

Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome

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Although health disparities in women presenting with acute coronary syndrome (ACS) have received growing attention in recent years, clinical outcomes from ACS are still worse for women than for men. Women continue to experience higher patient and system delays and receive less aggressive invasive treatment and pharmacotherapies. Gender- and sex-specific variables that contribute to ACS vulnerability remain largely unknown. Notwithstanding the sex differences in baseline coronary anatomy and function, women and men are treated the same based on guidelines that were established from experimental and clinical trial data over-representing the male population. Importantly, younger women have a particularly unfavourable prognosis and a plethora of unanswered questions remains in this younger population. The present review summarizes contemporary evidence for gender and sex differences in vascular biology, clinical presentation, and outcomes of ACS. We further discuss potential mechanisms and non-traditional risk conditions modulating the course of disease in women and men, such as unrecognized psychosocial factors, sex-specific vascular and neural stress responses, and the potential impact of epigenetic modifications.

Keywords

Acute coronary syndrome • Gender • Sex • Women

Introduction

Cardiovascular disease (CVD) remains the most common cause of morbidity and mortality in Europe, accounting for 49% of deaths in women and 40% of deaths in men.¹ Over the last four decades, age-adjusted mortality for CVD has continuously declined, however, to a lesser extent in women than in men.² Most intriguingly, recent studies report a significant increase in case fatality rates of acute coronary syndromes (ACS) in young women <55 years of age, while a decrease in mortality from coronary artery disease (CAD) has occurred in younger men.^{3–6} Despite growing evidence demonstrating sex and gender differences in baseline risk factors, coronary anatomy and function, symptoms presentation, comorbidities, treatment efficacy, and outcomes of ACS, mechanisms behind these differences are largely unexplored.^{6,7} These knowledge gaps are nourished by the

persistent underrepresentation of women in cardiovascular clinical trials and a lack of basic science evidence obtained from female animals and cells owing to a manifold refuted concern that inclusion of females will increase variability, as well as double sample size and costs.^{8–12} This review provides a summary of contemporary evidence shedding light on sex and gender differences in the clinical presentation of ACS as well as in diagnostic accuracy of tests, invasive treatment, pharmacotherapy, and outcomes.

Sex differences in coronary biology

Women have significantly smaller epicardial coronary arteries than men, even after adjustment for age, body habitus, and left ventricular

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mass.¹³ Baseline and hyperaemic myocardial blood flow, as assessed by positron emission tomography (PET), is typically higher in women as compared to men resulting in a similar global coronary flow reserve (CFR) in men and women.^{14,15} Although exact mechanisms are lacking, the smaller diameter of female epicardial coronary arteries together with their higher baseline myocardial blood flow have been suggested to result in a significant increase in endothelial shear stress conditions in women.¹⁶ Given that low endothelial shear stress has been associated with focal lipid accumulation, pathologic remodelling, and plaque instability,¹⁷ it has been hypothesized that higher shear stress conditions in female coronary arteries may contribute to sex differences in susceptibility to CAD.¹⁸ These sex differences might be particularly relevant during premenopausal ages owing to oestrogen-dependent effects on endothelial mediators such as nitric oxide, prostaglandins, and endothelium-derived hyperpolarizing factor^{19,20} (Figure 1). The vascular actions of oestrogen are primarily mediated via oestrogen receptor α signalling promoting an anti-inflammatory, low-vascular resistance phenotype that is protected from CVD.²¹ Oestrogen receptor α -mediated effects are blunted in the absence of oestrogen which is consistent with variations seen in vascular stiffness throughout the lifespan of women.²² Importantly, increased vascular stiffness strongly correlates with blood pressure, diastolic dysfunction, impaired ventricular coupling, and left ventricular remodelling and is thought to play a role in disease conditions preferentially affecting postmenopausal women such as heart failure with preserved ejection fraction (HFpEF) or isolated systolic hypertension.²³ Finally, women display distinct coronary plaque characteristics with a more diffuse and non-obstructive disease pattern, reduced overall plaque burden, and calcium content as well as less signs of necrosis in the plaque core²⁴ (Figure 1). Accordingly, while plaque rupture is the primary mechanisms responsible for myocardial infarction (MI) in men, plaque erosion is the major cause of coronary thrombosis in women, particularly in premenopausal women^{25,26} (Figure 2). Despite an overall lower plaque burden in women, coronary artery calcium scoring has recently been demonstrated to be a stronger risk predictor for future cardiovascular events in women as compared to men.²⁷ Thus, coronary artery calcium scoring has been recommended for evaluation of asymptomatic women with a 10-year CVD risk >7.5% by a recent expert consensus statement.²⁸

Influence of sex and gender on cardiovascular risk

Traditional risk factors

Although traditional risk factors for CVD are the same in women and men, differences in prevalence and impact of these risk factors vary between the sexes^{29,30} (Figure 3). This is especially seen in ACS, as women who present with ACS are generally older and have more comorbidities, including a higher prevalence of hypertension, dyslipidaemia, diabetes, heart failure, and atrial fibrillation.^{31,32} Women with early-onset type 1 and type 2 MI³³ have received growing attention as a group affected by inequalities in health outcomes.^{4,34} Mechanisms for these differential outcomes are unclear, but data from the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study indicate that younger women

have a worse pre-event health status vs. men, including lower overall and mental health qualities of life.³⁵ Smoking, like diabetes mellitus, has been shown to have a stronger impact on women, as there is a 25% increased risk for fatal and non-fatal cardiovascular events in female smokers as compared to male ones, independent of other risk factors^{36–38} (Figure 3). Smoking-related cardiovascular risk was highest among young and middle-aged women.³⁶ Diabetes also carries a differential risk between sexes, with diabetic women being at significantly higher risk of developing CAD or HFpEF than their male counterparts^{39–42} (Figure 3). Finally, a significant role in the case of younger women is also played by family history as women <65 years with a maternal history of MI encounter a four times higher risk of ACS than same-aged men or older women.⁴³

