differences in the phenotypes of coronary spasm revealed notable variations. Japanese studies indicate that diffuse epicardial spasm is more prevalent in women than men (60% vs 40%) and focal epicardial spasm is more frequent in men (67% vs 33%),[81] whereas microvascular spasm is more frequent in women (21% vs 3%).[82] In contrast, a large European study found that all phenotypes of coronary spasm were significantly more prevalent in women than men (70% vs 43%), for both epicardial (either focal or diffuse) and microvascular spasms (odds ratios: 2.3 and 4.3, respectively).[50] The discrepancy between Japanese and European populations may stem from different diagnostic criteria, such as the threshold for diameter reduction defining epicardial spasm (>90% in Japan vs >75% in Europe). Genetic factors may also play a role, with variants like aldehyde dehydrogenase 2 and Rho-associated kinase 2 identified predominantly in Asian patients, and polymorphisms in the endothelial NO synthase gene or endothelin-1 pathway noted in both Asian and European populations.[83,84] Further research is required to explore genetic and ethnic influences on sex-based differences.

Atheroma burden

Even at early stages of coronary atherosclerosis, men have more severe structural and functional abnormalities in epicardial arteries than women.[85] Sex differences in the haemodynamic of coronary stenoses are limited. Most imaging studies indicate that women have a lower plaque burden,[86] and that angiographic lesions of similar severity are less likely to produce ischaemia in women than men.[87] Additionally, men have higher coronary calcium, whereas women have higher prevalence of non-calcified plaques, and lower plaque burden at minimal lumen area, reflecting sex differences in the pathophysiology of plaque formation.[51,88] Women also tend to have condensed lipid plaques within a smaller atheroma volume, making them more likely to respond to hypolipidemic treatment.[89,90] Recent studies suggest that post-menopausal women are at higher risk for ACS compared to men with similar atherosclerotic burden.[91] This may be attributed to the sudden oestrogen withdrawal post-menopause, leading to changes in serum lipid levels. A recent understanding from preclinical studies suggests that aged female mice with a pro-atherogenic profile, such as those with down-regulated LDL-receptor (LDLR) exhibit a higher inflammatory response in atherosclerotic plaques compared to males.[92]

Plaque rupture/erosion/calcified nodules

Overall, a similar distribution of culprit plaque morphology is observed between men and women with ACS.[52] However, pronounced inter-sex differences become apparent upon closer examination. In this regard, the prevalence of plaque rupture and plaque vulnerability features increases with age in women, but not in men, likely due to increased vascular inflammation after menopause.[52,53] Plaque erosion is most prevalent in young women and decreases with age, suggesting that oestrogen might protect against plaque rupture but not erosion.[52,53] Finally, the presence of calcified culprit plaques increases with age in both sexes, with a delay of several years in women compared to men.[93] No calcifications are observed in young women ≤50 years, suggesting a protective role of oestrogen.[52]

Thrombus burden and composition

In general, women with ACS tend to have a slightly lower thrombus burden than men.[94] However, women with high thrombus burden have a higher risk of death compared to men, while there is no sex-related difference in the outcome for patients with low thrombus burden.[94] Still, clinical studies are limited by the confounding effect of age,

which is closely linked to oestrogen levels and their potential antithrombogenic effects.[95] In ST-elevation myocardial infarction (STEMI) patients, the composition of coronary thrombi is similar between sexes, except for women <55 years of age, who show reduced thrombogenic components (such as fibrin, p-selectin, and von Willebrand factor) despite having a worse prognosis.[96]

Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is a frequent non-atherosclerotic cause of ACS.[97] Around 90% of SCAD patients are women, typically in the pre- and peri-menopausal period (42–55 years old).[97,98] SCAD accounts for approximately 35% of ACS cases in young women.[98] While the pathological mechanism remains incompletely understood, hormonal changes may play a role, as evidenced by associations with gestational hypertension, gestational diabetes, pre-eclampsia, and exposure to fertility hormonal treatment and hormonal replacement treatment.[99] Physical stressors appear to be more common in men, while emotional stressors are more common in women.[100] Women with SCAD have a higher prevalence of anxiety and depression compared to men.[99,100] However, there are no gender differences regarding SCAD outcomes.[98,99]

Coronary embolism

Coronary artery embolism causes AMI more frequently in women than men (9% vs 3%).[101] Coronary embolism can result from atrial fibrillation or other cardiac causes (dilated cardiomyopathy, valve prostheses, infective endocarditis, and cardiac tumour), or extra-cardiac causes (malignancy or paradoxical venous thromboembolism through patent foramen ovale).[101] It can arise with or without hypercoagulable disorders. Women may experience higher rates due to more frequent hypercoagulable states. About 30% of ACS during pregnancy is due to coronary embolism related to the gestational hypercoagulable state.[102] The antiphospholipid syndrome, more frequent in women, represents 7.5% of all AMIs caused by coronary embolism.[101] Prothrombotic factors as factor V Leiden and prothrombin G20210A variant, confer a high risk for AMI in women <45 years, but not in young men.[103]

Sex and gender differences in symptoms and diagnostics

The existence of sex and gender differences in the manifestation of symptoms associated with IHD is a primary cause for the occurrence of delayed or missed diagnoses. Several non-invasive imaging and functional tests are currently available for studying coronary circulation. The choice among them is largely dependent on the availability of hospital resources. They have a combination of strengths and weaknesses, particularly in women. The algorithm presented in *Figure 5* outlines a management strategy for IHD that is informed by sex-related considerations.

