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CLINICAL REVIEW
Clinical update

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 core[24] (*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 MI[33] 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 men[44] (*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 men[48] (*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, cardiometabolic 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

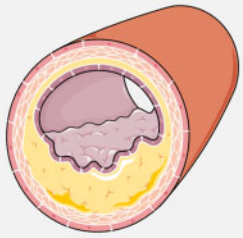
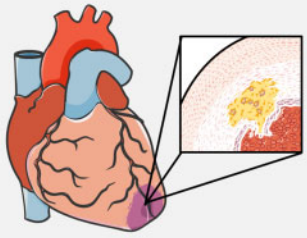
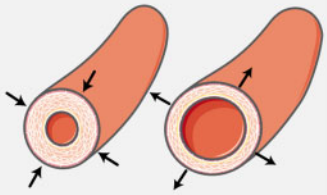
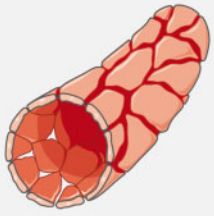
	Estrogens	Testosterone
Atherosclerosis Risk Factors 	LDL oxidation↓ LDL binding↓ VSMC proliferation↓ VSMC migration↓ EC proliferation↑ EC migration↑ CRP↑ Pro-inflammatory (TNF-α, IFNγ, IL-6, CCL2) cytokine production↑ Hematopoietic stem cell differentiation↑ Coronary calcification↓	Conflicting effects on lipids Expression of pro-atherogenic genes↑ WBC adherence to EC↑ Pro-inflammatory cytokines (TNF-α, IL-1β, 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 PGI2↑ Platelet response to ADP↑ TXA2 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 Ca2+ channels Vasoconstriction (aorta) Attenuation of the vasodilatory effect of adenosine Endothelium-independent VSMC relaxation↑ Thromboxane A2 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; IFNγ, 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. [a]Controversial data exist with regard to the effect of oestrogen and testosterone on platelet aggregation responses and myocardial injury.

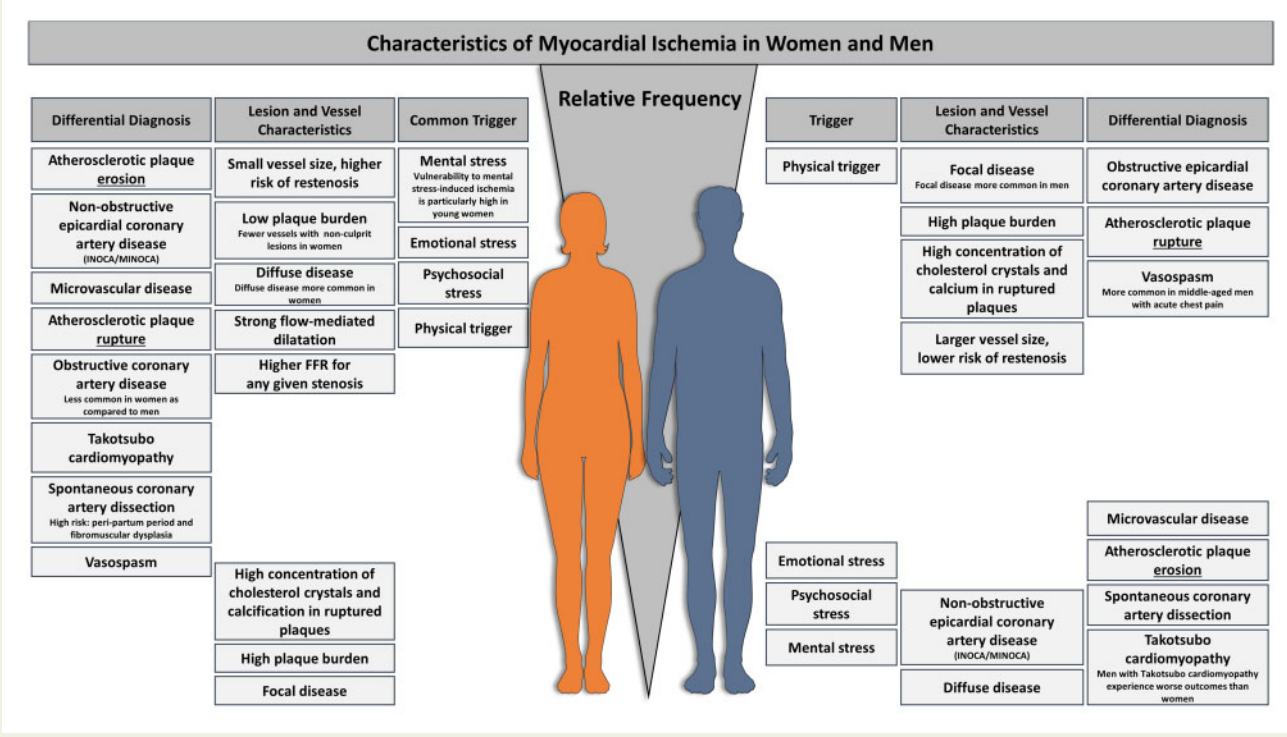


Figure 2 Mechanisms and characteristics of myocardial ischaemia in women and men. FFR, fractional flow reserve; INOCA, ischaemia and no obstructive coronary artery disease; MINOCA, myocardial infarction with no obstructive coronary artery disease.

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 diabetes[86] (*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]

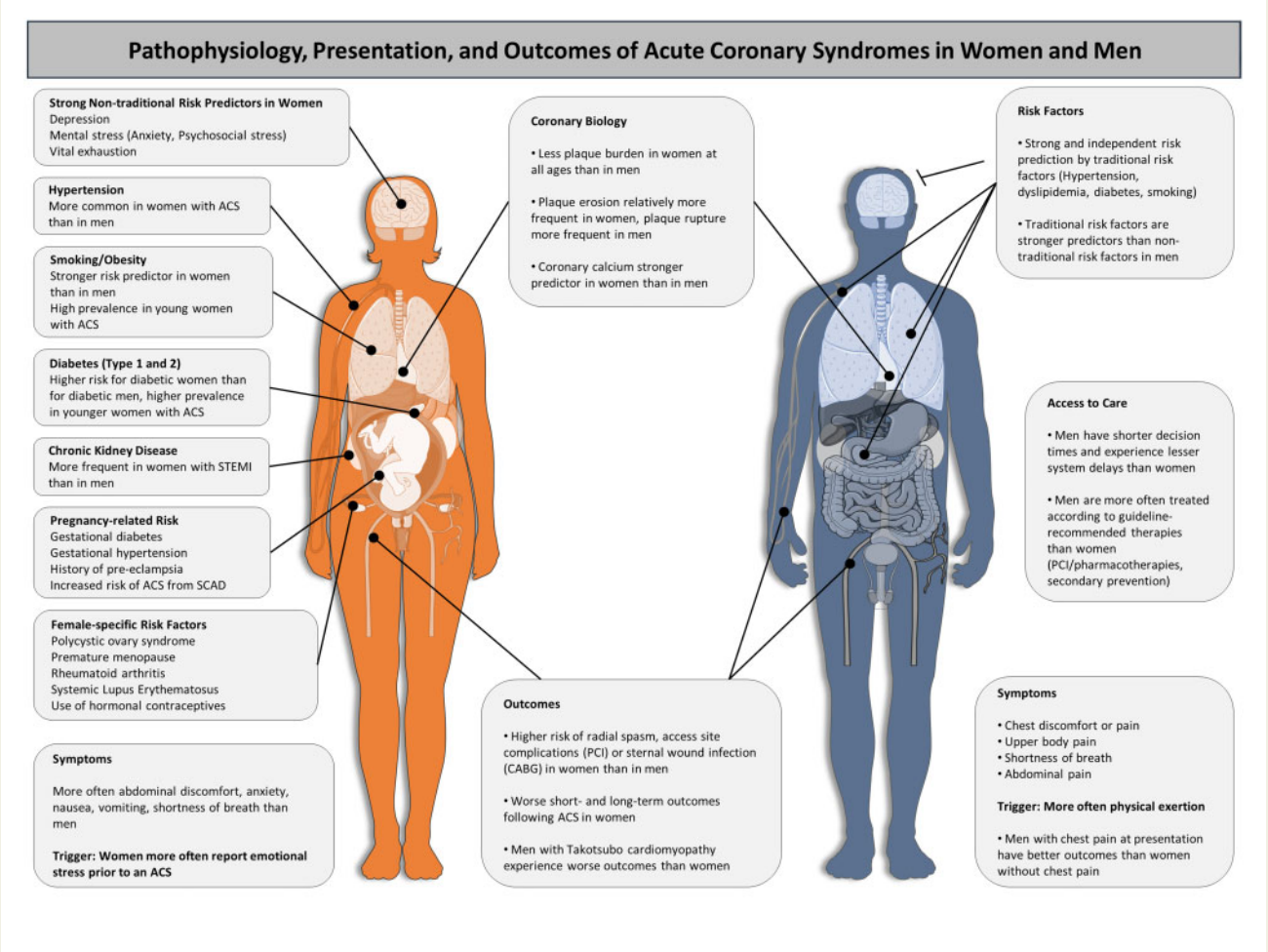


Figure 3 Sex differences in pathophysiology, presentation and outcomes of acute coronary syndromes. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection; STEMI, ST-elevation myocardial infarction.