Non-traditional risk conditions

Data emerging from the VIRGO study indicate that young and middle-aged women hospitalized for type 1 and type 2 MI were more likely to have lower socioeconomic status, higher levels of psychosocial burden, such as depression and poorer physical/mental health, and overall lower quality of life compared to men⁴⁴ (Figure 2). Accordingly, depression, trauma, and perceived stress have been identified as powerful predictors of cardiovascular risk in young and middle-aged women.^{45,46} This trend is not surprising, given that psychosocial stress has substantially increased for women during the last two decades due to a continuous increase in women's economic participation and educational attainment.⁴⁷ Further, low socioeconomic status is an established variable inversely associated with global coronary risk and imposes a higher excess risk on women as compared to men⁴⁸ (Figure 2). Of note, recent work states that feminine roles and personality traits, but not female sex itself, are associated with higher rates of ACS as compared to masculine characteristics, however, objective evidence of this vulnerability is still insufficient.⁴⁹

It is increasingly appreciated that the gut microbiome, harbouring trillions of microbial cells, plays an important role in the development of CAD.^{50–52} Indeed, systemic trimethylamine N-oxide levels—a pro-atherogenic and pro-thrombotic metabolite produced by the gut microbiome—was shown to predict 30-day and 6-month event-free survival in women and men with suspected ACS.^{53,54} In addition, there is emerging evidence for sex differences in microbiome-mediated contribution to cardiovascular risk factors and comorbidities including inflammatory processes, autoimmune disease, cardio-metabolic disorders, and major depression.^{55–57} Men and women have different genetic backgrounds, energy and nutritional requirements across the lifespan, as well as differences in gastrointestinal transit time, which can contribute to sex differences in microbiome.⁵⁸ Future studies will show the potential of gut microbes to provide novel diagnostic and therapeutic targets tailored to the female and male cardiovascular system.

Female-specific risk factors

Premenopausal women are thought to be relatively protected against CVD when compared to age-matched men, with early menopausal transition and postmenopausal status shown to be associated with adverse risk for CVD and mortality.^{59,60} Oestrogen withdrawal at menopause has many negative effects on cardiovascular function and metabolism including alterations in body fat distribution, endothelial dysfunction, vascular inflammation, sympathetic tone, and a higher

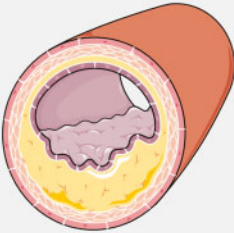
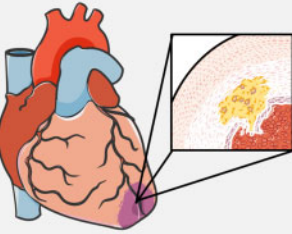
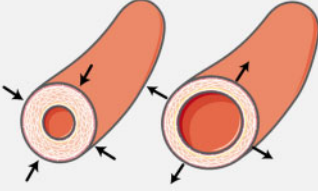
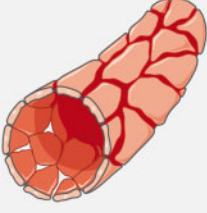
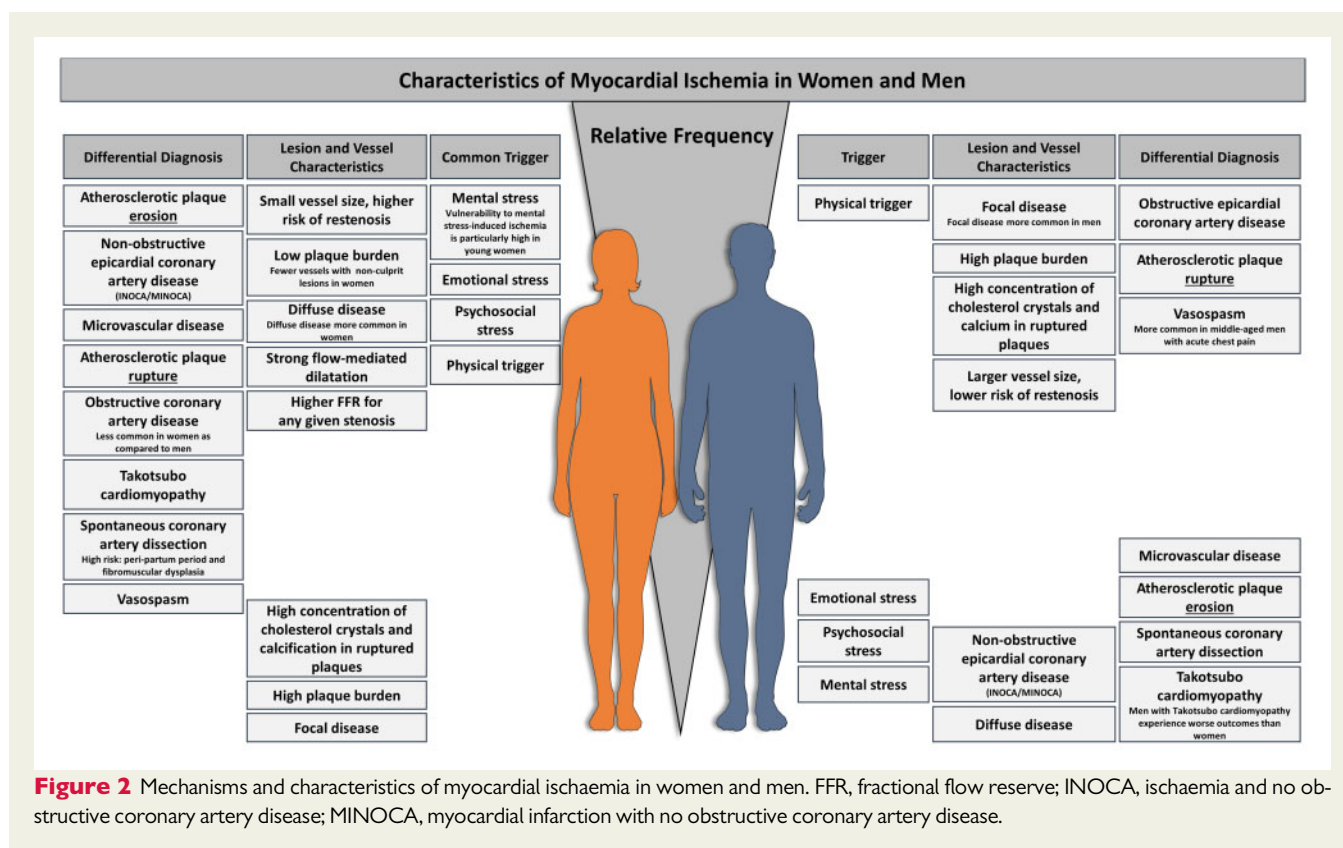
	Estrogens	Testosterone
Atherosclerosis Risk Factors 	LDL oxidation↓ LDL binding↓ VSMC proliferation↓ VSMC migration↓ EC proliferation↑ EC migration↑ CRP↑ Pro-inflammatory (TNF- α , IFN γ , IL-6, CCL2) cytokine production↑ Hematopoietic stem cell differentiation↑ Coronary calcification↓	Conflicting effects on lipids Expression of pro-atherogenic genes↑ WBC adherence to EC↑ Pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, IFN- γ)↓ CRP↓ IL-10↑ Plaque volume↑, VCAM-1 expression↑ (controversial data) Coronary calcification↑
Thrombus Formation 	Coagulation factors (FVII, X, XII, XIII), pro-thrombin fragments↑ PAI-1↓ Collagen-induced platelet activation/aggregation↓↑* Baseline platelet activity↑ Release of mast cell proteases and TNF- α ↓	Platelet inhibition by PGI ₂ ↑ Platelet response to ADP↑ TXA ₂ platelet aggregation↑ Plasma fibrinogen level↑ Infarct size↓, protection from ischemic injury*
Vasoreactivity 	Vasodilatation eNOS activity↑ Nitric oxide bioavailability↑ EDHF-mediated relaxation↑ Endothelin↓ PGI ₂ ↑ Sympathoadrenal responsiveness↓ Blood pressure↓	Vasodilatation (coronaries) via inhibition of L-type Ca ²⁺ channels Vasoconstriction (aorta) Attenuation of the vasodilatory effect of adenosine Endothelium-independent VSMC relaxation↑ Thromboxane A ₂ synthase↑ Blood pressure↑
Vascular Apoptosis 	Mitochondrial ROS production↓ Antioxidant defense mechanism↑ Antioxidant gene expression↑ NADPH oxidase activity↓ Endothelial progenitor cells↑ EC apoptosis↓ VEGF expression↑ EC proliferation↑ EC migration↑	Pro-apoptotic effect (Caspase-3↑ Bcl-2↓) Apoptosis following ischemia/reperfusion injury↓ via STAT3 activation↑ Mitochondrial stabilization via K _{ATP} channels following ischemia/reperfusion injury↑