Symptoms

Chest pain/discomfort is the most frequent symptom of myocardial ischaemia in both sexes.[104,105] However, women often have more diverse symptoms than men and experience chest pain/discomfort that is not characterized by tightness, squeezing, pressure, or heaviness, but rather by symptoms like dyspnoea, extreme fatigue, upper back pain, jaw pain, diaphoresis, indigestion, nausea, vomiting, dizziness, and palpitations.[106–111] Dyspnoea (even in the absence of any pain) is common in older women.[108] The absence of the typical chest pain/discomfort is also frequent in pre-menopausal women and in patients with coronary syndromes without significant atherosclerosis (which is prevalent in women).[107,108,110] In women, angina often occurs at rest or is precipitated by emotional/mental stress.[26] Prolonged chest pain at rest or during emotional stress, rather than classic exertional angina, may lead to delays in diagnosis and treatment, which can affect women's quality of life by increasing uncertainty about their condition and its management.[112] In ACS, the difficulty in early recognition may result in late revascularization and increased mortality.[113] Regarding the association between symptoms and CAD severity, data from the CASS (Coronary Artery Surgery Study) indicate that typical angina is associated with more severe CAD,[109] while the WISE (Women's Ischaemia Syndrome Evaluation) study found that 65% of women with coronary atherosclerotic lesions do not present with typical angina.[110] Furthermore, according to the recently published International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHAEMIA) trial, women experience angina more frequently, despite having less extensive CAD and less severe ischaemia than men.[114] Sex differences may be influenced by advanced age and comorbidities such as DM or chronic kidney disease.[108,115]

The relationship among RFs, age, and angina severity has been shown to influence the probability of obstructive CAD differently in men and women. According to the 2024 ESC guidelines for the management of chronic coronary syndromes (CCS), the 'Risk Factor-weighted Clinical Likelihood of Obstructive CAD' algorithm is recommended as a pre-test for further diagnostic evaluations.[105]

Strengths and weaknesses of diagnostic tools

Anatomical, physiological, and pathophysiological sex differences in the coronary vasculature should be carefully evaluated in the selection and interpretation of cardiac diagnostic tests.

Markers of necrosis, ventricular dysfunction, and inflammation

In healthy subjects, serum levels of cardiac troponin (the gold-standard marker of myocardial cell damage) are significantly lower in women than in men and are stronger predictors of events in healthy women over a 7.9-year follow-up.[116] Mechanistic basis for these sex differences in normal cardiac troponin levels includes variations in cardiac mass, hormonal influences, and CV RF interactions [117]

In the setting of ACS, the use of a standard male threshold may lead to underdiagnosis of AMI or underestimation of the extent of myocardial necrosis in women, resulting in undertreatment and high mortality.[118] In this regard, the Fourth Universal Definition of Myocardial Infarction points to the use of sex-specific cut-offs for high-sensitivity cardiac troponin assay to improve the diagnosis of AMI in women.[119] The evidence for the benefits of sex-specific high-sensitivity troponin thresholds is still inconclusive.[120] However, recent results suggest that the predictive value of cardiac troponin is higher in women than in men presenting with acute chest pain, using both neutral and sex-specific cut-off values.[121] Moreover, troponin as a continuous variable may improve risk stratification by capturing the full spectrum of cardiac injury.[122]

B-type natriuretic peptide (BNP) levels, unlike troponin, tend to be higher in healthy women than in healthy men. N-terminal proBNP (NT-proBNP) levels increase with age in healthy older adults, with women showing higher levels than men.[123] The sex-specific differences in BNP levels are not useful as a diagnostic and prognostic tool.