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

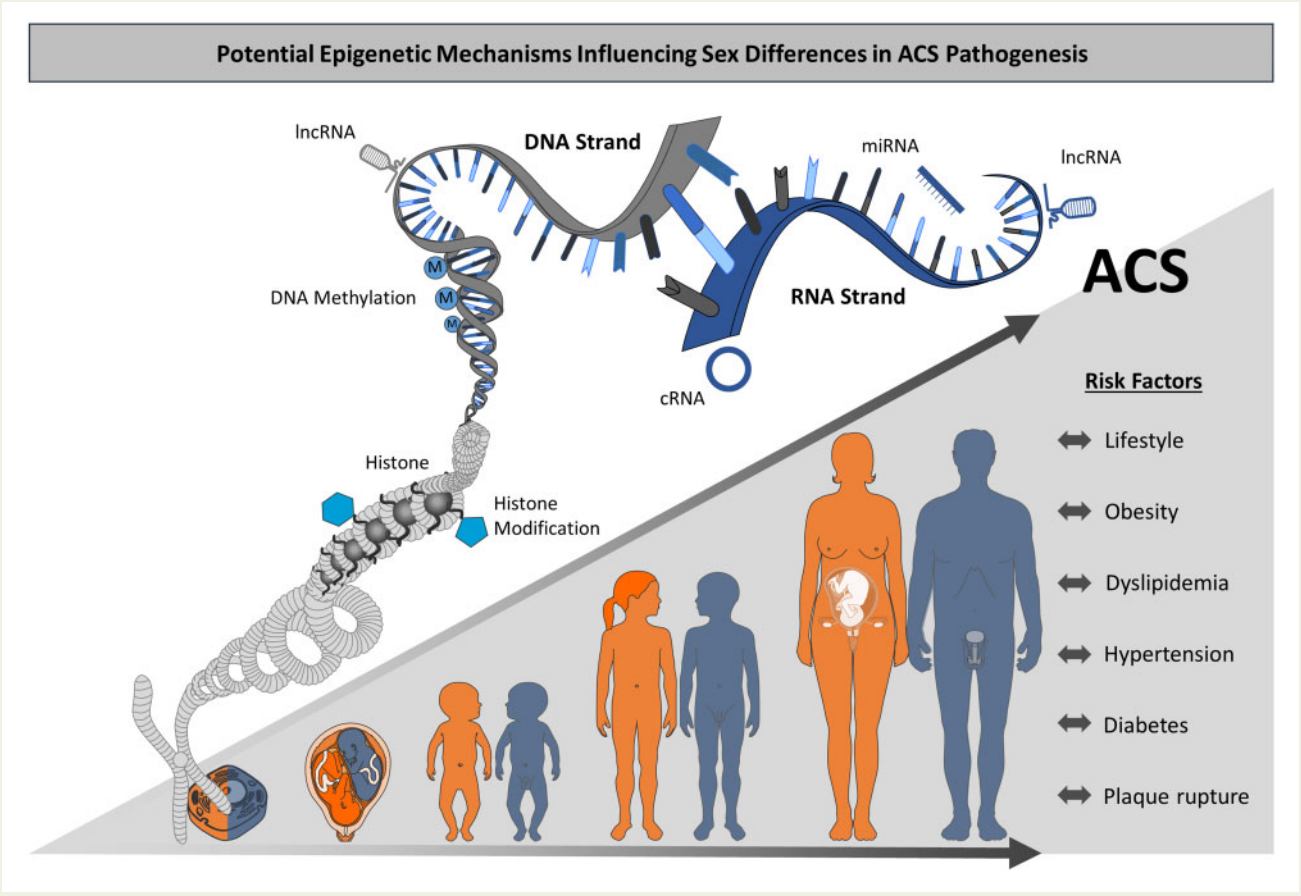


Figure 4 Sexually dimorphic epigenetic regulation of acute coronary syndrome. Potential sex-specific interplay between environmental changes, cardiovascular risk factors, and epigenetic modifications (e.g. DNA methylation or histone modification) impacting atherosclerotic plaque development and cardiovascular risk during a lifetime. ACS, acute coronary syndrome; cRNA, coding RNA; DNA, deoxyribonucleic acid; lncRNA, long non-coding RNA; miRNA, micro RNA; RNA, ribonucleic acid.

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 demonstrated[114] 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, is it 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 women[134] (*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 ACS[136] (*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 countries[139] (*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 $P2Y_{12}$ 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 $P2Y_{12}$ 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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References

1. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* 2016;**37**:3232–3245.
2. Gupta A, Wang Y, Spertus JA, Geda M, Lorenze N, Nkonde-Price C, D'Onofrio G, Lichtman JH, Krumholz HM. Trends in acute myocardial infarction in young patients and differences by sex and race, 2001 to 2010. *J Am Coll Cardiol* 2014;**64**:337–345.
3. Smilowitz NR, Gupta N, Guo Y, Zhong J, Weinberg CR, Reynolds HR, Bangalore S. Acute myocardial infarction during pregnancy and the puerperium in the United States. *Mayo Clin Proc* 2018;**93**:1404–1414.
4. Gabet A, Danchin N, Juilliere Y, Olie V. Acute coronary syndrome in women: rising hospitalizations in middle-aged French women, 2004-14. *Eur Heart J* 2017;**38**:1060–1065.
5. Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, Porterfield D, Blankstein R, Rosamond WD, Bhatt DL, Caughey MC. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. *Circulation* 2019;**139**:1047–1056.
6. Vaccarino V. Myocardial infarction in young women. *Circulation* 2019;**139**:1057–1059.
7. Pagidipati NJ, Peterson ED. Acute coronary syndromes in women and men. *Nat Rev Cardiol* 2016;**13**:471–480.
8. Buch T, Moos K, Ferreira FM, Frohlich H, Gebhard C, Tresch A. Benefits of a factorial design focusing on inclusion of female and male animals in one experiment. *J Mol Med (Berl)* 2019;**97**:871–877.
9. Mogil JS. Perspective: equality need not be painful. *Nature* 2016;**535**:S7.
10. Scott PE, Unger EF, Jenkins MR, Southworth MR, McDowell TY, Geller RJ, Elahi M, Temple RJ, Woodcock J. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *J Am Coll Cardiol* 2018;**71**:1960–1969.
11. Shah K, McCormack CE, Bradbury NA. Do you know the sex of your cells? *Am J Physiol Cell Physiol* 2014;**306**:C3–C18.
12. Ghare MI, Chandrasekhar J, Mehran R, Ng V, Grines C, Lansky A. Sex disparities in cardiovascular device evaluations: strategies for recruitment and retention of female patients in clinical device trials. *JACC Cardiovasc Interv* 2019;**12**:301–308.
13. Hiteshi AK, Li D, Gao Y, Chen A, Flores F, Mao SS, Budoff MJ. Gender differences in coronary artery diameter are not related to body habitus or left ventricular mass. *Clin Cardiol* 2014;**37**:605–609.
14. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, Dorbala S, Blankstein R, Rimoldi O, Camici PG, Di Carli MF. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 2014;**129**:2518–2527.
15. Haider A, Bengs S, Maredziak M, Messerli M, Fiechter M, Giannopoulos AA, Treyer V, Schwyzer M, Kamani CH, Patriki D, von Felten E, Benz DC, Fuchs TA, Grani C, Pazhenkottil AP, Kaufmann PA, Buechel RR, Gebhard C. Heart rate reserve during pharmacological stress is a significant negative predictor of impaired coronary flow reserve in women. *Eur J Nucl Med Mol Imaging* 2019;**46**:1257–1267.
16. Patel MB, Bui LP, Kirkeeide RL, Gould KL. Imaging microvascular mysfunction and mechanisms for female-male differences in CAD. *JACC Cardiovasc Imaging* 2016;**9**:465–482.
17. Koskinas KC, Sukhova GK, Baker AB, Papafaklis MI, Chatzizisis YS, Coskun AU, Quillard T, Jonas M, Maynard C, Antoniadis AP, Shi GP, Libby P, Edelman ER, Feldman CL, Stone PH. Thin-capped atheromata with reduced collagen content

