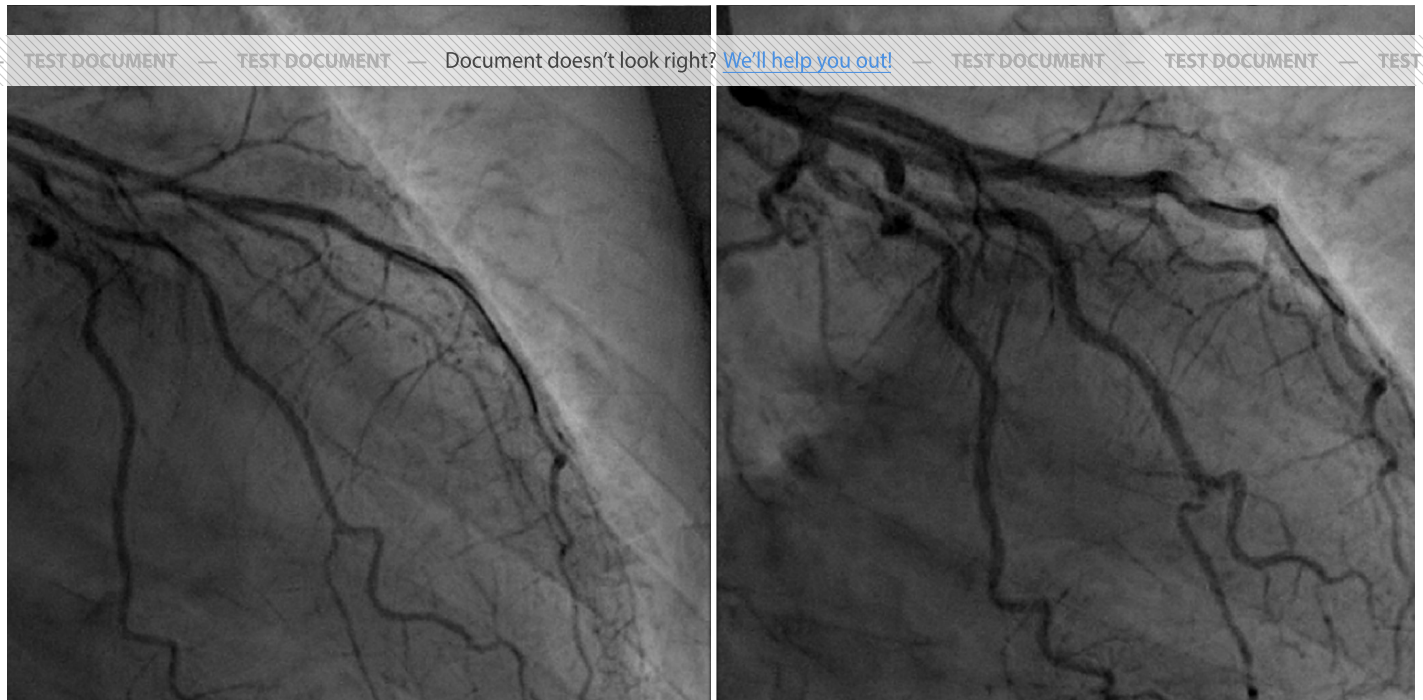




Diagnosis and Therapy

Sex-Specific Aspects of the Chronic Coronary Syndrome

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Abstract

Ischaemic heart disease is the number one cause of death in women and men, both worldwide and in Switzerland. Sex- and gender-related differences in the presentation, treatment and outcomes of patients with coronary artery disease are increasingly recognised and the disease entity of ischaemia with non-obstructive coronary arteries (INOCA), including coronary microvascular dysfunction and vasospastic disease has been identified as an important cause of myocardial ischaemia. INOCA predominantly affects women and is associated with a high symptomatic burden and an increased risk of cardiovascular events. Despite the high prevalence of ischaemic heart disease in women and the increased risk of morbidity and mortality observed particularly in young women with acute coronary syndromes, women are still underrepresented in cardiovascular randomised trials and specific diagnostic and therapeutic concepts taking sex and gender differences into account are lacking.

This article summarises sex and gender differences in patients with coronary artery disease, with a particular focus on INOCA.