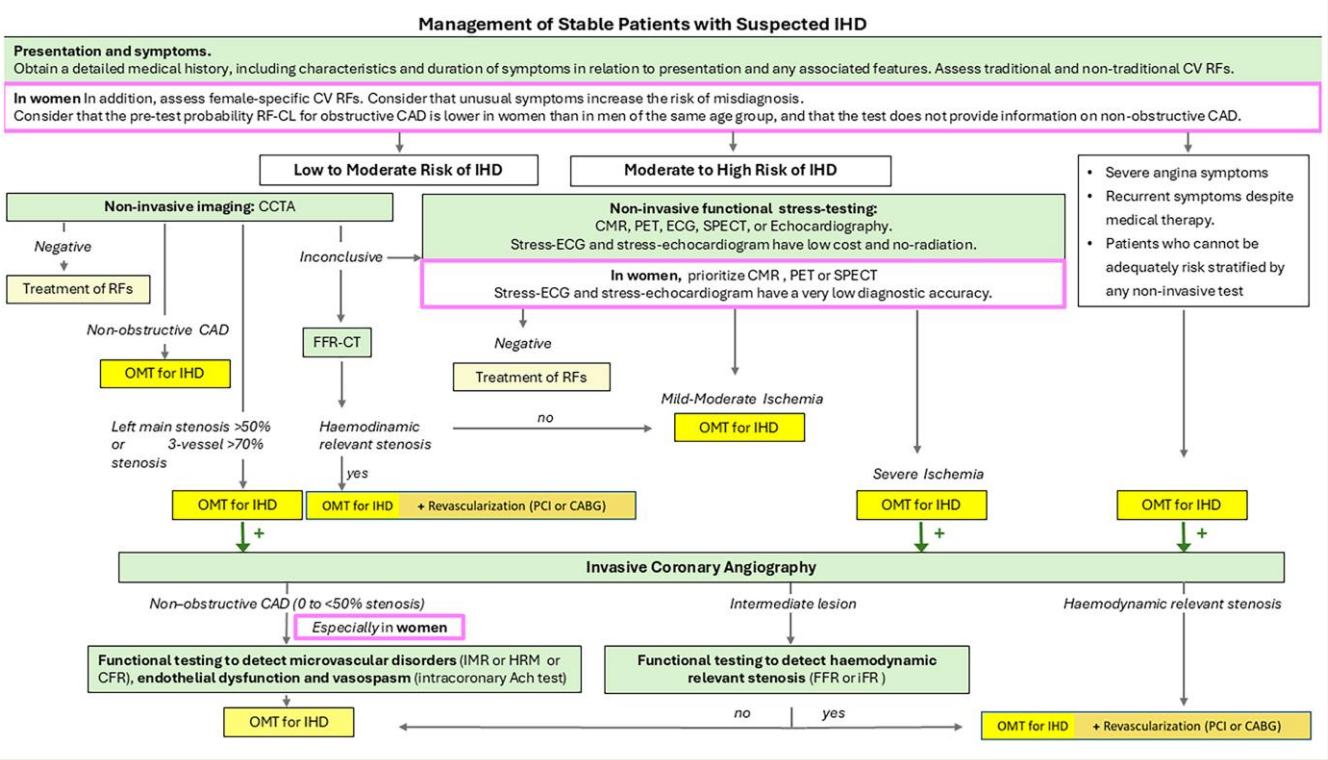

Figure 5 Management of stable patients with suspected ischaemic heart disease. The figure outlines a stepwise evaluation of stable patients with suspected IHD, integrating clinical assessment, non-invasive testing, and invasive strategies, with a focus on the differences between the sexes. Management should always begin with a detailed medical history to collect all information regarding symptoms and cardiovascular RFs, including non-traditional RFs, which are prevalent in women. Based on their risk profile, patients should undergo imaging or functional testing to exclude or characterize IHD and subsequently receive adequate preventive medical therapy. When non-invasive testing indicates possible severe ischaemia, or when IHD is confirmed, and patients still have symptoms despite receiving guideline-directed medical therapy, invasive coronary angiography should be considered either to plan invasive treatment or to perform additional tests in cases of non-obstructive CAD (which is prevalent in women) with the aim of driving physiology-stratified therapy. Ach, acetylcholine; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CFR, coronary flow reserve; CMR, cardiac magnetic resonance; ECG, electrocardiogram; HMR, hyperaemic microvascular resistance; FFR, fractional flow reserve; FFR-CT, fractional flow reserve derived from computed tomography; iFR, instantaneous fractional flow reserve; IHD, ischaemic heart disease; OMT, optimal medical therapy; PET, positron emission tomography; RF, risk factor; SPECT, single-photon emission computed tomography

The inflammatory marker CRP, measured with a high-sensitivity CRP assay, also tends to be higher in women than in men, with values influenced by various factors, including hormonal variations and subcutaneous adipose tissue.[124] In the setting of IHD, the prognostic value of high-sensitivity CRP levels shows inconclusive sex-specific differences.[125,126] Recent data have identified the neutrophil-to-lymphocyte ratio, calculated from routine hemograms, as a potentially effective marker for the presence and severity of CAD in men, but not in women.[127]

Widespread sex differences in circulating biomarkers linked to CV disease are observed between pre-menopausal women and men, with smaller differences after menopause.[128]

Non-invasive and invasive tests

Differences between men and women in cardiac anatomy and pathophysiology of IHD also translate into various diagnostic strengths and weaknesses in the female population. *Table 3* summarizes key differences in non-invasive testing between men and women.[129–134] Among these, computed tomography coronary angiography (CTCA) appears to be the most useful tool for assessing epicardial arteries, therefore excluding obstructive CAD in subjects with a low or moderate pre-test probability of significant coronary atherosclerosis.[105,135] In addition, recent studies have shown that analysis of perivascular fat inflammation by CTCA can predict major CV events independently of the presence or extent of CAD[136] (see Supplementary data online, *Supplementary File, Section S4*).

Several non-invasive tests can be used to assess myocardial perfusion in the microvascular bed, with the aim of excluding/confirming IHD or identifying areas that could benefit from reperfusion.[105] Cardiac magnetic resonance imaging, positron emission tomography myocardial perfusion imaging, and contrast echocardiography all have high sensitivity and specificity, but their own weaknesses and limitations, particularly when used in women of young age, during gestation, or in the presence of comorbidities such as cancer or obesity (*Table 3* and Supplementary data online, *Supplementary Appendix, Section S4*).

Invasive coronary angiography remains the cornerstone in the diagnosis of obstructive vs non-obstructive CAD in both sexes. However, its performance in women has specific challenges related to the smaller calibre of the radial artery, leading to a higher incidence of spasm and, consequently, a potentially higher rate of crossover from radial to femoral access.[137] Overall, rates of invasive angiography-related vascular

Table 3 Sex-related strength and weakness of non-invasive diagnostic tests for IHD in women.[105,129–134]

ECG at rest *(to detect an abnormal baseline ECG)* • In young women, oestrogen-dependent non-specific changes can mimic ischaemia, making interpretation challenging.
ECG stress test *(to detect transient ECG changes related to stress-induced myocardial ischaemia)*. • In women, it has lower sensitivity and specificity for detection of obstructive CAD than in men.
Stress-echocardiography *(to detect transient ventricular wall motion abnormalities related to stress-induced myocardial ischaemia)* • Provides similar sensitivity but a better specificity than ECG-stress test and SPECT.
SPECT *(to detect areas of transient low radiotracer uptake that are potentially related to stress-induced myocardial ischaemia)* • It is more accurate than ECG-stress testing, but it has lower sensitivity and specificity in women than in men, primarily due to smaller vessel size and breast tissue attenuation.
PET *(to detect areas of low perfusion and normal metabolic activity related to stress-induced myocardial ischaemia)* • In women, it offers advantages by reducing attenuation breast artefacts compared to SPECT. • Cardiac PET represents the most validated imaging exam for the non-invasive identification of microvascular dysfunction.
CMR *(to collect structural and functional information on myocardial tissue and perfusion, at rest and under a stressor drug)* • It is the best technique without radiation for visualizing myocardial ischaemia without obstructive CAD, which is prevalent in women. • Identifying oedema, inflammation, fibrosis, and scar tissue it is the gold-standard non-invasive imaging modality for the comprehensive evaluation of MINOCA, which is prevalent in women.
CCTA *(to quantify the amount of calcium in the coronary arteries and detect stenosis by injecting a contrast agent)*. • In both sexes, it is a useful modality to rule out obstructive CAD. • CT effectively quantifies coronary Ca + which is lower in women than in men in all age groups. Thus, similar Agatston Ca + score values are associated with worse outcomes in women. • Women have a lower coronary plaque burden than men and significantly lower levels of all plaque subtypes assessed by CCTA.
CT perfusion *(to provide additional functional information on the severity of the coronary lesion detected by CCTA)* • Advanced imaging technique that improves the specificity of CCTA for detecting hemodynamically significant coronary artery stenosis in women.
Machine learning FFRCT *(to provide additional functional information on the severity of coronary lesion detected by CCTA, without the use of a contrast agent)* • Advanced imaging technique for non-invasive detecting of hemodynamically significant coronary artery stenosis; there is no evidence of sex difference in its prognostic value.