in pigs develop in coronary arterial regions exposed to persistently low endothelial shear stress. *Arterioscler Thromb Vasc Biol* 2013;**33**:1494–1504.
18. Kerkhof PLM, Miller VM. *Sex-Specific Analysis of Cardiovascular Function*. Basel, Switzerland: Springer International Publishing; 2018.
19. Weiner CP, Lizasoain I, Baylis SA, Knowles RG, Charles IG, Moncada S. Induction of calcium-dependent nitric oxide synthases by sex hormones. *Proc Natl Acad Sci USA* 1994;**91**:5212–5216.
20. Miller VM, Duckles SP. Vascular actions of estrogens: functional implications. *Pharmacol Rev* 2008;**60**:210–241.
21. Deroo BJ, Korach KS. Estrogen receptors and human disease. *J Clin Invest* 2006; **116**:561–570.
22. Staessen JA, van der Heijden-Spek JJ, Safar ME, Den Hond E, Gasowski J, Fagard RH, Wang JG, Boudier HA, Van Bortel LM. Menopause and the characteristics of the large arteries in a population study. *J Hum Hypertens* 2001;**15**:511–518.
23. DuPont JJ, Kenney RM, Patel AR, Jaffe IZ. Sex differences in mechanisms of arterial stiffness. *Br J Pharmacol* 2019;**176**:4208–4225.
24. Lansky AJ, Ng VG, Maehara A, Weisz G, Lerman A, Mintz GS, De Bruyne B, Farhat N, Niess G, Jankovic I, Lazar D, Xu K, Fahy M, Serruys PW, Stone GW. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. *JACC Cardiovasc Imaging* 2012; **5**(3 Suppl):S62–S72.
25. Dai J, Xing L, Jia H, Zhu Y, Zhang S, Hu S, Lin L, Ma L, Liu H, Xu M, Ren X, Yu H, Li L, Zou Y, Zhang S, Mintz GS, Hou J, Yu B. *In vivo* predictors of plaque erosion in patients with ST-segment elevation myocardial infarction: a clinical, angiographical, and intravascular optical coherence tomography study. *Eur Heart J* 2018;**39**:2077–2085.
26. Johnson TW, Räber L, di Mario C, Bourantas C, Jia H, Mattesini A, Gonzalo N, de la Torre Hernandez JM, Prati F, Koskinas K, Joner M, Radu MD, Erlinge D, Regar E, Kunadian V, Maehara A, Byrne RA, Capodanno D, Akasaka T, Wijns W, Mintz GS, Guagliumi G. Clinical use of intracoronary imaging. Part 2: acute coronary syndromes, ambiguous coronary angiography findings, and guiding interventional decision-making: an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions: endorsed by the Chinese Society of Cardiology, the Hong Kong Society of Transcatheter Endocardiovascular Therapeutics (HKSTENT) and the Cardiac Society of Australia and New Zealand. *Eur Heart J* 2019;**40**:2566–2584.
27. Shaw LJ, Min JK, Nasir K, Xie JX, Berman DS, Miedema MD, Whelton SP, Dardari ZA, Rozanski A, Rumberger J, Bairey Merz CN, Al-Mallah MH, Budoff MJ, Blaha MJ. Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC Consortium. *Eur Heart J* 2018;**39**: 3727–3735.
28. Truong QA, Rinehart S, Abbara S, Achenbach S, Berman DS, Bullock-Palmer R, Carrascosa P, Chinnaiyan KM, Dey D, Ferencik M, Fuechtner G, Hecht H, Jacobs JE, Lee SE, Leipsic J, Lin F, Meave A, Pugliese F, Sierra-Galan LM, Williams MC, Villines TC, Shaw LJ. Coronary computed tomographic imaging in women: an expert consensus statement from the Society of Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr* 2018;**12**:451–466.
29. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation* 2011; **124**:2145–2154.
30. Garcia M, Mulvagh SL, Merz CN, Buring JE, Manson JE. Cardiovascular disease in women: clinical perspectives. *Circ Res* 2016;**118**:1273–1293.
31. Berger JS, Elliott L, Gallup D, Roe M, Granger CB, Armstrong PW, Simes RJ, White HD, Van de WF, Topol EJ, Hochman JS, Newby LK, Harrington RA, Califf RM, Becker RC, Douglas PS. Sex differences in mortality following acute coronary syndromes. *JAMA* 2009;**302**:874–882.
32. Udell JA, Koh M, Qiu F, Austin PC, Wijeysundera HC, Bagai A, Yan AT, Goodman SG, Tu JV, Ko DT. Outcomes of women and men with acute coronary syndrome treated with and without percutaneous coronary revascularization. *J Am Heart Assoc* 2017;**6**:e004319.
33. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;**40**:237–269.
34. Sabbag A, Matetzky S, Porter A, Iakobishvili Z, Moriel M, Zwas D, Fefer P, Asher E, Beigel R, Gottlieb S, Goldenberg I, Segev A. Sex differences in the management and 5-year outcome of young patients (<55 years) with acute coronary syndromes. *Am J Med* 2017;**130**:1324.e15–1324.e22.
35. Dreyer RP, Smolderen KG, Strait KM, Beltrame JF, Lichtman JH, Lorenze NP, D'Onofrio G, Bueno H, Krumholz HM, Spertus JA. Gender differences in pre-event health status of young patients with acute myocardial infarction: a VIRGO study analysis. *Eur Heart J Acute Cardiovasc Care* 2016;**5**:43–54.
36. Njolstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. *Circulation* 1996;**93**:450–456.
37. Bolego C, Poli A, Paoletti R. Smoking and gender. *Cardiovasc Res* 2002;**53**: 568–576.
38. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet* 2011;**378**:1297–1305.
39. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J* 2008;**29**:932–940.
40. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia* 2014;**57**:1542–1551.
41. Savji N, Meijers WC, Bartz TM, Bhambhani V, Cushman M, Nayor M, Kizer JR, Sarma A, Blaha MJ, Gansevoort RT, Gardin JM, Hillege HL, Ji F, Kop WJ, Lau ES, Lee DS, Sadreyev R, van Gilst WH, Wang TJ, Zanni MV, Vasan RS, Allen NB, Psaty BM, van der Harst P, Levy D, Larson M, Shah SJ, de Boer RA, Gottdiener JS, Ho JE. The association of obesity and cardiometabolic traits with incident HFpEF and HFrEF. *JACC Heart Fail* 2018;**6**:701–709.
42. Beckowski M, Gierlotka M, Gasior M, Polonski L, Zdrojewski T, Dabrowski R, Karwowski J, Kowalik I, Drygas W, Szwed H. Risk factors predisposing to acute coronary syndromes in young women ≤45years of age. *Int J Cardiol* 2018;**264**: 165–169.
43. Banerjee A, Silver LE, Heneghan C, Welch SJ, Bull LM, Mehta Z, Banning AP, Rothwell PM. Sex-specific familial clustering of myocardial infarction in patients with acute coronary syndromes. *Circ Cardiovasc Genet* 2009;**2**:98–105.
44. Bucholz EM, Strait KM, Dreyer RP, Lindau ST, D'Onofrio G, Geda M, Spatz ES, Beltrame JF, Lichtman JH, Lorenze NP, Bueno H, Krumholz HM. Editor's choice-sex differences in young patients with acute myocardial infarction: a VIRGO study analysis. *Eur Heart J Acute Cardiovasc Care* 2017;**6**:610–622.
45. Shah AJ, Veledar E, Hong Y, Bremner JD, Vaccarino V. Depression and history of attempted suicide as risk factors for heart disease mortality in young individuals. *Arch Gen Psychiatry* 2011;**68**:1135–1142.
46. Rich-Edwards JW, Mason S, Rexrode K, Spiegelman D, Hibert E, Kawachi I, Jun HJ, Wright RJ. Physical and sexual abuse in childhood as predictors of early-onset cardiovascular events in women. *Circulation* 2012;**126**:920–927.
47. Schwab K, Samans R, Zahidi S, Leopold TA, Ratcheva V, Hausmann R, D'Andrea Tyson L. Global gender gap report 2016. Insight Report of the World Economic Forum, 2016, pp. 8–30.
48. Backholer K, Peters SA, Bots SH, Peeters A, Huxley RR, Woodward M. Sex differences in the relationship between socioeconomic status and cardiovascular disease: a systematic review and meta-analysis. *J Epidemiol Community Health* 2016**71**:550–557.
49. Pelletier R, Khan NA, Cox J, Daskalopoulou SS, Eisenberg MJ, Bacon SL, Lavoie KL, Daskupta K, Rabi D, Humphries KH, Norris CM, Thanassoulis G, Behlouli H, Pilote L. Sex versus gender-related characteristics: which predicts outcome after acute coronary syndrome in the young? *J Am Coll Cardiol* 2016;**67**: 127–135.
50. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, Feldstein AE, Britt EB, Fu X, Chung Y-M, Wu Y, Schauer P, Smith JD, Allayee H, Tang WHW, DiDonato JA, Lusis AJ, Hazen SL. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 2011;**472**:57–63.
51. Pedersen HK, Gudmundsdottir V, Nielsen HB, Hyotylainen T, Nielsen T, Jensen BAH, Forslund K, Hildebrand F, Prifti E, Falony G, Le Chatelier E, Levenez F, Doré J, Mattila I, Plichta DR, Pöhö P, Hellgren LI, Arumugam M, Sunagawa S, Vieira-Silva S, Jørgensen T, Holm JB, Trošt K, Consortium M, Kristiansen K, Brix S, Raes J, Wang J, Hansen T, Bork P, Brunak S, Oresic M, Ehrlich SD, Pedersen O. Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature* 2016;**535**:376–381.
52. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, Britt EB, Fu X, Wu Y, Li L, Smith JD, DiDonato JA, Chen J, Li H, Wu GD, Lewis JD, Warrier M, Brown JM, Krauss RM, Tang WHW, Bushman FD, Lusis AJ, Hazen SL. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med* 2013;**19**:576–585.
53. Li XS, Obeid S, Klingenberg R, Gencer B, Mach F, Raber L, Windecker S, Rodondi N, Nanchen D, Muller O, Miranda MX, Matter CM, Wu Y, Li L, Wang Z, Alamri HS, Gogonea V, Chung YM, Tang WH, Hazen SL, Luscher TF. Gut microbiota-dependent trimethylamine N-oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors. *Eur Heart J* 2017;**38**:814–824.
54. Wang Z, Tang WH, Buffa JA, Fu X, Britt EB, Koeth RA, Levison BS, Fan Y, Wu Y, Hazen SL. Prognostic value of choline and betaine depends on intestinal microbiota-generated metabolite trimethylamine-N-oxide. *Eur Heart J* 2014;**35**: 904–910.
55. Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U, von Bergen M, McCoy KD, Macpherson AJ, Danska JS. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. *Science* 2013;**339**:1084–1088.