Keywords: Sex-differences; INOCA; coronary microvascular dysfunction; microvascular resistance; coronary flow reserve

Background and Overview

Ischaemic heart disease is the number one cause of death in male and female adults, worldwide and in Switzerland [1, 2]. The number of people affected is steadily increasing, while the mortality due to ischaemic heart disease is decreasing. However, ischaemic heart disease still accounts for a third of deaths in women [3, 4]. The prevalence of ischaemic heart disease in the US in adults over the age of 20 is 8.3% for males and 6.2% for females [4]. Depending on the prevalence of cardiovascular risk factors, up to 60% of men and women over the age of 60 develop a coronary artery disease (CAD) during their life [4]. Autopsy studies have demonstrated that in patients without cardiovascular risk factors, 60% of patients over 80 years of age had a CAD [5]. Table 1 gives an overview of the incidence and prevalence of

ischaemic heart disease in women and men according to age.

1: Prevalence of stable ischaemic heart disease is defined as history of previous myocardial infarction, angina pectoris based on medication use, coronary revascularisation, physical examination, or electrocardiogram.

	Age (years)	Men	Women
Prevalence	75–79	30.2%	21.7%
	80–84	36.6%	24.6%
	85–89	40.8%	29.7%
Prevalence	75–79	34.6%	18.0%
	80–84	38.7%	24.8%
	85–89	35.5%	23.8%

Coronary artery disease presents as sudden cardiac death, acute coronary syndrome (ACS), or chronic coronary syndrome (CCS). It entails both abnormalities of the epicardial coronary arteries as well as the coronary - microcirculation. Functional disorders of the coronary arteries are summarised under the umbrella term ischaemia with non-obstructive coronary arteries (INOCA) or angina with non-obstructive coronary arteries (ANOCA) when information on myocardial ischaemia is lacking. INOCA replaces the now obsolete term syndrome X. The umbrella term INOCA includes coronary microvascular dysfunction (CMD) as well as epicardial or microvascular coronary vasospasm. The former manifests as increased microvascular resistance (IMR) or impaired coronary flow reserve (CFR).

In recent years, sex- and gender-specific aspects in patients with CAD have become evident. As clinicians, we need to be aware of these differences when taking care of women with CCS. This review focuses on clinically - relevant aspects of CCS in women and gives insights into the complex interplay of biological, social, and environmental factors contributing to sex- and gender-related differences in CCS.

Obstructive Coronary Artery Disease: Prevalence, Presentation, and Pathophysiology

Over the last decades, the ageing of the population and the decrease in cardiovascular mortality led to an increasing prevalence of CCS. Despite the popular belief that CAD mainly affects men, the prevalence of CAD is similar in women and men [1, 4, 6]. Women are about ten years older when CAD becomes clinically relevant. Their cardiovascular risk increases significantly when they reach the age of 55, having undergone hormonal changes due to menopause. Therefore, women are older and have more traditional cardiovascular risk factors than men once

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Women with CCS present with similar symptoms compared to men, such as exercise-induced chest pain [7, 9]. However, women can show a plethora of associated symptoms such as shortness of breath, decrease in exercise capacity, nausea, palpitations, lightheadedness and fatigue. This led to the widespread false notion that women's symptoms are mostly "atypical". Now, it is increasingly recognised that most women with CAD presents with chest pain [7]. The authors therefore believe that the presence of associated symptoms in women should no longer be labelled as atypical. Most important for missing the diagnosis of CAD in women is the misperception that women are at a low risk for CAD. This underestimation of risk is prevalent both in health care providers and patients. In the VIRGO (Examining Heart Attacks in Women) study, less than half of the young female patients believed that they were at risk for ACS despite having relevant risk factors [10]. This is reflected in the assessment and treatment of classical cardiovascular risk factors in women. Women less often receive guideline directed medical therapy (GDMT) in primary prevention for CAD, which is of particular importance given the fact that traditional cardiovascular risk factors carry an increased risk in women [10]. A family history of premature cardiovascular events, diabetes and smoking appear to be more important in the development of CAD for women than for men. Smoking confers a 25% higher relative risk of CAD in women than in men [11]. With diabetes, the risk for women is three-fold [12]. Conventional risk factor calculators such as the Framingham risk calculator, might underestimate the risk of cardiovascular events in women, particularly in those at increased risk [7]. In the large PROMISE (Prospective Multicentre Imaging Study for Evaluation of Chest Pain) trial, women were more likely to be characterised at low risk based on standard cardiovascular risk assessment scores, despite an increased prevalence of all risk factors except smoking and diabetes [7]. For this reason, the Reynolds Risk score has been specifically developed for the risk assessment in women [13, 14]. Validation of the score has shown reclassification of up to half of intermediate risk female patients into lower risk or – in most cases – higher risk categories. Most recently, the limited discriminatory performance of the Global Registry of Acute Coronary Events

in women with non-ST segment elevation

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more, the GRACE 3.0 score was developed and proven to perform better in men and women reducing sex inequalities in risk stratification.