Figure 1 Effects of oestrogen and testosterone on plaque development, atherothrombosis, coagulation, vascular injury and healing. Evidence from experimental and clinical studies. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Bcl-2, B-cell lymphoma 2 (inhibitor of apoptosis); CCL2, C-C Motif chemokine ligand 2; CRP, C-reactive protein; EC, endothelial cell; EDHF, endothelium-derived hyperpolarizing factor; eNOS, endothelial nitric oxide synthase; F, factor; IFN γ , interferon γ ; IL, interleukin; LDL, low density lipoprotein; NADPH, nicotinamide adenine dinucleotide phosphate; PAI-1, plasminogen activator inhibitor-1; PGI₂, prostaglandin I₂; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TNF- α , tumour necrosis factor- α ; TXA₂, thromboxane A₂; VCAM-1, vascular cell adhesion protein 1; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell; WBC, white blood cell. *Controversial data exist with regard to the effect of oestrogen and testosterone on platelet aggregation responses and myocardial injury.



insulin resistance contributing to hypertension.^{61,62} In fact, menopause is accompanied by an accelerated age-related rise in cardiac and peripheral sympathetic nerve activity, most likely related to an impaired central modulation of baroreflex function or a direct inhibitory influence of oestrogen on sympathetic nerve activity.^{63,64} However, although initially supported by large observational studies,^{65,66} randomized controlled trials largely failed to show any cardiovascular benefit of menopausal hormone replacement therapy (HRT) and even demonstrated an increased event rate in postmenopausal women with a recent ACS.^{67–69} Thus, the use of HRT for primary and secondary prevention of CVD remains controversial and is currently not recommended.^{70,71} Nevertheless, a re-analysis of the Women's Health Initiative data led to the so-called 'timing hypothesis', indicating that HRT might be beneficial when initiated during early menopause.^{72–74} Notably, while these data suggest that specific subgroups of postmenopausal women might profit from HRT, the use of oestrogen-containing contraceptives in premenopausal women with known CVD is generally not recommended.⁷⁵ In fact, although the risk is small in absolute numbers, combined oral contraceptives have been associated with hypertension as well as a significant increase in venous and arterial thrombosis.^{76–78}