56. Chella Krishnan K, Mehrabian M, Lusis AJ. Sex differences in metabolism and cardiometabolic disorders. *Curr Opin Lipidol* 2018;**29**:404–410.
57. Chen J-J, Zheng P, Liu Y-Y, Zhong X-G, Wang H-Y, Guo Y-J, Xie P. Sex differences in gut microbiota in patients with major depressive disorder. *Neuropsychiatr Dis Treat* 2018;**14**:647–655.
58. Gomez A, Luckey D, Taneja V. The gut microbiome in autoimmunity: sex matters. *Clin Immunol* 2015;**159**:154–162.
59. de Kat AC, Dam V, Onland-Moret NC, Eijkemans MJ, Broekmans FJ, van der Schouw YT. Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. *BMC Med* 2017;**15**:2.
60. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol* 2016;**1**:767–776.
61. Rosano GM, Vitale C, Marazzi G, Volterrani M. Menopause and cardiovascular disease: the evidence. *Climacteric* 2007;**10**(Suppl 1):19–24.
62. Vitale C, Mendelsohn ME, Rosano GM. Gender differences in the cardiovascular effect of sex hormones. *Nat Rev Cardiol* 2009;**6**:532–542.
63. Vongpatanasin W. Autonomic regulation of blood pressure in menopause. *Semin Reprod Med* 2009;**27**:338–345.
64. Burger IA, Lohmann C, Messerli M, Bengs S, Becker A, Maredziak M, Treyer V, Haider A, Schwyzer M, Benz DC, Kudura K, Fiechter M, Giannopoulos AA, Fuchs TA, Grani C, Pazhenkottil AP, Gaemperli O, Buechel RR, Kaufmann PA, Gebhard C. Age- and sex-dependent changes in sympathetic activity of the left ventricular apex assessed by 18F-DOPA PET imaging. *PLoS One* 2018;**13**:e0202302.
65. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens CH. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. *N Engl J Med* 1991;**325**:756–762.
66. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;**133**:933–941.
67. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;**349**:523–534.
68. Hodis HN, Mack WJ, Azen SP, Lobo RA, Shoupe D, Mahrer PR, Faxon DP, Cashin-Hemphill L, Sanmarco ME, French WJ, Shook TL, Gaarder TD, Mehra AO, Rabbani R, Sevanian A, Shil AB, Torres M, Vogelbach KH, Selzer RH. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003;**349**:535–545.
69. Alexander KP, Newby LK, Hellkamp AS, Harrington RA, Peterson ED, Kopecky S, Langer A, O'Gara P, O'Connor CM, Daly RN, Califf RM, Khan S, Fuster V. Initiation of hormone replacement therapy after acute myocardial infarction is associated with more cardiac events during follow-up. *J Am Coll Cardiol* 2001;**38**:1–7.
70. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC Jr, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women–2011 update: a guideline from the American Heart Association. *Circulation* 2011;**123**:1243–1262.
71. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159–2219.
72. Boardman HM, Hartley L, Eisinga A, Main C, Roque I Figuls M B, Cosp X G, Sanchez R, Knight B. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev* 2015;**3**:CD002229.
73. Salpeter SR, Walsh JM, Greyber E, Ormiston TM, Salpeter EE. Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. *J Gen Intern Med* 2004;**19**:791–804.
74. Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, Li Y, Feng M, Dustin L, Kono N, Stanczyk FZ, Selzer RH, Azen SP. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med* 2016;**374**:1221–1231.
75. Roos-Hesselink JW, Cornette J, Sliwa K, Pieper PG, Veldtman GR, Johnson MR. Contraception and cardiovascular disease. *Eur Heart J* 2015;**36**:1728–1734, 1734a–1734b.
76. Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009;**339**:b2890.
77. Lidegaard O, Lokkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012;**366**:2257–2266.
78. Dong W, Colhoun HM, Poulter NR. Blood pressure in women using oral contraceptives: results from the Health Survey for England 1994. *J Hypertens* 1997;**15**:1063–1068.
79. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet* 2007;**370**:511–520.
80. Muka T, Chowdhury R, Franco OH. Effect of iron levels on women after premature or early-onset menopause-reply. *JAMA Cardiol* 2017;**2**:458–459.
81. Karakas M, Waldeyer C, Ojeda F, Schnabel R, Lackner K, Anker S, Westermann D, Blankenberg S, Zeller T. Iron deficiency independently and strongly predicts risk of cardiovascular death and myocardial infarction in patients with acute coronary syndrome. *Circulation* 2016;**134**(suppl_1):A18474.
82. Zeller T, Waldeyer C, Ojeda F, Schnabel RB, Schäfer S, Altay A, Lackner KJ, Anker SD, Westermann D, Blankenberg S, Karakas M. Adverse outcome prediction of iron deficiency in patients with acute coronary syndrome. *Biomolecules* 2018;**8**:60.
83. Farhan S, Baber U, Mehran R. Anemia and acute coronary syndrome: time for intervention studies. *J Am Heart Assoc* 2016;**5**:e004908.
84. Kobayashi M, Suhara T, Baba Y, Kawasaki NK, Higa JK, Matsui T. Pathological roles of iron in cardiovascular disease. *Curr Drug Targets* 2018;**19**:1068–1076.
85. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? *Epidemiol Rev* 2014;**36**:57–70.
86. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, Smith GN, Gore GC, Ray JG, Nerenberg K, Platt RW. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications. *Circulation* 2019;**139**:1069–1079.
87. McKenzie-Sampson S, Paradis G, Healy-Profitós J, St-Pierre F, Auger N. Gestational diabetes and risk of cardiovascular disease up to 25 years after pregnancy: a retrospective cohort study. *Acta Diabetol* 2018;**55**:315–322.
88. Tanz LJ, Stuart JJ, Williams PL, Rimm EB, Missmer SA, Rexrode KM, Mukamal KJ, Rich-Edwards JW. Preterm delivery and maternal cardiovascular disease in young and middle-aged adult women. *Circulation* 2017;**135**:578–589.
89. Riise HK, Sulo G, Tell GS, Igland J, Nygard O, Vollset SE, Iversen AC, Austgulen R, Daltveit AK. Incident coronary heart disease after preeclampsia: role of reduced fetal growth, preterm delivery, and parity. *J Am Heart Assoc* 2017;**6**:e004158.
90. Markovitz AR, Stuart JJ, Horn J, Williams PL, Rimm EB, Missmer SA, Tanz LJ, Haug EB, Fraser A, Timpka S, Klykken B, Dalen H, Romundstad PR, Rich-Edwards JW, Åsvold BO. Does pregnancy complication history improve cardiovascular disease risk prediction? Findings from the HUNT study in Norway. *Eur Heart J* 2019;**40**:1113–1120.
91. Feinberg AP. The key role of epigenetics in human disease prevention and mitigation. *N Engl J Med* 2018;**378**:1323–1334.
92. Braun KV, Voortman T, Dhana K, Troup J, Bramer WM, Troup J, Chowdhury R, Dehghan A, Muka T, Franco OH. The role of DNA methylation in dyslipidaemia: a systematic review. *Prog Lipid Res* 2016;**64**:178–191.
93. Muka T, Nano J, Voortman T, Braun KVE, Ligthart S, Stranges S, Bramer WM, Troup J, Chowdhury R, Dehghan A, Franco OH. The role of global and regional DNA methylation and histone modifications in glycemic traits and type 2 diabetes: a systematic review. *Nutr Metab Cardiovasc Dis* 2016;**26**:553–566.
94. Muka T, Koromani F, Portilla E, O'Connor A, Bramer WM, Troup J, Chowdhury R, Dehghan A, Franco OH. The role of epigenetic modifications in cardiovascular disease: a systematic review. *Int J Cardiol* 2016;**212**:174–183.
95. Brown HL, Warner JJ, Gianos E, Gulati M, Hill AJ, Hollier LM, Rosen SE, Rosser ML, Wenger NK. Promoting risk identification and reduction of cardiovascular disease in women through collaboration with obstetricians and gynecologists: a presidential advisory from the American Heart Association and the American College of Obstetricians and Gynecologists. *Circulation* 2018;**137**:e843–e852.
96. Nguyen A, Mamarbachi M, Turcot V, Lessard S, Yu C, Luo X, Lalonge J, Hayami D, Gayda M, Juneau M, Thorin-Trescases N, Lettre G, Nigam A, Thorin E. Lower methylation of the ANGPTL2 gene in leukocytes from post-acute coronary syndrome patients. *PLoS One* 2016;**11**:e0153920.
97. Garcia-Calzon S, Perfilyev A, de Mello VD, Pihlajamaki J, Ling C. Sex differences in the methylome and transcriptome of the human liver and circulating HDL-cholesterol levels. *J Clin Endocrinol Metab* 2018;**103**:4395–4408.
98. Cash HL, McGarvey ST, Houseman EA, Marsit CJ, Hawley NL, Lambert-Messerlian GM, Viali S, Tuitele J, Kelsey KT. Cardiovascular disease risk factors