Ca, calcium; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; CT, computed tomography; ECG, electrocardiogram; PET, positron emission tomography; SPECT, single emission computed tomography; CCTA, coronary computed tomography angiography; FFRCT, CT fractional flow reserve.

complications are slightly higher in women.[137] During invasive coronary angiography, several functional tests can be performed to evaluate both epicardial and microvascular function, as well as vasomotor disorders.[138]

Coronary flow reserve (CFR) measures the ratio of hyperaemic to resting blood flow downstream of the target lesion, reflecting both epicardial and microvascular causes of ischaemia. CFR is often lower in women, partially due to higher resting coronary blood flow.[139] Fractional flow reserve (FFR) is used to detect epicardial haemodynamically significant stenosis. It consistently shows higher values in women than in men for the same percentage of stenosis.[140] Long-term outcome differs between women and men in favour of women after FFR-guided revascularization deferral.[141,142] In the setting of non-obstructive CAD, invasive functional assessment of the coronary microcirculation can be performed by either intracoronary Doppler, bolus thermodilution, or continuous thermodilution, the latter requiring an additional dedicated infusion catheter.[143] However, the higher prevalence of coronary tortuosity among women[144] may lead to more challenging wiring and potentially suboptimal traces derived from Doppler and bolus thermodilution.[145] Continuous thermodilution is more reproducible and operator-independent but still requires vessel wiring and incurs additional costs related to the infusion microcatheter.[146] The prognostic value of common microvascular resistance metrics (i.e. index of microvascular resistance, hyperaemic microvascular resistance, microvascular resistance reserve) has not yet been verified in a sex-specific manner. Nevertheless, for all patients with angina and non-obstructive CAD, a physiology-stratified therapy may be preferable to an empirical treatment. Identifying the phenotypes of non-obstructive CAD (e.g. microvascular angina or vasospastic angina) could help personalize treatment, improving patient outcomes by reducing angina severity and enhancing quality of life, as shown by recent trials involving a greater number of females than males.[147–149] The gold-standard test for detecting epicardial or microvascular coronary artery spasms is invasive coronary angiography with pharmacological provocation using bolus administration or graded infusion of acetylcholine.[105] Women often respond to lower doses of acetylcholine.[50]

It is important to note that the choice of diagnostic test, especially when multiple tests are performed, should consider the cumulative effect of radiation exposure.[105,150] The estimated cancer risk is higher in women than in men due to the high radiosensitivity of breast tissue.[151,152]

Women may require CV imaging with exposure to ionizing radiation during pregnancy. Current evidence suggests that keeping radiation as low as possible, primary PCI is the preferred reperfusion therapy for STEMI.[153] The maximum accepted foetal radiation exposure is an accumulative dose of 5 rad (50 mSv or 50 mGy).[154]

Artificial intelligence and machine learning tools

Emerging studies suggest that the integration of imaging and clinical data through machine learning algorithms will greatly assist physicians in providing a more comprehensive risk assessment for optimal acute and chronic care, such as detecting and characterizing atherosclerotic lesions,[155] defining CV risk,[156] and improving outcome prediction,[157] and subsequent decision-making.[158,159]

The Global Registry of Acute Coronary Events (GRACE) score has recently been updated using machine learning techniques and sex-disaggregated data to address observed differences in the accuracy of in-hospital mortality prediction following non-ST-elevation ACS (NSTE-ACS). The GRACE 3.0 score corrected the previous underestimation of risk of in-hospital mortality in women.[160,161] Additional information and confirmation are needed to ensure the GRACE 3.0 score is consistently applied in clinical practice. The development and implementation of artificial intelligence and machine learning tools could support the identification of sex- and gender-specific RFs, disease patterns, and clinical trajectories. Still, there are no data on this issue.

Table 4 Sex differences in the outcome of ACS

Study	Setting	Study population	Time of enrolment	Number of patients (Women %)	Follow-up	Rate of death
Canto JG[175]	AMI	NRMI registry (USA)	1994–2006	1 143 513 (42.1%)	In-hospital	14.6% W vs 10.3% M
Dey S[111]	ACS	GRACE registry (Global)	1999–2006	26 755 (28.5%)	In-hospital	4.5% W vs 2.6% M
Smilowitz NR[176]	AMI with CAD	ACTION-GWTG registry (USA)	2007–2014	303 605 (33.2%)	In-hospital	3.9% W vs 2.4% M
Cenko E[177]	ACS	ISACS-ARCHIVES registry (Europe)	2003–2019	87 812 (35.2%)	30-day	12.9% W vs 9.4% M
Cenko E[166]	STEMI	ISACS-TC registry (Europe)	2010–2016	8 834 (30%)	30-day	11.6% W vs 6% M
Lawless M[178]	AMI with CAD	UK registry	2015–2019	11 763 (29.6%)	1-year	9.2% W vs 6.9% M

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; STEMI, ST-elevation myocardial infarction; W, women; M, men; ACTION-GWTG, Acute Coronary Treatment and Intervention Outcomes Network Registry–Get with the Guidelines; ISACS-TC, International Survey of Acute Coronary Syndromes in Transitional Countries; GRACE, Global Registry of Acute Coronary Events; NRMI, National Registry of Myocardial Infarction.

Sex and gender differences in clinical subsets and outcomes

The prognosis of patients with IHD is significantly influenced by the type of syndrome, age, comorbidities, and time to diagnosis. Angina is the predominant initial manifestation of IHD in women, whereas AMI or sudden death is more common in men.

This section reports on sex and gender differences in the phenotype and outcome of CCS and ACS; findings are particularly relevant in the setting of young and advanced age, as well as in patients without standard modifiable RFs and non-obstructive CAD.

Chronic coronary syndromes

Differences in symptom onset, discrepancies in non-invasive diagnostic tests, and potential barriers to accessing health care, especially in some lower-middle-income countries, might explain women's lower subjective risk estimation[162] and delay in treatment of women with myocardial ischaemia compared to men.[113] However, when comparing sex-related outcomes in CCS, it should be noted that women are only 20%–30% of the study population in clinical trials, which limits comparison.[163,164] Furthermore, at CAD presentation, women are older than men, which may contribute to a higher prevalence of comorbidities such as hypertension, DM, and chronic kidney disease, as well as higher mortality.[105,165] This contrasts with ACS, where the main age-sex difference in prognosis is the higher mortality in women aged <60 years compared to men of the same age.[10,166,167] Women also show higher mortality following coronary artery bypass graft (CABG).[168,169] No significant sex differences in major adverse cardiac events (MACE) have been found in CCS patients after PCI, according to a large contemporary Japanese registry.[170] Another recent study confirmed that women undergoing complex revascularization, such as chronic total occlusion PCI, have similar rates of in-hospital MACE as men, but higher rates of procedural complications despite less complex lesion anatomy.[171]