Interestingly, changes in iron status have been suggested as an alternative mechanism accounting for the risk increase seen in postmenopausal women. Indeed, concurrent but inverse alterations occur between iron and oestrogen levels in healthy women during menopausal transition; whereas oestrogen decreases because of the cessation of ovarian functions, iron increases as a result of decreasing menstrual period.⁷⁹ Higher iron plasma levels and associated

alterations in iron metabolism after early-onset menopause are believed to exert detrimental effects on the cardiovascular system via induction of inflammatory cascades.⁸⁰ Conversely, several observational reports claim that iron deficiency independently predicts adverse cardiovascular outcomes in women and men.^{81–83} Thus, the iron hypothesis remains controversial owing to the lack of adequately designed clinical trials and the fact that current biomarkers of iron status are not validated. As iron deposits in the heart tissue might impact cardiovascular endpoints, T2 star (T2*) cardiac magnetic resonance imaging may offer an opportunity to improve our mechanistic understanding for the role of iron in CAD.⁸⁴

Pregnancy is often quoted as providing a glimpse into a woman's future health status with numerous pregnancy-related complications associated with increased cardiovascular risk.⁸⁵ A recent meta-analysis concluded that the risk of CAD was highest in women with a history of preeclampsia, placental abruption, gestational hypertension, and diabetes⁸⁶ (Figure 2). Moreover, the development of gestational diabetes has been shown to increase the risk for CAD by two- to three-fold even 25 years after delivery,⁸⁷ while preterm delivery (<37 weeks gestation) in the first pregnancy was independently associated with a 1.5-fold increased risk of CAD.⁸⁸ Notably, a combination of these risk factors seems to potentiate cardiovascular risk as the occurrence of major coronary events and mortality was nearly six-fold increased after preeclampsia in combination with preterm delivery and/or infants born small for gestational age.⁸⁹ Accordingly, adding pregnancy complications to traditional risk models led to significant improvements of CVD risk prediction among a representative sample of Norwegian women.⁹⁰

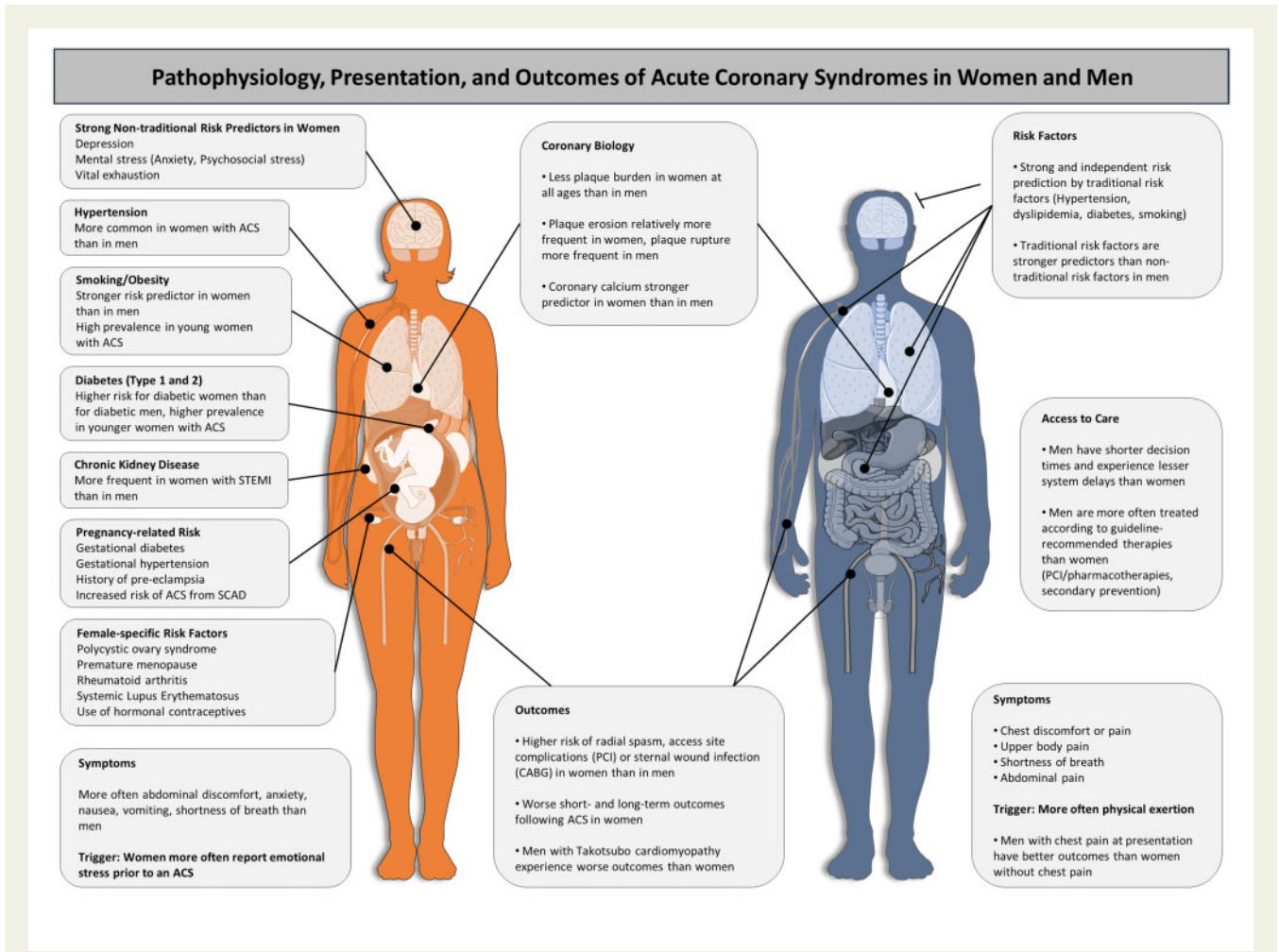


Figure 3 Sex differences in pathophysiology, presentation and outcomes of acute coronary syndromes. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection; STEMI, ST-elevation myocardial infarction.