Additional risk factors associated with an accelerated development of CAD specific to women are not included in commonly used risk scores [16]. These include gestational - hypertension, diabetes, polycystic ovary syndrome and early menopause among others. These risk factors do enable early detection of women at increased lifetime risk of CAD [6]. Other factors that are associated with an increased risk of CAD are autoimmune diseases, such as lupus erythematosus or rheumatoid arthritis [17]. Further, depression and low household income also show strong associations with CAD [18]. Whilst all these conditions are not specific to the female sex, they do occur more often in women than in men.

In CCS, pathological changes in the coronary arteries lead to the formation of atherosclerotic plaques [19]. Coronary atherosclerosis in women is characterised by a smaller plaque burden [20]. As women have smaller coronary arteries (except for the left main), symptoms can occur even with a smaller plaque burden [21]. Observational data is inconclusive with regard to coronary plaque morphology differences between women and men [22]. Most studies showed an increased prevalence of plaque erosion and fewer unstable plaques in non-culprit arteries in women, while others could not demonstrate any sex-specific differences [23]. Sex differences seem to mitigate in patients aged 65 and above [24]. Differences in coronary flow characteristics comprise a stenosis diameter-fractional flow reserve (FFR) mismatch, with women having higher FFR values for the same luminal narrowing [25, 26]. However, sex specific studies of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trials showed that despite different FFR values, an FFR-guided revascularisation strategy resulted in a similar relative risk reduction for both women and men [26].

Ischaemia with Non-obstructive Coronary Arteries (INOCA): Prevalence, Presentation and Pathophysiology

Coronary microvascular dysfunction represents a dysfunctional coronary microcirculation, which includes coronaries <400 µm in diameter (prearterioles, arterioles and capil-

lation, increased vasoconstriction, small vessel disease, and functional microvasculature manifests either as decreased CFR, increased IMR or microvascular vasospasm [28]. The risk factors known for obstructive CAD also apply to CMD. Other associated mechanisms include anxiety disorders, viral diseases, inflammatory conditions and alterations in the female hormone balance [29].

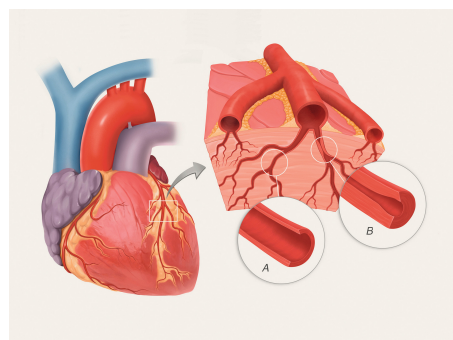


Figure 1: Coronary microcirculation including coronaries <400 μm in diameter (prearterioles, arterioles and capillaries). A Normal microcirculation function. B Microvascular vasospasm.

The prevalence of CMD has been underestimated in the past. In recent years, through the use of targeted diagnostics, it has been recognised that CMD is more common than previously thought, particularly in women [30]. When systematic testing is performed, a diagnosis of coronary dysfunction can be made in 70% of female and 40% of male patients with stable angina with exclusion of epicardial stenosis on coronary angiography [30]. In most cases, CMD presents as the primary disease. However, secondary forms may occur as a sequela of structural alterations of the microvasculature in left ventricular hypertrophy or cardiomyopathies. Further, CMD and vasospastic diseases may coexist with obstructive CAD. Thus, one form of the disease does not exclude the other. Hence, it may also be indicated to specifically look for CMD and coronary vasospasm in selected cases, even if obstructive CAD is present.

Patients with CMD typically describe exercise-induced angina symptoms, with pain episodes typically lasting longer than in patients with epicardial stenoses [31]. Common additional symptoms include atypical chest pain, dyspnoea and decreased exercise capacity [32]. Microvascular vasospasm is typically characterised by chest pain at rest, often in the morning hours. However, it is not possible to differentiate CMD and vasospastic disease from angina in the setting of obstructive

cardiovascular disease. Patients with CMD, especially in a substudy of the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, demonstrating that the extent of coronary artery calcifications on CCTA was the only non-invasive parameter which predicted both benefit from coronary revascularisation and future cardiovascular events [41].