Compared to men, women undergoing angiography have a higher prevalence of CMD alongside minor (<50%) stenosis of epicardial coronary arteries,[172,173] but no significant sex difference in event rates of cardiac death and non-fatal AMI was found in patients with angina and normal angiograms or non-obstructive lesion.[174]

Acute coronary syndromes

Mortality associated with ACS has significantly decreased over recent decades (*Table 4*), with a shift in the pattern of ACS towards a rise in NSTE-ACS and a decline of STEMI, alongside improvements in therapies and PCI.[153,179,180] However, women with STEMI still have higher mortality rates than men.[175,179] Additionally, the survival gain has not been equally shared across demographic groups,[181] and young women are at significantly higher risk of mortality after STEMI.[10,166] The reasons for this sex gap are not completely understood but may partly be explained by atypical presentation, delayed presentation, and under-recognition of STEMI at first medical contact.[113,182] Recent studies have shown that women are more likely to experience longer prehospital delays than men, although no significant differences are observed between women and men in door-to-balloon times.[183] Delayed presentation increases mortality in both sexes but is linked to higher rates of postprocedural TIMI flow grade 0–2 in women compared to men, which may suggest additional mechanisms for the reduced survival in women. The delay to hospital presentation also affects the comparative effectiveness of treatment between sexes. Importantly, hospital presentation within 2 h of symptoms onset eliminates the sex difference in mortality rates.[113,183] These observations indicate that women are more vulnerable to prolonged untreated ischaemia and underscore the need to increase awareness among the general public and healthcare professionals about the importance of timely treatment to ensure the best outcomes for women and men.

Sex/gender differences in ACS related to age

Mortality in ACS is mainly related to sex, age, and ACS subtype (STEMI vs NSTE-ACS).[175,182,184] Younger women (<60 years) with STEMI

have significantly higher mortality than men, even when matched for baseline characteristics, treatments, time to hospital presentation, and PCI.[10,166,175,184,185] In contrast, the mortality risk in NSTE-ACS is similar between sexes[186] or even greater in older men.[187,188] The increased risk of death in younger women with STEMI is not fully understood.[189] Smoking is the most common RF in younger women,[13] while older patients often have DM, hypercholesterolaemia, and hypertension.[10] Younger women (≤55 years) more frequently present without chest pain, which is associated with higher mortality than in young men.[86,175] Early coronary revascularization is associated with improved survival in older and younger men who present to the hospital in stable conditions after NSTE-ACS, but not in young women.[190] Nevertheless, younger women are more likely than older women to present within 2 h after symptom onset.[166] Heart failure is common at hospital admission in STEMI patients[177] and complicates STEMI more often in women than men, which may partly explain the sex difference in mortality.[177,191,192] The topic is expanded in the Supplementary data online, *Supplementary Material (Section S5)*

Patients without standard modifiable risk factors

Patients without standard modifiable risk factors (SMuRFs) (DM, smoking, hypertension, and dyslipidaemia), who develop ACS, are a unique group that has been largely unexplored until recently. The SWEDEHEART study[11,193] found that AMI in patients without SMuRFs was linked to a significantly higher risk of all-cause mortality, cardiac mortality, and MACE, especially in women. Similar findings were observed in a recent multi-ethnic study, where elderly women without SMuRFs had the highest in-hospital and short-term mortality rates following STEMI.[194] The mechanisms behind these observations remain unclear, and the higher MACE risk in SMuRFs-less patients is controversial.[6,195] In South-East Europe, having all four RFs is associated with a 5-year reduction in life expectancy free of ACS compared to those without SMuRFs.[6] Interestingly, men without a history of CV disease and without SMuRFs have a higher mortality risk from ACS than their female counterparts.[194]

Myocardial infarction with non-obstructive coronary artery disease

Women are more likely to present with myocardial infarction with non-obstructive coronary arteries (MINOCA), although the absolute numbers are similar to men due to the higher prevalence of ACS in men.[71] The incidence of MINOCA varies between STEMI (two times more in women) and non-ST-elevation myocardial infarction (NSTEMI) (three times more in women).[71,196] Early studies on NSTE-ACS showed a 2% death and relapse AMI rate within 1 year.[111,197] In a large cohort of 322 523 AMI patients, 5.9% had MINOCA (10.5% of women vs 3.4% of men), with no significant sex difference in the rate of in-hospital death (1.0% vs 1.1%).[176] Adverse outcomes in MINOCA patients extend beyond short-term follow-up, with 4.7% mortality at 12 months,[198] and 10%[178] to 13%[199] at 4 years, and an AMI recurrence rate of 7.1%.[199] There was no sex difference in long-term mortality among patients with MINOCA.[199,200]

MINOCA has various pathogenetic causes (microvascular dysfunction, coronary spasm, SCAD, non-obstructive thrombosis, thromboembolism).[71,201] Sex dissimilarities in the incidence of underlying mechanistic precipitating factors (e.g. hormonal regulation, vascular structure, autonomic and stress response, immune and inflammatory profile) are unknown.

Table 5 Reasons for sex-specific disparities in the treatment of IHD

- Physician inertia
- Lack of patient referral to cardiologists
- Lack of awareness regarding the cardiovascular risk
- Patient decline due to disbelief in medication effectiveness
- Inadequate sex-specific evidence-based treatment
- Use of non-evidence-based therapies
- Discontinuation due to perceived side effects

IHD, ischaemic heart disease.

Sex and gender differences in management and strategies

The ESC Guideline recommendations for the management of coronary syndrome do not differ based on sex, except during pregnancy, for certain restrictions in medical treatment[102,105,153] (see Supplementary data online, *Supplementary File, Section S6.0*). Nevertheless, women are less likely to receive aspirin, angiotensin-converting enzyme inhibitors, and beta blockers.[202] Additionally, in both primary and secondary prevention, a significantly lower proportion of eligible female patients receive lipid-lowering treatment with any statin compared to eligible male patients.[203–205] Among the reasons for this discrepancy, it was found that women were more likely than men to report never being offered, refusing, or stopping statin therapy.[206] Women also tend to be less likely to get aggressive treatment when hospitalized.[111,207–211] Disparities are unacceptable (*Table 5*). Some sex differences in response to and complications from treatment have been reported, mainly due to a poorer understanding of disease onset in women and the low rates of women enrolled in randomized controlled trials (RCTs). Both aspects need to be resolved to define optimal treatments for women, not based on the extension of the results from men's data.