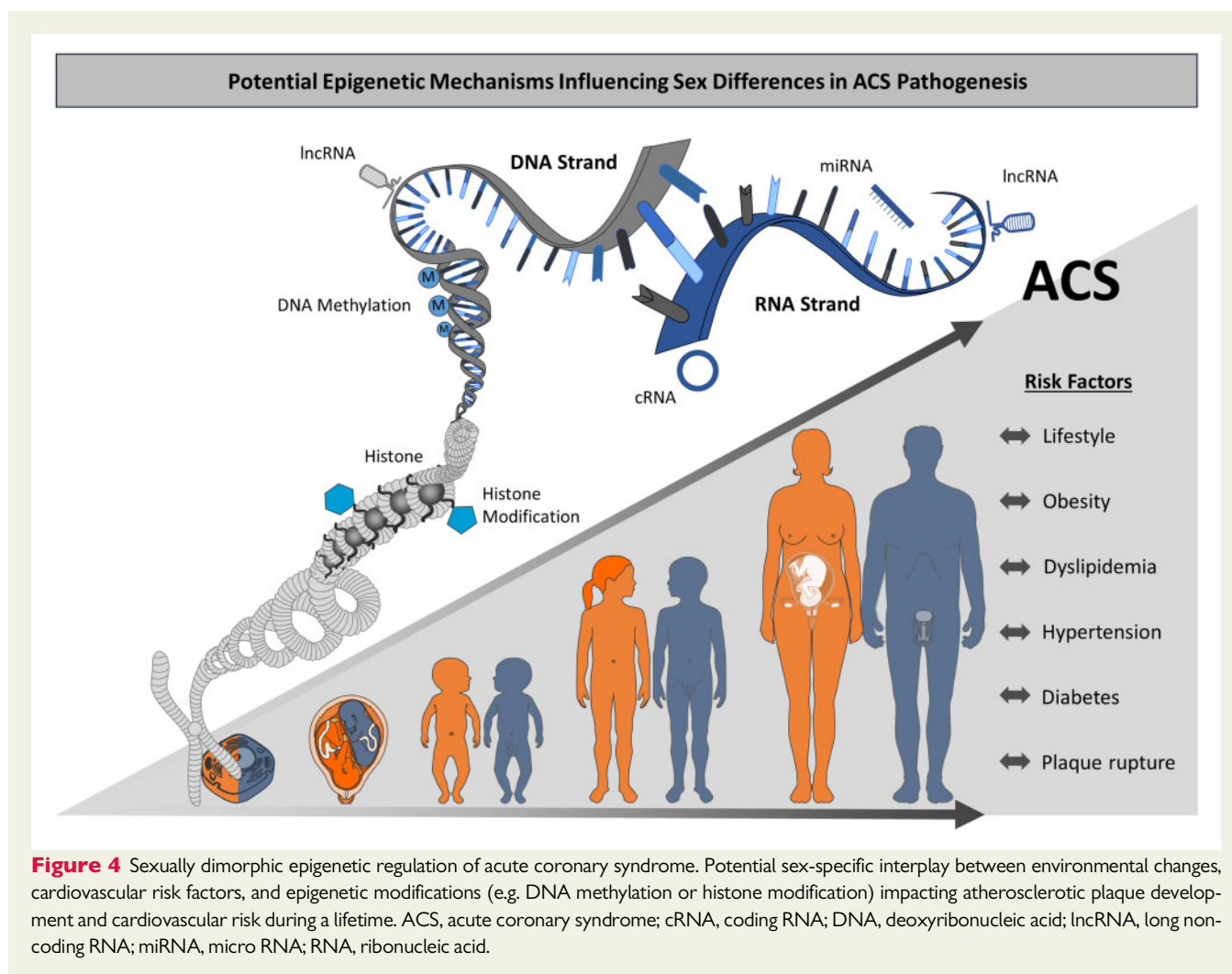
Potential future risk marker: epigenetic modifications

Epigenetic modifications of the genome might constitute a novel pathway leading to sexual dimorphism in ACS. DNA-methylation (DNAm), the best-understood epigenetic modification, defines cell's identity, is vital for normal cellular processes and adaptation to environmental changes.⁹¹ However, dysregulated DNAm contributes to adverse changes in gene expression and may affect cardiovascular risk factors including obesity, atherosclerosis, inflammation, hypertension, blood lipids, and glucose metabolism, subsequently leading to increased risk of developing CAD.^{92–94} Although epigenetic mechanisms have emerged as potential future risk factors in CVD, this field of research is still in a pioneer stage; to date, few studies with small sample sizes have investigated associations of DNAm with ACS. Of note, Li *et al.* reported that more than 11 000 differentially methylated CpGs exist between ACS cases and controls, thereby covering 5071 genes involved in ACS-related biological processes.⁹⁵ Similarly, alterations in DNAm of *ANGPTL2*, a pro-inflammatory gene, were found in post-ACS patients as compared to their healthy age-matched controls.⁹⁶ Sex differences at the level of DNAm and

associations of global and gene-specific DNAm with traditional risk factors have been described, supporting the hypothesis that epigenetic mechanisms may play a role in shaping sex differences in ACS^{97–107} (Figure 4). However, despite epigenetics being increasingly linked to sexual dimorphism in the cardiovascular system, there is lack of adequately designed epigenetic studies assessing sex-specific effects of epigenetics in the development of ACS.