Diagnostic Algorithm for Patients with Suspected Coronary Artery Disease

The diagnostic work-up of patients with suspected CAD is the same for both women and men and is discussed in detail in the 2019 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of CCS [19, 34]. Patient history, physical status and cardiovascular risk assessment form the basis of any work-up of a patient with angina and associated symptoms. Emphasis should be given on conditions that are either specific to female sex or have a higher prevalence in women than men as discussed above. Further diagnostic steps include the performance of a 12-lead ECG and transthoracic echocardiography for the assessment of the pre-test probability of CAD. Exercise ECG has both lower specificity and sensitivity in women than in men and therefore plays only a minor role in the workup of patients with suspected CAD nowadays [35, 36]. However, occurrence of angina, dyspnoea, ST-depressions on ECG and ventricular arrhythmias on exercise ECG are useful clinical parameters [37]. Further evaluation can be performed by either non-invasive testing or invasive coronary angiography, depending on the pre-test probability [19]. The choice of the investigative modality (coronary computed tomography angiography [CCTA], stress echocardiography, single-photon emission computed tomography [SPECT], cardiac magnetic resonance imaging, cardiac positron emission tomography) depends on availability and local expertise. Currently, women are more frequently referred for imaging stress testing, specifically for SPECT and are less likely to have a test result interpreted as positive [7]. Notably, SPECT may be less accurate in women [34]. An important difference exists between anatomical testing (i.e., CCTA) and functional testing. In the early days of CCTA, its domain was mainly to exclude CAD in patients with a low pre-test probability. However, recent data showed that CCTA represents the most accurate way to quantify the extent of CAD. As such, CCTA is more accurate and has greater predictive power for determining the risk of cardiovascular mortality or myocardial infarction as compared to ischaemia testing [38, 39]. Women seem to de-

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activity testing with intracoronary acetylcholine. In patients with suspected coronary microvascular dysfunction (CMD), increasing doses of acetylcholine are administered intracoronary and the patient's symptoms, ischaemia-specific ECG changes and coronary artery diameter are observed. Whereas acetylcholine causes endothelium-dependent vasodilation by the release of nitric oxide in the healthy endothelium, in patients with endothelial dysfunction acetylcholine-induced vasospasm occurs. The diagnosis of microvascular vasospasm is made when intracoronary acetylcholine administration can elicit the patient's typical symptoms and ischaemia-specific ECG changes are observed. In this case, the coronary angiogram shows either no spasm or <90% spasm (fig. 4). This contrasts with epicardial coronary vasospasm, in which a >90%, usually focal epicardial spasm is observed (fig. 5). By intracoronary administration of nitroglycerine, spasms are resolved immediately after documentation and diagnosis. Once the diagnosis of CMD or coronary epicardial or microvascular vasospastic disease has been made, further unnecessary examinations can be avoided and specific therapy can be initiated.

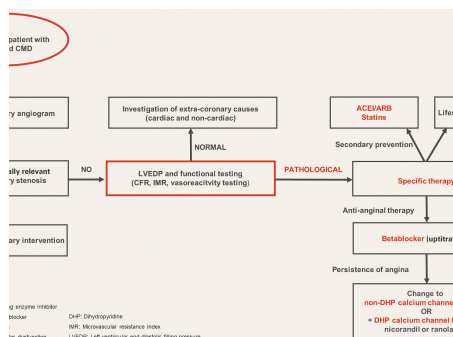


Figure 2: Diagnostic and therapeutic algorithm for patients with suspected coronary microvascular dysfunction (CMD).

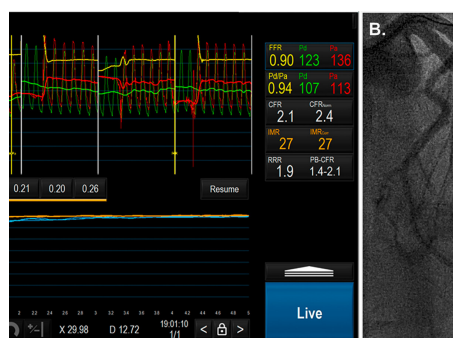


Figure 3: A Coronary microvascular dysfunction with an index of microcirculatory resistance (IMR) of 27 and a coronary flow reserve (CFR) of 2.1. B Normal coronary arteries during vasoreactivity testing with intracoronary acetylcholine.