and DNA methylation at the LINE-1 repeat region in peripheral blood from Samoan Islanders. *Epigenetics* 2011;**6**:1257–1264.
99. Rodriguez-Rodero S, Menendez-Torre E, Fernandez-Bayon G, Morales-Sanchez P, Sanz L, Turienzo E, Gonzalez JJ, Martinez-Faedo C, Suarez-Gutierrez L, Ares J, Diaz-Naya L, Martin-Nieto A, Fernandez-Morera JL, Fraga MF, Delgado-Alvarez E. Altered intragenic DNA methylation of HOOK2 gene in adipose tissue from individuals with obesity and type 2 diabetes. *PLoS One* 2017;**12**: e0189153.
100. Jiang D, Zheng D, Wang L, Huang Y, Liu H, Xu L, Liao Q, Liu P, Shi X, Wang Z, Sun L, Zhou Q, Li N, Xu L, Le Y, Ye M, Shao G, Duan S. Elevated PLA2G7 gene promoter methylation as a gender-specific marker of aging increases the risk of coronary heart disease in females. *PLoS One* 2013;**8**:e59752.
101. Giannakopoulou E, Konstantinou F, Ragia G, Tavridou A, Karaglani M, Chatzaki E, Papapetropoulos A, Mikroulis D, Manolopoulos VG. Epigenetics-by-sex interaction for coronary artery disease risk conferred by the cystathionine gamma-lyase gene promoter methylation. *OMICS* 2017;**21**:741–748.
102. Metivier R, Penot G, Hubner MR, Reid G, Brand H, Kos M, Gannon F. Estrogen receptor-alpha directs ordered, cyclical, and combinatorial recruitment of cofactors on a natural target promoter. *Cell* 2003;**115**:751–763.
103. Kinyamu HK, Archer TK. Modifying chromatin to permit steroid hormone receptor-dependent transcription. *Biochim Biophys Acta* 2004;**1677**:30–45.
104. Parmar P, Lowry E, Cugliari G, Suderman M, Wilson R, Karhunen V, Andrew T, Wiklund P, Wielscher M, Guarrera S, Teumer A, Lehne B, Milani L, de Klein N, Mishra PP, Melton PE, Mandaviya PR, Kasela S, Nano J, Zhang WH, Zhang Y, Uitterlinden AG, Peters A, Schottker B, Gieger C, Anderson D, Boomsma DI, Grabe HJ, Panico S, Veldink JH, van Meurs JBJ, van den Berg L, Beilin LJ, Franke L, Loh M, van Greevenbroek MMJ, Nauck M, Kahonen M, Hurme MA, Raitakari OT, Franco OH, Slagboom PE, van der Harst P, Kunze S, Felix SB, Zhang T, Chen W, Mori TA, Bonnefond A, Heijmans BT, Muka T, Kooner JS, Fischer K, Waldenberger M, Froguel P, Huang RC, Lehtimaki T, Rathmann W, Relton CL, Matullo G, Brenner H, Verweij N, Li SX, Chambers JC, Jarvelin MR, Sebert S;GLOBAL Meth QTL Consortium. Association of maternal prenatal smoking GFI1-locus and cardio-metabolic phenotypes in 18,212 adults. *EBioMedicine* 2018;**38**:206–216.
105. Zeilinger S, Kuhnel B, Klopp N, Baurecht H, Kleinschmidt A, Gieger C, Weidinger S, Lattka E, Adamski J, Peters A, Strauch K, Waldenberger M, Illig T. Tobacco smoking leads to extensive genome-wide changes in DNA methylation. *PLos One* 2013;**8**:e63812.
106. Keleher MR, Zaidi R, Hicks L, Shah S, Xing XY, Li DF, Wang T, Cheverud JM. A high-fat diet alters genome-wide DNA methylation and gene expression in SM/J mice. *Bmc Genomics* 2018;**19**:888.
107. Landen S, Voisin S, Craig JM, McGee SL, Lamon S, Eynon N. Genetic and epigenetic sex-specific adaptations to endurance exercise. *Epigenetics* 2019;**14**:523.
108. Rutledge T, Kenkre TS, Thompson DV, Bittner VA, Whittaker K, Eastwood JA, Eteiba W, Cornell CE, Krantz DS, Pepine CJ, Johnson BD, Handberg EM, Bairey Merz CN. Psychosocial predictors of long-term mortality among women with suspected myocardial ischemia: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation. *J Behav Med* 2016;**39**:687–693.
109. Pimple P, Shah AJ, Rooks C, Douglas Bremner J, Nye J, Ibeanu I, Raggi P, Vaccarino V. Angina and mental stress-induced myocardial ischemia. *J Psychosom Res* 2015;**78**:433–437.
110. Vaccarino V, Sullivan S, Hammadah M, Wilmot K, Al Mheid I, Ramadan R, Elon L, Pimple PM, Garcia EV, Nye J, Shah AJ, Alkhoder A, Levantsevych O, Gay H, Obideen M, Huang M, Lewis TT, Bremner JD, Quyyumi AA, Raggi P. Mental stress-induced-myocardial ischemia in young patients with recent myocardial infarction: sex differences and mechanisms. *Circulation* 2018;**137**:794–805.
111. Vaccarino V, Wilmot K, Al Mheid I, Ramadan R, Pimple P, Shah AJ, Garcia EV, Nye J, Ward L, Hammadah M, Kutner M, Long Q, Bremner JD, Esteves F, Raggi P, Quyyumi AA. Sex differences in mental stress-induced myocardial ischemia in patients with coronary heart disease. *J Am Heart Assoc* 2016;**5**:e003630.
112. Xu X, Bao H, Strait K, Spertus JA, Lichtman JH, D'Onofrio G, Spatz E, Bucholz EM, Geda M, Lorenze NP, Bueno H, Beltrame JF, Krumholz HM. Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction. *Circulation* 2015;**131**:614–623.
113. Hogarth AJ, Graham LN, Mary DA, Greenwood JP. Gender differences in sympathetic neural activation following uncomplicated acute myocardial infarction. *Eur Heart J* 2009;**30**:1764–1770.
114. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, Truong QA, Solomon CJ, Calcagno C, Mani V, Tang CY, Mulder WJ, Murrough JW, Hoffmann U, Nahrendorf M, Shin LM, Fayad ZA, Pitman RK. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet* 2017;**389**:834–845.
115. Fiechter M, Roggo A, Burger IA, Bengs S, Treyer V, Becker A, Marędziak M, Haider A, Portmann A, Messerli M, Patriki D, Mühlematter UJ, von Felten E, Benz DC, Fuchs TA, Gräni C, Pazhenkottil AP, Buechel RR, Kaufmann PA, Gebhard C. Association between resting amygdalar activity and abnormal cardiac function in women and men: a retrospective cohort study. *Eur Heart J Cardiovasc Imaging* 2019;**20**:625.
116. Pizzi C, Xhyheri B, Costa GM, Faustino M, Flacco ME, Gualano MR, Fragassi G, Grigioni F, Manzoli L. Nonobstructive versus obstructive coronary artery disease in acute coronary syndrome: a meta-analysis. *J Am Heart Assoc* 2016;**5**: e004185.
117. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, Kaski JC, Bairey Merz CN. International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 2018;**250**:16–20.
118. Jespersen L, Hvelplund A, Abildstrom SZ, Pedersen F, Galatius S, Madsen JK, Jorgensen E, Kelbaek H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J* 2012;**33**:734–744.
119. Taqueti VR, Shaw LJ, Cook NR, Murthy VL, Shah NR, Foster CR, Hainer J, Blankstein R, Dorbala S, Di Carli MF. Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease. *Circulation* 2017;**135**: 566–577.
120. AlBadri A, Bairey Merz CN, Johnson BD, Wei J, Mehta PK, Cook-Wiens G, Reis SE, Kelsey SF, Bittner V, Sopko G, Shaw LJ, Pepine CJ, Ahmed B. Impact of abnormal coronary reactivity on long-term clinical outcomes in women. *J Am Coll Cardiol* 2019;**73**:684–693.
121. Srivaratharajah K, Coutinho T, deKemp R, Liu P, Haddad H, Stadnick E, Davies RA, Chih S, Dwivedi G, Guo A, Wells GA, Bernick J, Beanlands R, Mielniczuk LM. Reduced myocardial flow in heart failure patients with preserved ejection fraction. *Circ Heart Fail* 2016;**9**:e002562.
122. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, Dorbala S, Blankstein R, Di Carli MF. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation* 2015;**131**:19–27.
123. Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, Daneshvar M, Spertus JA, D'Onofrio G. Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction: evidence from the VIRGO study (Variation in Recovery: role of Gender on Outcomes of Young AMI Patients). *Circulation* 2018;**137**:781–790.
124. Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ, Long T. Symptom presentation of women with acute coronary syndromes: myth vs reality. *Arch Intern Med* 2007;**167**:2405–2413.
125. Gebhard CE, Gebhard C, Maafi F, Bertrand MJ, Stahli BE, Maredziak M, Bengs S, Haider A, Zhang ZW, Smith DC, Ly HQ. Impact of summer season on prehospital time delays in women and men undergoing primary percutaneous coronary intervention. *Sci Total Environ* 2019;**656**:322–330.
126. Meyer MR, Bernheim AM, Kurz DJ, O'Sullivan CJ, Tüller D, Zbinden R, Rosemann T, Eberli FR. Gender differences in patient and system delay for primary percutaneous coronary intervention: current trends in a Swiss ST-segment elevation myocardial infarction population. *Eur Heart J Acute Cardiovasc Care* 2019;**8**:283–290.
127. Roswell RO, Kunkes J, Chen AY, Chiswell K, Iqbal S, Roe MT, Bangalore S. Impact of sex and contact; Device time on clinical outcomes in acute; Segment elevation myocardial infarction; Findings from the National Cardiovascular Data Registry. *J Am Heart Assoc* 2017;**6**:e004521.
128. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, Brogan GX Jr, Boden WE, Roe MT, Ohman EM, Gibler WB, Newby LK. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;**45**:832–837.
129. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, Griffith JL, Selker HP. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000;**342**:1163–1170.
130. Chandrasekhar J, Gill A, Mehran R. Acute myocardial infarction in young women: current perspectives. *Int J Womens Health* 2018;**10**:267–284.
131. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation* 2016;**133**:916–947.
132. Dokainish H, Pillai M, Murphy SA, DiBattiste PM, Schweiger MJ, Lotfi A, Morrow DA, Cannon CP, Braunwald E, Lakkis N. Prognostic implications of elevated troponin in patients with suspected acute coronary syndrome but no critical epicardial coronary disease: a TACTICS-TIMI-18 substudy. *J Am Coll Cardiol* 2005;**45**:19–24.
133. Baccouche H, Mahrholdt H, Meinhardt G, Merher R, Voehringer M, Hill S, Klingel K, Kandolf R, Sechtem U, Yilmaz A. Diagnostic synergy of non-invasive cardiovascular magnetic resonance and invasive endomyocardial biopsy in