Mental stress and myocardial injury

Recent data indicate that women, especially young women, are particularly vulnerable to the detrimental associations of mental stress and cardiovascular health^{108–111} (Figure 2). Accordingly, women seem to perceive greater psychological stress following an acute type 1 or type 2 MI as compared to men, which, in turn, is associated with worse recovery and prognosis.¹¹² As young women with ischaemic heart disease are a group with unexplained high mortality, these gender differences in mental stress responses are of particular importance and emphasize the need for a better evaluation of the psychosocial domain in order to risk stratify these women. The underlying psychological and biological mechanisms accounting for



the adverse vascular response to psychological stress in women are not well understood. Besides vascular determinants, variation in baseline sympathetic activity and women's propensity towards microcirculatory abnormalities,¹¹⁰ excess serotonin, a worse overall mental health status in women,³⁵ as well as a differential activation of the limbic system and the hypothalamic–adrenocortical axis in men and women are notable. Indeed, women have higher baseline cardiac sympathetic activity and excessive sympathetic discharge after an acute type 1 MI than men.^{64,113} Further, a link between the limbic system and long-term cardiovascular outcomes has recently been demonstrated¹¹⁴ and gender-stratified data indicate that this link might be pathogenic in women, but not in men.¹¹⁵

Ischaemia and non-obstructive coronary artery disease

Increasing evidence supports the notion that obstructive CAD alone is insufficient to explain symptoms of myocardial ischaemia.¹¹⁶ Indeed, microvascular angina, defined as symptoms and objective evidence of myocardial ischaemia along with non-obstructive CAD (<50% coronary diameter reduction and/or fractional flow reserve >0.80) and a reduction of CFR and/or inducible microvascular

spasm,¹¹⁷ affects approximately 50% of patients with non-obstructive CAD or normal imaging findings.¹¹⁸ Despite the absence of obstructive epicardial stenosis in these patients, they may present with severe myocardial ischaemia (ischaemia and non-obstructive CAD) or even MI (MI and non-obstructive CAD). These conditions are more frequently observed in women, given the lower burden of obstructive CAD in the female population (Figure 2). In fact, the presence of microvascular angina is twice as prevalent in women than men.¹¹⁸ The former portends a particularly high risk in women, as event-free survival is reduced in women with impaired CFR or coronary reactivity.^{119,120} As PET-derived CFR reflects the haemodynamic effects of focal, diffuse and microvascular CAD on myocardial tissue perfusion, impaired CFR seems to be an important target for coronary microvascular disease (CMVD) risk reduction in women. Indeed, CMVD might also contribute to the pathogenesis of HFpEF, another condition more commonly observed in women.¹²¹ Thus, it is crucial that symptomatic patients who do not show regional ischaemia associated with flow-limiting epicardial CAD undergo further testing. Although some studies demonstrate an improvement of prognosis by revascularization therapies (coronary artery bypass grafting, CABG) in patients with severely impaired CFR,¹²² treatment of

CMVD usually includes standard anti-ischaemic drugs (β -blockers, angiotensin-converting enzyme inhibitors, and nitrates). The diagnosis of CMVD requires a complex diagnostic work-up such as myocardial perfusion PET or invasive vasoreactivity testing; thus, optimal clinical assessment and pre-test risk stratification is crucial in order to avoid unnecessary costs and risk. In this regard, a blunted heart rate response during pharmacological stress testing has recently been shown to be a strong predictor of impaired CFR in women and may be a helpful marker to risk-stratify the heterogeneous population of patients with non-obstructive CAD.¹⁵

Gender and symptoms of myocardial ischaemia

Chest pain or pressure is the presenting symptom in >80% of women and men with ACS. However, women present with a greater number of additional non-chest pain symptoms than men such as neck pain, fatigue, dyspnoea, or nausea.¹²³ Further, women are more likely than men to present without chest pain and more often attribute their symptoms to a non-heart-related condition such as acid reflux, stress, or anxiety.¹²³ Also, women in general wait longer to seek medical attention and are less likely to have diagnostic electrocardiography changes and elevated troponin levels on admission^{124–126} (Figure 3). Accordingly, women are at an increased risk for an incorrect diagnosis and delayed treatment as evidenced by numerous studies reporting substantial system delays in women.^{125–127} In addition, women who present with ACS tend to be older and have more comorbidities than their male counterparts.¹²⁸ Of note, however, young age and the absence of chest discomfort are among the strongest predictors of a missed diagnosis of ACS and inappropriate discharge from the emergency department.¹²⁹ Further, recent observational studies in younger demographic groups report a higher prevalence of comorbidities including depression, hypertension, diabetes, and obesity in younger women with ACS as compared to age-matched men, suggesting that gender-disparities in effective management and outcomes of ACS cannot be attributed to age alone.¹³⁰

Differential diagnosis of acute coronary syndrome

Contemporary strategies for managing patients presenting with typical or atypical symptoms, an abnormal electrocardiography and raised serum troponin presume a diagnosis of an acute type 1 MI. However, in up to 10% of all patients, and in up to one-third of female patients, no culprit coronary lesion is identified angiographically.^{131,132} In these cases, the differential diagnosis includes apparently non-significant CAD such as plaque erosion, arrhythmias, coronary vasospasm (CVS), spontaneous coronary artery dissection (SCAD), Takotsubo cardiomyopathy, and myocarditis (Figure 3). While magnetic resonance imaging studies indicate that the latter seems to be present in the majority of cases where a culprit lesion is not identified,¹³³ a high index of suspicion for Takotsubo cardiomyopathy, CVS, and SCAD should be maintained when evaluating women.^{134,135} Takotsubo cardiomyopathy is characterized by transient left ventricular dysfunction resulting from severe emotional stress and usually resolves with a favourable prognosis. Although Takotsubo cardiomyopathy only accounts for up to 3% of all ACS cases, it is twice as prevalent in postmenopausal women¹³⁴ (Figure 3).