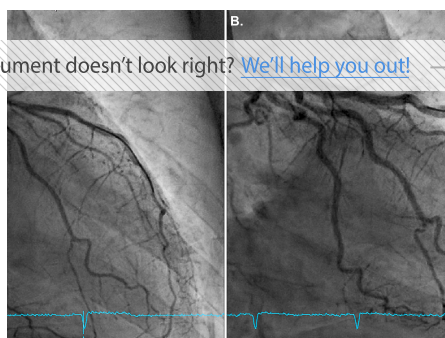


Figure 4: A Diffuse microvascular spasm extending to the epicardial coronary arteries after administration of intracoronary acetylcholine. B Complete resolution of vasospasm after intracoronary administration of nitroglycerine.

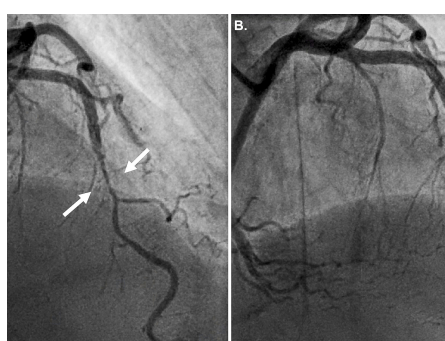


Figure 5: A Focal epicardial vasospasm in the distal left anterior descending coronary artery (LAD) after administration of intracoronary acetylcholine. B Complete resolution of vasospasm after intracoronary administration of nitroglycerine.

Treatment

Lifestyle Modification and Secondary Prevention

Lifestyle changes, control of cardiovascular risk factors and optimal drug therapy form the basis for the treatment of patients with CCS [19]. Despite proven benefits, women less often receive optimal secondary prevention compared to men [43]. Particularly the underuse of statins has been documented in women, even though sex-specific analyses have shown strong benefits of lowering low-density lipoprotein (LDL) cholesterol in women [44, 45]. The VIRGO trial demonstrated that in young women suffering from an ACS, less than half of patients had discussed their risk for an ACS or possible risk modification with their health care providers prior to the event, despite obviously present risk factors [10]. Angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blockers if intolerant), which are recommended in the presence of arterial hypertension, impaired left ventricular systolic function, type 2 diabetes or chronic re-

nal failure show equal benefits in women and

In patients with CMD, lifestyle changes and optimal control of cardiovascular risk factors are of particular importance. Lifestyle changes such as endurance training have been shown to positively affect angina symptoms and exercise capacity [47]. Drug therapy with statins and ACE inhibitors or angiotensin receptor blockers is recommended in patients with CMD [27]. As antianginal medications, beta blockers (e.g., nebivolol 2.5–10 mg daily) should be used primarily. If beta blockers are not tolerated or if symptoms do not improve, calcium channel blockers can be added. For these patients, either non-dihydropyridine calcium channel blockers (e.g., verapamil 40 mg twice daily escalating to 240 mg sustained release [SR] daily or diltiazem 90 mg twice daily escalating to 360 mg daily) or dihydropyridine-type calcium antagonists (e.g., amlodipine 2.5–10 mg daily) are recommended [48, 49]. Both beta blockers and calcium channel blockers should be carefully uptitrated. Alternatively, nicorandil (10–20 mg twice daily) or ranolazine (375–750 mg twice daily) are recommended in addition to calcium channel blockers [48, 49].

For the first time, the randomised CorMicA (CORonary MICrovascular Angina) trial demonstrated that a stratified drug therapy, based on results of invasive testing, led to a significant reduction of angina symptoms and a better quality of life compared to standard of care in patients with INOCA [48]. The randomised EXAMINE-CAD (first prospective randomised trial to examine a differential therapeutic response in symptomatic patients with non-obstructive coronary artery disease after coronary physiological testing) trial, the first to prospectively evaluate a stratified therapeutic approach based on invasive testing, is currently ongoing [50]. The comparison of different non-drug therapeutic strategies and the development of optimised or alternative diagnostic algorithms are further research priorities in the field of INOCA.

Antiplatelet Therapy

So far, no randomised trials have specifically evaluated dual antiplatelet therapy (DAPT) - after percutaneous coronary intervention (PCI) in women and specific DAPT recommendations for women after PCI are lacking [51, 52]. Female sex is generally associated

in women, the less frequent use of the radial approach during PCI. Prespecified subanalyses of randomised trials with regard to sex differences in bleeding events have shown controversial results [54, 55]. Interestingly, a sex-specific variability in platelet response to clopidogrel exists with increased levels of residual platelet reactivity observed in women as compared to men [56]. Currently, there is no evidence for antiplatelet therapy in CMD patients.