troponin-positive patients without coronary artery disease. *Eur Heart J* 2009;**30**:2869–2879.
134. Ghadri J-R, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International expert consensus document on Takotsubo syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018;**39**:2032–2046.
135. Kawamoto KR, Davis MB, Duvernoy CS. Acute coronary syndromes: differences in men and women. *Curr Atheroscler Rep* 2016;**18**:73.
136. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, Ganesh SK, Gulati R, Lindsay ME, Mieres JH, Naderi S, Shah S, Thaler DE, Tweet MS, Wood MJ; American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Stroke. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation* 2018;**137**:e523–e557.
137. Tweet MS, Hayes SN, Codsi E, Gulati R, Rose CH, Best P. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol* 2017;**70**:426–435.
138. Ong P, Athanasiadis A, Hill S, Vogelsberg H, Voehringer M, Sechtem U. Coronary artery spasm as a frequent cause of acute coronary syndrome: the CASPAR (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) Study. *J Am Coll Cardiol* 2008;**52**:523–527.
139. Hung M-J, Hu P, Hung M-Y. Coronary artery spasm: review and update. *Int J Med Sci* 2014;**11**:1161–1171.
140. Egashira K, Katsuda Y, Mohri M, Kuga T, Tagawa T, Shimokawa H, Takeshita A. Basal release of endothelium-derived nitric oxide at site of spasm in patients with variant angina. *J Am Coll Cardiol* 1996;**27**:1444–1449.
141. Pozzati A, Pancaldi LG, Di Pasquale G, Pinelli G, Bugiardini R. Transient sympathovagal imbalance triggers "ischemic" sudden death in patients undergoing electrocardiographic Holter monitoring. *J Am Coll Cardiol* 1996;**27**:847–852.
142. Nielsen S, Bjorck L, Berg J, Giang KW, Zverkova Sandstrom T, Falk K, Maatta S, Rosengren A. Sex-specific trends in 4-year survival in 37 276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987-2006: a register-based cohort study. *BMJ Open* 2014;**4**:e004598.
143. Agrawal S, Van Eyk J, Sobhani K, Wei J, Bairey Merz CN. Sex, myocardial infarction, and the failure of risk scores in women. *J Womens Health (Larchmt)* 2015;**24**:859–861.
144. Cullen L, Greenslade JH, Carlton EW, Than M, Pickering JW, Ho A, Greaves K, Berndt SL, Body R, Ryan K, Parsonage WA. Sex-specific versus overall cut points for a high sensitivity troponin I assay in predicting 1-year outcomes in emergency patients presenting with chest pain. *Heart* 2016;**102**:120–126.
145. Worrall-Carter L, McEvedy S, Wilson A, Rahman MA. Gender differences in presentation, coronary intervention, and outcomes of 28,985 acute coronary syndrome patients in Victoria, Australia. *Womens Health Issues* 2016;**26**:14–20.
146. Bugiardini R, Yan AT, Yan RT, Fitchett D, Langer A, Manfrini O, Goodman SG. Factors influencing underutilization of evidence-based therapies in women. *Eur Heart J* 2011;**32**:1337–1344.
147. Resurreccion DM, Moreno-Peral P, Gomez-Herranz M, Rubio-Valera M, Pastor L, Caldas de Almeida JM, Motrico E. Factors associated with non-participation in and dropout from cardiac rehabilitation programmes: a systematic review of prospective cohort studies. *Eur J Cardiovasc Nurs* 2019;**18**:38–47.
148. Peters SAE, Colantonio LD, Zhao H, Bittner V, Dai Y, Farkouh ME, Monda KL, Safford MM, Muntner P, Woodward M. Sex differences in high-intensity statin use following myocardial infarction in the United States. *J Am Coll Cardiol* 2018;**71**:1729–1737.
149. Koopman C, Vaartjes I, Heintjes EM, Spiering W, van Dis I, Herings RM, Bots ML. Persisting gender differences and attenuating age differences in cardiovascular drug use for prevention and treatment of coronary heart disease, 1998-2010. *Eur Heart J* 2013;**34**:3198–3205.
150. Li S, Fonarow GC, Mukamal KJ, Liang L, Schulte PJ, Smith EE, DeVore A, Hernandez AF, Peterson ED, Bhatt DL. Sex and race/ethnicity-related disparities in care and outcomes after hospitalization for coronary artery disease among older adults. *Circ Cardiovasc Qual Outcomes* 2016;**9**(2 Suppl 1):S36–S44.
151. Ghadri JR, Sarcon A, Jaguszewski M, Diekmann J, Bataiosu RD, Hellermann J, Csordas A, Baumann L, Schoni AA, Luscher TF, Templin C. Gender disparities in acute coronary syndrome: a closing gap in the short-term outcome. *J Cardiovasc Med (Hagerstown)* 2015;**16**:355–362.
152. Berg J, Bjorck L, Nielsen S, Lappas G, Rosengren A. Sex differences in survival after myocardial infarction in Sweden, 1987-2010. *Heart* 2017;**103**:1625–1630.
153. Cenko E, Yoon J, Kedev S, Stankovic G, Vasiljevic Z, Krljanac G, Kalpak O, Ricci B, Milicic D, Manfrini O, van der Schaar M, Badimon L, Bugiardini R. Sex differences in outcomes after STEMI: effect modification by treatment strategy and age. *JAMA Intern Med* 2018;**178**:632–639.
154. Hao Y, Liu J, Liu J, Yang N, Smith SC Jr, Huo Y, Fonarow GC, Ge J, Taubert KA, Morgan L, Zhou M, Xing Y, Ma CS, Han Y, Zhao D. Sex differences in in-hospital management and outcomes of patients with acute coronary syndrome. *Circulation* 2019;**139**:1776–1785.
155. Cenko E, van der Schaar M, Yoon J, Kedev S, Valvukis M, Vasiljevic Z, Asanin M, Milicic D, Manfrini O, Badimon L, Bugiardini R. Sex-specific treatment effects after primary percutaneous intervention: a study on coronary blood flow and delay to hospital presentation. *J Am Heart Assoc* 2019;**8**:e011190.
156. Vaccarino V, Rathore SS, Wenger NK, Frederick PD, Abramson JL, Barron HV, Manhapra A, Mallik S, Krumholz HM. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. *N Engl J Med* 2005;**353**:671–682.
157. Zachura M, Wilczek K, Janion M, Gąsior M, Gierlotka M, Sadowski M. Long-term outcomes in men and women with ST-segment elevation myocardial infarction and incomplete reperfusion after a primary percutaneous coronary intervention: a 2-year follow-up. *Coron Artery Dis* 2019;**30**:171–176.
158. Bucholz EM, Butala NM, Rathore SS, Dreyer RP, Lansky AJ, Krumholz HM. Sex differences in long-term mortality after myocardial infarction. *Circulation* 2014;**130**:757–767.
159. Johansson S, Bergstrand R, Ulvenstam G, Vedin A, Wilhelmsson C, Wedel H, Wilhelmsen L, Aberg A. Sex differences in preinfarction characteristics and longterm survival among patients with myocardial infarction. *Am J Epidemiol* 1984;**119**:610–623.
160. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. *N Engl J Med* 1999;**341**:217–225.
161. Dreyer RP, Ranasinghe I, Wang Y, Dharmarajan K, Murugiah K, Nuti SV, Hsieh AF, Spertus JA, Krumholz HM. Sex differences in the rate, timing, and principal diagnoses of 30-day readmissions in younger patients with acute myocardial infarction. *Circulation* 2015;**132**:158–166.
162. Vaccarino V, Krumholz HM, Yarzebski J, Gore JM, Goldberg RJ. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med* 2001;**134**:173–181.
163. Kumbhani DJ, Shishehbor MH, Willis JM, Karim S, Singh D, Bavry AA, Zishiri E, Ellis SG, Menon V. Influence of gender on long-term mortality in patients presenting with non-ST-elevation acute coronary syndromes undergoing percutaneous coronary intervention. *Am J Cardiol* 2012;**109**:1087–1091.
164. D'Onofrio G, Safdar B, Lichtman JH, Strait KM, Dreyer RP, Geda M, Spertus JA, Krumholz HM. Sex differences in reperfusion in young patients with ST-segment elevation myocardial infarction. *Circulation* 2015;**131**:1324–1332.
165. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
166. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
167. Kofoed KF, Kelbæk H, Hansen PR, Torp-Pedersen C, Høfsten D, Kløvgaard L, Holmvang L, Helqvist S, Jørgensen E, Galatius S, Pedersen F, Bang L, Saunamaki K, Clemmensen P, Linde JJ, Heitmann M, Wendelboe Nielsen O, Raymond IE, Kristiansen OP, Svendsen IH, Bech J, Dominguez Vall-Lamora MH, Kragelund C, Hansen TF, Dahlgaard Hove J, Jørgensen T, Fornitz GG, Steffensen R, Jurlander B, Abdulla J, Lyngbæk S, Elming H, Therkelsen SK, Abildgaard U, Jensen JS, Gislason G, Køber LV, Engstrøm T. Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome. *Circulation* 2018;**138**:2741–2750.
168. O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, Fox KA, Lagerqvist B, McCullough PA, Murphy SA, Spacek R, Swahn E, Wallentin L, Windhausen F, Sabatine MS. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2008;**300**:71–80.
169. Lichtman JH, Wang Y, Jones SB, Leifheit-Limson EC, Shaw LJ, Vaccarino V, Rumsfeld JS, Krumholz HM, Curtis JP. Age and sex differences in inhospital complication rates and mortality after percutaneous coronary intervention procedures: evidence from the NCDR((R)). *Am Heart J* 2014;**167**:376–383.

170. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, Ohman ME, Witzenbichler B, Guagliumi G, Lansky AJ, Stone GW. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol* 2010;**55**:2556–2566.
171. Mason PJ, Shah B, Tamis-Holland JE, Bittl JA, Cohen MG, Safirstein J, Drachman DE, Valle JA, Rhodes D, Gilchrist IC. An update on radial artery access and best practices for transradial coronary angiography and intervention in acute coronary syndrome: a scientific statement from the American Heart Association. *Circ Cardiovasc Interv* 2018;**11**:e000035.
172. Cantor WJ, Miller JM, Hellkamp AS, Kramer JM, Peterson ED, Hasselblad V, Zidar JP, Newby LK, Ohman EM. Role of target vessel size and body surface area on outcomes after percutaneous coronary interventions in women. *Am Heart J* 2002;**144**:297–302.
173. Regitz-Zagrosek V, Lehmkuhl E, Hocher B, Goesmann D, Lehmkuhl HB, Hausmann H, Hetzer R. Gender as a risk factor in young, not in old, women undergoing coronary artery bypass grafting. *J Am Coll Cardiol* 2004;**44**: 2413–2414.
174. Vaccarino V, Abramson JL, Veledar E, Weintraub WS. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. *Circulation* 2002;**105**:1176–1181.
175. Swaminathan RV, Feldman DN, Pashun RA, Patil RK, Shah T, Geleris JD, Wong SC, Girardi LN, Gaudino M, Minutello RM, Singh HS, Bergman G, Kim LK. Gender differences in in-hospital outcomes after coronary artery bypass grafting. *Am J Cardiol* 2016;**118**:362–368.
176. Dalen M, Nielsen S, Ivert T, Holzmann MJ, Sartipy U. Coronary artery bypass grafting in women 50 years or younger. *J Am Heart Assoc* 2019;**8**:e013211.
177. Schoell T, Genser L, Clement M, Amour J, Leprince P, Lebreton G, Tavakoli R. Bilateral internal thoracic artery grafting in women: a word of caution. *Heart Surg Forum* 2019;**22**:E045–E049.
178. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P, Lang IM, Morais J, Pieper PG, Presbitero P, Price S, Rosano GMC, Seeland U, Simoncini T, Swan L, Warnes CA; ESC Scientific Document Group. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: the task force for the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:3165–3241.
179. Renda G, Patti G, Lang IM, Siller-Matula JM, Hylek EM, Ambrosio G, Haas S, De Caterina R; Working Group on Thrombosis of the Italian Society of Cardiology. Thrombotic and hemorrhagic burden in women: gender-related issues in the response to antithrombotic therapies. *Int J Cardiol* 2019;**286**: 198–207.
180. Trigg DE, Wood MG, Kouides PA, Kadir RA. Hormonal influences on hemostasis in women. *Semin Thromb Hemost* 2011;**37**:77–86.
181. Caulin-Glaser T, García-Cardeña G, Sarrel P, Sessa WC, Bender JR. 17 beta-estradiol regulation of human endothelial cell basal nitric oxide release, independent of cytosolic Ca2+ mobilization. *Circ Res* 1997;**81**:885–892.
182. Moscucci M, Fox KA, Cannon CP, Klein W, Lopez-Sendon J, Montalescot G, White K, Goldberg RJ. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;**24**:1815–1823.
183. Alexander KP, Chen AY, Newby LK, Schwartz JB, Redberg RF, Hochman JS, Roe MT, Gibler WB, Ohman EM, Peterson ED, Investigators C. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative. *Circulation* 2006;**114**:1380–1387.
184. Sowers MR, Matthews KA, Jannausch M, Randolph JF, McConnell D, Sutton-Tyrrell K, Little R, Lasley B, Pasternak R. Hemostatic factors and estrogen during the menopausal transition. *J Clin Endocrinol Metab* 2005;**90**:5942–5948.
185. Haque SF, Matsubayashi H, Izumi S, Sugi T, Arai T, Kondo A, Makino T. Sex difference in platelet aggregation detected by new aggregometry using light scattering. *Endocr J* 2001;**48**:33–41.
186. Bobbert P, Stellbaum C, Steffens D, Schutte C, Bobbert T, Schultheiss HP, Rauch U. Postmenopausal women have an increased maximal platelet reactivity compared to men despite dual antiplatelet therapy. *Blood Coagul Fibrinolysis* 2012;**23**:723–728.
187. Breet NJ, Sluman MA, van Berkel MA, van Werkum JW, Bouman HJ, Harmsze AM, Kelder JC, Zijlstra F, Hackeng CM, Ten Berg JM. Effect of gender difference on platelet reactivity. *Neth Heart J* 2011;**19**:451–457.
188. Singla A, Bliden KP, Jeong YH, Abadilla K, Antonino MJ, Muse WC, Mathew DP, Bailon O, Tantry US, Gurbel PA. Platelet reactivity and thrombogenicity in postmenopausal women. *Menopause* 2013;**20**:57–63.
189. Lawrence JB, Leifer DW, Moura GL, Southern P, Emery JD, Bodenheimer SL, Kramer WS. Sex differences in platelet adherence to subendothelium: relationship to platelet function tests and hematologic variables. *Am J Med Sci* 1995; **309**:201–207.
190. Becker DM, Segal J, Vaidya D, Yanek LR, Herrera-Galeano JE, Bray PF, Moy TF, Becker LC, Faraday N. Sex differences in platelet reactivity and response to low-dose aspirin therapy. *JAMA* 2006;**295**:1420–1427.
191. Faraday N, Goldschmidt-Clermont PJ, Bray PF. Gender differences in platelet GPIIb-IIIa activation. *Thromb Haemost* 1997;**77**:748–754.
192. Bain B, Forster T. A sex difference in the bleeding time. *Thromb Haemost* 1980; **43**:131–132.
193. Ahmed B, Piper WD, Malenka D, VerLee P, Robb J, Ryan T, Herne M, Phillips W, Dauerman HL. Significantly improved vascular complications among women undergoing percutaneous coronary intervention: a report from the Northern New England Percutaneous Coronary Intervention Registry. *Circ Cardiovasc Interv* 2009;**2**:423–429.
194. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON–TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**: 2001–2015.
195. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
196. Berger JS, Bhatt DL, Cannon CP, Chen Z, Jiang L, Jones JB, Mehta SR, Sabatine MS, Steinhubl SR, Topol EJ, Berger PB. The relative efficacy and safety of clopidogrel in women and men a sex-specific collaborative meta-analysis. *J Am Coll Cardiol* 2009;**54**:1935–1945.
197. Lau ES, Braunwald E, Murphy SA, Wiviott SD, Bonaca MP, Husted S, James SK, Wallentin L, Clemmensen P, Roe MT, Ohman EM, Harrington RA, Mega JL, Bhatt DL, Sabatine MS, O'Donoghue ML. Potent P2Y12 inhibitors in men versus women: a collaborative meta-analysis of randomized trials. *J Am Coll Cardiol* 2017;**69**:1549–1559.