Spontaneous coronary artery dissection is an infrequent and often missed differential diagnosis of ACS and is characterized by a spontaneous separation of coronary arterial layers ultimately leading to intramural haematoma and impairment of anterograde coronary blood flow.¹³⁶ Recent epidemiological series suggest that SCAD occurs in 1–4% of ACS cases and may be the cause of ACS in up to 35% of women ≤ 50 years of age and in 43% of pregnancy-related ACS¹³⁶ (Figure 3). The latter is associated with a poorer prognosis than pregnancy-unrelated SCAD.¹³⁷ In-hospital mortality rates of SCAD are low, however, up to 14% of patients require urgent in-hospital revascularization. Non-atherosclerotic SCAD is typically associated with female sex, multiparity, physical, and emotional stress triggers, systemic arteriopathies including fibromuscular dysplasia, inflammatory, connective tissue disorders, coronary artery spasm, and hormonal therapy.¹³⁶ Although hormonal changes seem to play a major role in female SCAD, much remains to be explored on detailed molecular mechanisms by which sex hormones modulate arterial wall architecture and endothelial function.

Coronary vasospasm is caused by intense vasoconstriction of coronary arteries occurring most often at rest, particularly between midnight and early morning. Although the prognosis is generally considered benign, CVS can lead to total or subtotal vessel occlusion and subsequent ACS. Coronary vasospasm is diagnosed by coronary angiography and provocative testing and has been detected in 49% of patients with ACS in a German population.¹³⁸ Coronary vasospasm appear to be more prevalent among men than women, affecting mainly age groups between 40 and 70 years and is more common in Asian populations as compared to Western countries¹³⁹ (Figure 2). Vascular mechanisms triggering CVS episodes include transient sympatho-vagal imbalance as well as decreased bioavailability of vasodilators such as nitric oxide.^{140,141} Age, high-sensitivity C-reactive protein, and smoking have all been identified as significant risk predictors of CVS.¹³⁹ The latter has been suggested to account for the higher prevalence of CVS seen in men.

Diagnosis and disease management of acute coronary syndrome

Another issue remaining actively debated is whether there are still inequities in diagnosis and disease management, leading to gender-disparities in outcomes among patients with ACS. An excess risk for mortality in women with ACS, in particular for younger women, persists in contemporary practice.¹⁴² Female coronary pathophysiology such as a higher prevalence of CMVD and non-obstructive CAD, atypical symptoms, delay in seeking care, underutilization of evidence-based diagnostics and therapies, and a higher rate of complications during revascularization have all been suggested to account for these findings. Indeed, management strategies for ACS have largely been the same for women and men while focused predominantly on obstructive CAD: risk stratification schemes for ACS including the HEART, the Global Registry of Acute Coronary Events (GRACE), and the Thrombolysis in Myocardial Infarction risk scores as well as the Killip classification are derived from predominantly male populations and their ability to adequately risk-stratify women with suspected ACS remains debatable.¹⁴³ Similarly, current clinical practice does not consider sex-specific cut-off values for cardiac troponin given the small differences in high sensitive troponin I between men

and women. However, evidence demonstrates improved risk stratification in patients with ACS when a sex-specific 99th centile threshold of high sensitive troponin I is being used.¹⁴⁴ Whether the lack of sex-specific guidelines or the high percentage of women presenting with atypical symptoms and comorbidities account for the fact that women are less likely than men to undergo invasive revascularization remains to be determined.^{145,146} In addition, low adherence to prescribed therapies as well as underutilization of cardiac rehabilitation and pharmacotherapies in women with ACS has been reported.¹⁴⁷ Indeed, women are less likely than men to receive optimal secondary prevention with anti-platelet and lipid-lowering therapies even after angiographic documentation of disease.^{146,148,149} These disparities persist in contemporary practice, despite studies documenting the reduction of this excess mortality when optimal care is provided.¹⁵⁰

Outcomes of acute coronary syndrome in women and men

Short- and long-term mortality

Although there is evidence that gender-disparities in short-term ACS mortality can be overcome in high-quality percutaneous coronary intervention (PCI) centres,¹⁵¹ studies have consistently demonstrated less favourable short-term outcomes in women with ACS as compared to men, particularly after ST-elevation myocardial infarction (STEMI).^{1,152,153} The female susceptibility to adverse short-term outcomes following STEMI was attributed to their older age at presentation, the higher prevalence of comorbid conditions in women as well as longer system delays and underutilization of guideline-directed therapies in women with ACS.^{150,154,155} Accordingly, sex and gender differences were attenuated when adjustment for comorbidities was performed.¹⁵⁶ In contrast to short-term outcomes, gender-specific data regarding long-term morbidity and mortality following ACS are conflicting. While long-term outcomes were similar for women and men in earlier studies, more recent work indicates that long-term morbidity and mortality following ACS is higher in women as compared to men, though these gender-disparities are no longer evident following adjustment for baseline variables.^{157–159} Of note, however, studies report consistently worse short- and long-term outcomes in young and middle-aged women as compared to age-matched men.^{160–163} As previously discussed, this demographic group presents with an overall worse health status and encounters significant system delays and inequities in diagnosis and treatment, all of which might explain the excess risk in this population.^{4,5,164}

Outcomes of coronary revascularization

Current guidelines recommend immediate coronary angiography in patients with type 1 MI—STEMI as well as in patients with type 1 MI—NSTEMI (non-ST-elevation myocardial infarction) presenting with refractory angina or electrical/haemodynamic instability independent of gender. An early invasive strategy (within 24 h of diagnosis) is recommended for individuals with NSTEMI and stable clinical presentation but high-risk features according to current (gender-unspecific) risk scores.^{165,166} Benefits of an early invasive strategy have been proven for both, men and women, while a very early invasive strategy within 12 h of diagnosis improved outcomes in high-risk

NSTEMI patients, but did not benefit women.^{167,168} Of note, despite an overall benefit of invasive revascularization, female sex has consistently been associated with an increased risk of bleeding and vascular complication during PCI^{169,170} which underscores the need to consider key biological differences such as vessel size and prevalence of non-obstructive CAD and to strictly apply guideline-directed care in women. Indeed, an increased risk of restenosis, repeat revascularization, and access-site complications in women attributable to their smaller coronary arteries and the frequent occurrence of radial artery vasospasm and subsequent radial-to-femoral access crossover all need to be taken into account when treatment decisions in women are made.^{171,172} (Figures 2 and 3).