Pharmacological therapy

Men and women respond differently to medications due to variations in physiology, pharmacokinetics, and pharmacodynamics. Several CV drugs have sex differences in their metabolism.[212] However, no significant clinical relevance has been demonstrated in large-scale studies.[213] Low response to aspirin is more prevalent in women than in men,[214] but sex appears to have no significant clinical relevance for the efficacy of aspirin in preventing serious vascular events.[105,215,216] In addition, women have higher hypersensitivity to aspirin, particularly in the context of asthma and other respiratory diseases.[217]

Women are also often less responsive to clopidogrel, but no sex-specific interaction in the efficacy of dual antiplatelet therapy (DAPT) has been reported, regardless of $P2Y_{12}$ inhibitor intensity.[213] Of note, a recent registry has highlighted, through multivariate analysis, an augmented bleeding risk with prasugrel/ticagrelor vs clopidogrel, in women during DAPT, but not in men[218] (expanded bleeding risk information in Supplementary data online, *Supplementary Appendix, Section S6*). A large-scale meta-analysis of both primary and secondary prevention trials found that statins are effective for preventing major vascular events in both men and women; however, in individuals with no history of CV disease the effect seemed slightly greater in men (rate ratio [RR] 0.72, 99% confidence interval [CI] 0.66–0.80) than in women (RR 0.85,

99% CI 0.72–1.00; heterogeneity adjusted $P = .023$).[219] Statins intolerance is reported more frequently in women than in men and is more strongly associated with an impaired quality of life in women.[220–222] Adverse effects reported for statins are significantly more subjective (potentially related to the nocebo effect) than objective (e.g. cellular injury) and are also reported more often by women than by men.[222] A crossover study confirmed the nocebo effects of statin, but results were not stratified by sex. Nevertheless, retrospective pharmacovigilance analysis of spontaneous Adverse Drug Event Reports showed that the incidence of DM associated with statin use is higher in women than in men.[223] In the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, angiotensin receptor blockers were better than amlodipine in reducing CV events in men but not women.[224] Angiotensin-converting enzyme inhibitors reduced major CV events in men but not in women in the Second Australian National Blood Pressure (ANBP-2) trial and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[225,226] In patients with no history of IHD, using beta-blockers to treat hypertension increases the risk of acute heart failure during incident ACS in women, but not men.[192] Digoxin increased mortality risk in women with stable depressed left ventricular systolic function, but not in men.[227] In contrast, it increases mortality in both sexes when heart failure complicates an ACS.[228]

In summary, all these studies emphasizing the importance of investigations on sex-based variations in treatment efficacy suggest the need for sex-specific guidelines[97] (further information in Supplementary data online, *Supplementary File, Section S6*).

Invasive treatment (PCI and CABG)

Several studies have investigated the impact of sex on outcomes after revascularization (PCI or CABG).[229–233] In a pooled analysis of PCI trials, the adjusted risk of MACE was higher in women than men at 5 years, driven mainly by myocardial infarction and ischaemia-driven target lesion revascularization, with no significant difference in all-cause or cardiac death.[233] Confirming no significant differences in the adjusted risk of CV mortality between sexes at 10-year follow-up, a recent meta-analysis of five trials on drug-eluting stents reported a lower risk of repeat revascularization in women.[231] Women had an increased risk of AMI in the first 30 days after drug-eluting stent implantation but a comparable risk thereafter, with a similar risk of stent thrombosis.[231] Similarly, a recent meta-analysis of four randomized trials on CABG showed that over 5 years of follow-up, women and men had similar adjusted risk of death. However, women had a significantly higher risk of MACE, driven by AMI and repeat revascularization, but not stroke.[232] The difference in MACE between sexes was not significant in elderly patients (>75 years). The use of off-pump surgery and multiple arterial grafting did not modify the sex differences.[232]

Nevertheless, among over 5 million CABG patients, women had a higher 30-day mortality than men (4.9% vs 3.3%; adjusted odds ratio [OR] 1.4, 95% CI 1.35–1.45),[169] with no significant improvement in the unadjusted risk of operative death observed over the course of the last decade.[234] Some studies suggest that smaller coronary arteries, rather than sex or gender differences, contribute to higher perioperative mortality in women and smaller people undergoing CABG.[235] However, most evidence comes from trials with predominantly white men. The ongoing RECHARGE and ROMA trials aim to fill this gap by investigating PCI and CABG outcomes in women and minorities.[236,237]

For more information on the outcomes of women and men by comparing PCI and CABG, see the Supplementary data online, *Supplementary File, Section S6.2*.

Differences in patients with cardiogenic shock complicating ACS

Most studies on sex differences in cardiogenic shock complicating ACS show dissimilarities in the risk profile, clinical presentation, and management.[238] Women with cardiogenic shock are typically older and have more comorbidities (e.g. hypertension, DM, renal insufficiency) but are less frequently smokers.[239,240] Women present less frequently with STEMI and more frequently with NSTEMI compared to men.[239] Regarding management, women with cardiogenic shock are less likely to be referred to a tertiary centre, receive guideline-directed medical therapies, get invasive haemodynamic monitoring, undergo diagnostic angiography, or receive mechanical circulatory support.[241,242] Ethnic minorities, including Black and Hispanic patients, also receive less mechanical circulatory support than white patients.[241] These findings underscore the complex interplay between sex, gender, race, ethnicity, access to health care, and health outcomes. Recently, observational data from a cohort of more than 150 000 patients also confirmed management disparites.[243] Women had a significantly lower probability of receiving circulatory support (adjusted OR 0.77, 95% CI 0.73–0.81, $P < .001$) and had a higher risk of in-hospital death (adjusted OR 1.09, 95% CI 1.00–1.18, $P = .045$) than men.[243] Moreover, the DanGer Shock trial showed that implanting the microaxial flow pump (Impella CP) before primary PCI in STEMI patients with cardiogenic shock improves 6-month survival compared to standard care (unadjusted hazard ratio [HR] 0.72, 95% CI 0.55–0–95) despite a high risk of complications, including severe bleeding, limb ischaemia, the need for renal replacement therapy, and sepsis.[240] However, sex sub-group (unadjusted) analysis reported a survival benefit in men (HR 0.66, 95% CI 0.47–0.93), but not in women (HR 1.01, 95% CI 0.58–1.79), probably due to the small number of females.[240] To date, in general, the evidence on sex differences in clinical outcome of cardiogenic shock complicating ACS is still inconclusive and is particularly affected by the low proportion of women enrolled in RCTs, which is around 30% (see Supplementary data online, *Table S1*).