While there are currently no gender-specific data available on outcomes in patients with acute type 1 MI unsuitable for PCI who undergo early CABG, observational studies report higher risks for short- and long-term mortality following CABG in women as compared to age-matched men, even when adjusted for age and comorbidities.^{173–176} Instead, perioperative complications seem to be similar in women and men, except for a higher incidence of sternal wound infections in female patients.¹⁷⁷ Women's smaller arteries and the challenges of surgical grafting to smaller targets, a longer cross-clamp time per graft, a lesser use of internal mammary artery grafts in women, and a worse preoperative health status in women might all account for the gender differences in outcomes following CABG surgery.

Importantly, recent studies report a significant increase in the incidence of ACS in pregnant women.³ The latter is consistent with the recent rise seen in prevalence of CAD in younger, premenopausal women.^{4,5} According to latest European Society of Cardiology guidelines, primary PCI is recommended in pregnant patients with acute type I MI—STEMI consistent with standard indications for revascularization (class I recommendation), while a non-invasive approach is favoured in stable, low-risk patients with type 1 MI—NSTEMI (class IIa recommendation).¹⁷⁸

Risk of thrombosis and bleeding

The risks of thrombosis and bleeding differ between men and women. These sex differences have been attributed to the higher age of women with ACS, comorbidities, and body weight.¹⁷⁹ In addition, women experience fluctuations of pro-thrombotic activity and haemostasis that are related to the menstrual cycle, the use of hormonal contraceptives or HRT, pregnancy, and menopause,^{179,180} all of which might contribute to sex differences in the thrombotic or haemorrhagic burden in women with ACS. Indeed, the higher risk of bleeding complications during PCI observed in women might in part be related to an oestrogen-dependent increase of prostacyclin secretion and nitric oxide bioavailability as well as a direct inhibitory effect of oestrogen on platelet aggregation.^{181–184} Of note, however, there is conflicting evidence regarding sex differences in baseline and on-treatment platelet reactivity.^{185–188} In fact, while some studies report a more pronounced platelet adhesion to the site of injury in men as compared to women,¹⁸⁹ others have demonstrated a greater baseline and agonist-induced platelet reactivity and aggregation in women.^{181,185,190–192} (Figure 1). The latter contrasts with an up to 25% longer *in vivo* bleeding time in women as compared to men. Thus, further research is necessary to disentangle the complex interaction between haemostasis, sex, and hormone status at baseline and

in the context of an ACS. In mainly postmenopausal cohorts, smaller arteries and related access-site complications as well as inappropriate dosing of antithrombotic agents irrespective of body weight have been suggested to account for their excess bleeding risk.¹⁹³ Indeed, female sex was associated with an enhanced risk of non-bypass-related bleeding events in the prasugrel and ticagrelor arms of the TRITON-TIMI 38 and the PLATO trials.^{194,195} In contrast, no interaction between female sex and excess bleeding was seen in a meta-analysis comparing clopidogrel plus aspirin vs aspirin,¹⁹⁶ and a recent meta-analysis reported a comparable efficacy and safety profile of potent P2Y₁₂ inhibitors including prasugrel, ticagrelor, and intravenous cangrelor in women and men.¹⁹⁷ In contrast, however, recent data from the CRUSADE initiative indicate that women with type 1 MI—NSTEMI were more likely to receive excess glycoprotein (GP)IIb/IIIa doses than men, with the latter being associated with an increased risk of bleeding.¹⁸³ Taken together, these data indicate that sex should not influence patient selection for the administration of P2Y₁₂ inhibitors; however, special attention has to be paid in women to properly apply weight- and age-adjustments of anti-thrombotic agents including GPIIb/IIIa inhibitors, heparins, and prasugrel. Indeed, up to one-fourth of sex-related differences in bleeding risk seem to be avoidable.¹⁸³

As previously outlined, a significant rise in the incidence of ACS is currently being observed in pregnant women.³ Pregnancy is a pro-coagulant state, aimed at preventing bleeding at the time of delivery and is characterized by an increase in the levels of coagulation factors, fibrinogen, and von Willebrand factor, a reduction of activity of protein S and C, and an increase in plasminogen activator inhibitor type 1 and 2.¹⁸⁰ Unfortunately, current guidelines provide little information regarding the use of antiplatelet therapy in pregnant women with ACS. A recommendation is only given for aspirin, short-term heparinization during PCI and for clopidogrel, which should solely be used when strictly necessary and for the shortest duration. The use of GPIIb/IIIa inhibitors, bivalirudin, prasugrel, and ticagrelor is not recommended due to the lack of data in pregnant women.¹⁷⁸

Conclusion and outlook

Although substantial progress has been made towards improving gender- and sex-specific ACS disease management and outcomes, contemporary reports indicate a persistent knowledge gap with regard to optimal risk-stratification and management in female ACS patients. Prominent patient and system delays in women with AMI result from limited awareness for the latent CVD risk in women, a lack of sex-specific thresholds within clinical guidelines, and subsequent limited performance of contemporary diagnostic approaches in women, all of which are the result of a persistent underrepresentation of women in cardiovascular studies.¹⁰ In addition, little is known about the influence of socioenvironmental and contextual factors on gender-specific disease manifestation and outcomes. Thus, future research will have to overcome barriers accounting for the low numbers of women enrolled in ACS trials and to explore sex and gender differences in biology, environment, and psychosocial complexity. Finally, improved interdisciplinary and cooperative care in women's health has recently been suggested as an attractive model to target

cardiovascular health inequalities between women and men linked to modifiable risk factors and social determinants of health.⁹⁵

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