Future perspectives addressing unmet needs

Despite the worrisome burden of ACS and CCS in women, progress in understanding sex-specific pathophysiological mechanisms is limited by the underrepresentation of women in RCTs. Women often present characteristics that are exclusion criteria in RCTs, such as advanced age, multiple comorbidities, and complex clinical and anatomical presentations.[97,173] In addition, women are more reluctant than men to participate in RCTs due to concerns about both time and health[97]

(extended information in Supplementary data online, *Supplementary File, Section S6.3*). Women's underrepresentation persists even in recent RCTs that influence current clinical practice (see Supplementary data online, *Table S2*). An adequate, tailored therapy can only be achieved if the patient's complexity is acknowledged in the investigation process. Therefore, the design of RCTs needs to be broadened to be more equal and inclusive, and barriers preventing sex-inclusive research need to be removed[244] (*Table 6* and *Table 7*).

While several sex and gender differences in IHD are acknowledged (see Supplementary data online, *Supplementary File, Table S3*), our understanding of their impact on CV outcomes and the tailoring of therapies based on sex and gender is still in its early stages.[245] To address disparities, it is crucial to ensure both horizontal and vertical equity in health care. Horizontal equity requires that men and women with similar health status have equal access to IHD diagnosis, treatment, and

Table 6 Critical issues in addressing sex-/gender- differences in IHD care

Key issue	Challenges	Solutions	Goals
Awareness and education	• Underdiagnosis in women. • IHD seen as male-dominant.	• Campaigns on sex-specific symptoms. • Educate public and professionals on gender disparities.	Enhance understanding of sex/gender differences in IHD outcomes and treatments.
Equality and equity	• Men and women with similar health conditions do not receive equitable treatment.	• Ensure equal access to IHD care regardless of sex. • Promote public awareness campaigns targeting equality in healthcare.	Achieve equitable access to CV care for men and women.
Training	• Limited training on sex-sensitive care. • Lack of clear screening guidelines.	• Develop sex-sensitive training programmes. • Establish clear screening guidelines.	Improve early recognition and timely intervention for women.
Research	• Insufficient sex-specific studies in CV health. • Gaps in understanding due to male-dominated research.	• Fund and prioritize sex-specific studies on ageing and CV health. • Focus on both traditional and novel risk factors.	Expand the knowledge based on sex-/gender-specific CVD.
Representation	• Paucity of well-conducted sex/gender-specific studies. • Underrepresentation of women in RCTs.	• Ensuring equal representation of women in RCTs	Generate evidence applicable to women by ensuring fair representation in research.
Policy	• Lack of support for sex-/gender-specific health initiatives. • Insufficient collection and analysis of sex-/gender-disaggregated data.	• Promotion of women's health programmes • Collection of sex-disaggregated data on clinical outcomes	Identify persistent sexgaps in care and promote initiatives to address these disparities.
Collaboration	• Limited collaboration between sectors to address sex and gender gaps in CV health.	• Foster partnerships between health organizations, research, medical care institutions, and communities	Strengthen efforts to close sex and gender gaps in CV health for equitable care and outcomes.

CV, cardiovascular; CVD, cardiovascular disease; IHD, ischaemic heart disease; RCTs, randomized controlled trials.

Table 7 Pitfalls in sex-inclusive cardiovascular disease research

Barriers to recruiting women in clinical trials	• Women perception of low life-threatening risk. • Lack of awareness of the benefit of enrolment. • Lack of specific recruitment strategies targeting women. • Socio-cultural and logistical barriers (e.g. caregiving, time, mistrust) *Practical steps:* • Improve outreach programmes. • Educate patients and healthcare professionals. • Develop targeted recruitment plans for women (considering also older age, comorbidities, and socio-cultural and logistical barriers). • Address healthcare access issues.
Shortcoming in measuring sex-related Variables	• Balanced representation of both sexes. • Few sex-stratified data for understanding CAD in women (i.e. different mechanisms, disease progression, risk stratification, and treatment responses). • Appropriate evaluation of statistical analysis (i.e. interaction test) *Note:* • Women-only studies may help to explore sex-specific factors.
Major knowledge gaps in IHD research	• Mechanisms underlying sex differences in CAD development and progression. • Impact of female-specific RFs along with traditional RFs on pre-test likelihood of IHD (i.e. score). • The role of hormones in cardiovascular health across the life course. • Sex-specific responses to pharmacological and interventional treatments. • Impact of pregnancy-related complications on long-term cardiovascular risk in women. • Diagnostic tools are not adequately validated in women

CAD, coronary artery disease; IHD, ischaemic heart disease; RF, risk factor.

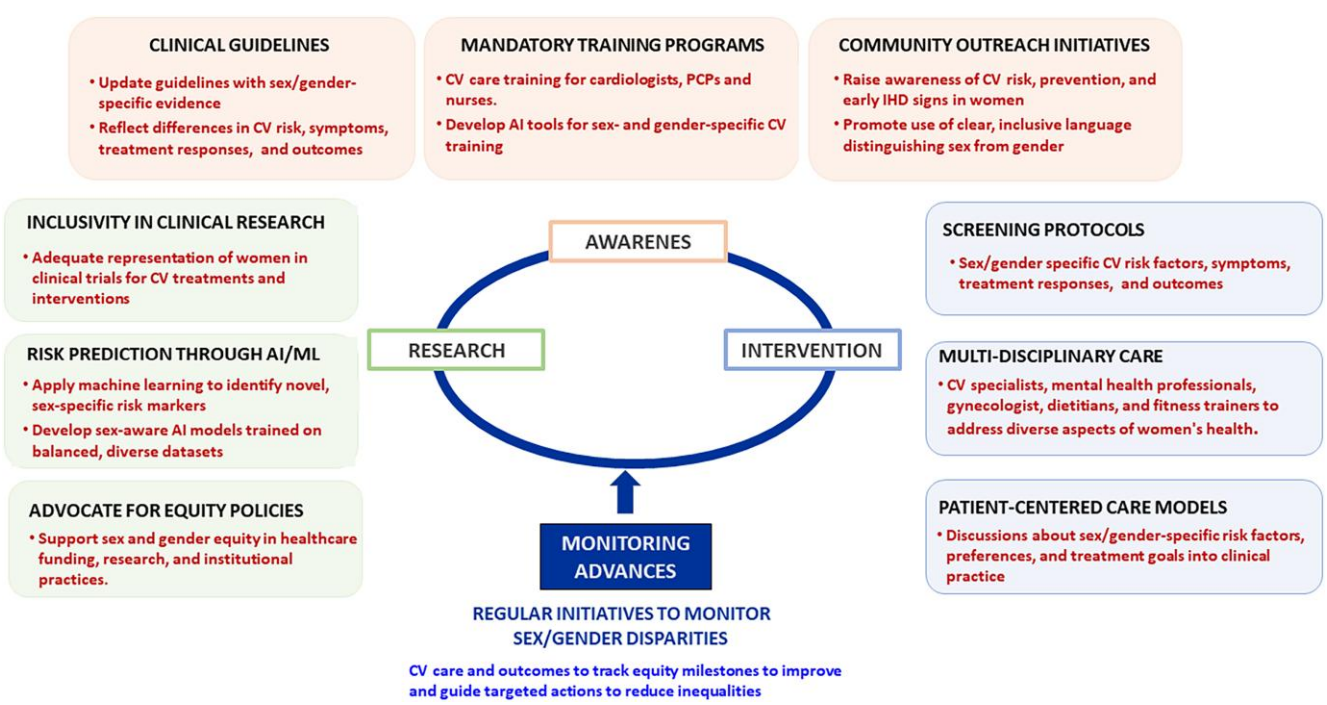

Figure 6 Directions to achieve horizontal and vertical healthcare equity. CV, cardiovascular; IHD, ischaemic heart disease; PCP, primary care physician

management. Currently, CV guidelines do not vary by sex, yet the application of these guidelines often does, leading to treatment disparities affecting women. Vertical equity, on the other hand, focuses on customizing health care to provide equitable care for all, particularly by recognizing the unique aspects of IHD in women. This approach involves the development and implementation of treatment protocols and guidelines that address sex-specific needs (*Table 6*). Significant progress towards gender equality and equity has been made in recent years, but much remains to be done[246] (*Figure 6*). First, it is essential to raise awareness of the differences in the way that myocardial ischaemia affects men and women. Health campaigns should inform not only health professionals but also the general public about sex- and gender-related symptoms, RFs, and outcomes. Education can contribute to early recognition of myocardial ischaemic syndromes and timely intervention in women (see Supplementary data online, *Supplementary File, Section S7*). Second, there is an urgent need for more research on sex differences in cardiac and vascular anatomy during the ageing process, as well as on traditional and novel CV RFs. In this context, the development and implementation of artificial intelligence and machine learning tools can support the identification of sex- and gender-specific RFs, disease patterns, and clinical trajectories. When applied to balanced, diverse datasets, these technologies can enhance early detection and enable more tailored, equitable prevention strategies. Despite the large number of studies on treatment of IHD, there is a paucity of well-conducted sex- and gender-specific studies. Moreover, RCTs to date have mainly included male participants, and do not report sex-disaggregated data, leading to a gap in our knowledge of how women respond differently to treatments and interventions. Ensuring equal representation of women in RCTs is essential to produce evidence that is fully applicable to women. Funding agencies should prioritize research that includes diverse populations to ensure that results are applicable to all. Third, it is crucial to improve professional training. Programmes should emphasize the importance of taking sex and gender into account when assessing and treating patients. Training should be supported by guidelines for screening and management. Interdisciplinary collaboration could provide an opportunity to start primary prevention in women in the postpartum period.[247] Fourth, institutional and government policies are needed to support sex- and gender-specific health initiatives, which should include the promotion of women's health programmes and the collection of sex-disaggregated data on clinical outcomes. Such policies can help identify persistent disparities and promote initiatives to address them. Finally, promoting partnerships between health organizations, research and medical care institutions, and communities can strengthen efforts to reduce the sex and gender differences in CV health to ensure equitable care and optimal outcomes for all individuals.

Acknowledgements

With the endorsement of the European Society of Cardiology Patient Forum: Julie Harris and Ingrid De Laval.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

C.A. is a founder, shareholder, and non-executive director of Caristo Diagnostics Ltd, a CT-image analysis company. He is the inventor of patents US10695023B2, US11393137B2, GB2018/1818049.7, GR20180100490, and GR20180100510, licenced to Caristo Diagnostics

by the University of Oxford. CA has a leadership role in the British Atherosclerosis Society, EU Marie Curie Fellowship committee, and received honoraria from Amarin, Covance, and consulting fees from Silence Therapeutics, Caristo, and AMGEN.

L.B. is a founder of the spin-off Ivastatin Therapeutics SL. and declares to have acted as a SAB member of Sanofi, Ionnis, MSD, and NovoNordisk; to have received speaker fees from Sanofi, Bayer, and AB-Biotics SA. (all unrelated to this work)

F.C. reports personal fees from Amgen, personal fees from AstraZeneca, personal fees from Abbott, personal fees from Menarini, personal fees from Chiesi, and personal fees from Daiichi Sankyo, outside the submitted work.

T.J.G. reports consulting fees from Moderna

J.P. Institutional research funded from the German Cardiac Society, Dr. Rolf M. Schwiete Foundation, German Heart Research Foundation, Maquet Cardiopulmonary GmbH

A.S. reports speaker fees or consulting from Boehringer, Organon, AstraZeneca, Pfizer, Daichi-Sankyo, outside the submitted work.

D.T.Z. reports consulting fees from CERC and honoraria for lectures from AstraZeneca, Boehringer Ingelheim, and Pfizer, outside the submitted work.

T.P. is the founder and shareholder of the Spin-off Ivastatin Therapeutics SL (unrelated to this work)

The other authors (O.M., D.T., R.B., A.C., G.DL., A.D.D., I.D., D.J.D., I.F., E.G., V.K., A.G., J.M., D.M., D.Mi., L.R., A.T., M.V., M.Z., E.C.) have nothing to disclose.

Data Availability

No data were generated or analysed for or in support of this paper.

Funding

All authors declare no funding for this contribution.

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