Coronary Revascularisation

The indication for coronary revascularisation in patients with CCS must be considered carefully. An individual risk-benefit analysis, considering comorbidities, coronary anatomy and severity of CAD as well as the increased risk of bleeding associated with DAPT is essential.

In selected patients with CCS, coronary revascularisation is associated with improved outcomes [57]. Numerous studies such as COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), FAME 2, or ISCHEMIA have demonstrated a symptomatic benefit of coronary revascularisation compared to optimal anti-anginal therapy alone in patients with CCS [10–13]. A prespecified subanalysis of the COURAGE trial demonstrated that women assigned to PCI showed an even greater benefit with regard to reduction in heart failure hospitalisations and need for future revascularisations compared to men [58]. Despite that, women are significantly less likely to be referred for invasive coronary angiography, even in the setting of a positive stress test [7]. According to the 2019 ESC Guidelines on Myocardial Revascularization, prognostic indications for coronary revascularisation include relevant left main or left anterior descending coronary artery disease, coronary two or three vessel disease with severely impaired left ventricular systolic function (not yet taking into account the results of the most recently published REVIVED-BICIS2 [Revascularization for Ischemic Ventricular Dysfunction] trial), relevant myocardial ischaemia and a “last remaining vessel” with relevant stenosis [57, 59].

Particularly in patients with type 2 diabetes and those with complex coronary anatomy, surgical revascularisation is often favoured over PCI [60, 61]. In the SYNTAX (Synergy Between PCI With TAXUS and Cardiac

with coronary artery bypass grafting (CABG)

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Outcomes

After increasing until 2000, cardiovascular mortality of women has been decreasing for the last 20 years. However, cardiovascular outcomes in men have already started to decrease in the early 1980s, resulting in a sex-related mortality gap, with women having a higher mortality than men for the last 40

years [71]. Due to their increased life ex-

pectancy, women have more lost life years. Studies investigating outcomes after PCI according to sex come to different conclusions. A recently published meta-analysis of 21 randomised trials compared outcomes of women and men after PCI [72]. As expected, women were older and had higher rates of comorbidities and therefore worse outcomes. After multivariable adjustment, female sex remained an independent risk factor for major adverse cardiovascular events (MACE) and ischaemia-driven target lesion revascularisation. Interestingly, the higher risk of adverse outcomes in women was predominantly observed within the first year following the index PCI. Importantly, there were no differences in all-cause or cardiovascular mortality between sexes. Possible explanations for worse outcomes observed in women after PCI are the following: 1) Women are reported to suffer more often from coronary and vascular access site complications and bleeding events [73]. Radial instead of femoral access has been demonstrated to lower bleeding rates, even more so in women [53]. However, radial access is still underused in women, independent of makers of body size and weight [74]. Bleeding after PCI is problematic, since it is known to be a strong predictor of antiplatelet therapy discontinuation which again triggers ischaemic events [75]. 2) Socioeconomic disparities have been shown to affect clinical outcomes following PCI more in women than men [76]. 3) Women are less often prescribed GDMT in both primary and secondary prevention [43]. 4) Due to the fear of bleeding, they receive conservative antithrombotic therapy more often. 5) Procedural factors, such as less rigorous lesion preparation and suboptimal treatment of the smaller coronary arteries could have influenced the worse outcomes in woman [72]. Other studies, such as a prespecified subgroup analysis of the GLOBAL LEADERS study found no difference in rates of MACE, including bleeding events, between women and men after PCI [55].

Interestingly, outcomes can also vary according to gender. Compared to sex which is defined according to genes, sex hormones and reproduction organs, gender is dependent on social norms. A person's gender can influence access to the healthcare system, disease perception and decision-making such as health care utilisation and medication intake [77]. These factors have been shown to predispose women to worse outcomes than men.

cular disease [78, 79]. Patients with INOCA associated with worse outcomes in patients with INOCA comprise a reduced CFR, higher calcium and higher CT plaque scores, among others. In addition to increased rates of MACE, patients with INOCA also have an impaired quality of life [81, 82].

Future

With less than 30% of the study populations, women remain underrepresented in cardiovascular clinical trials despite their high prevalence of CAD [83]. This has resulted in interventional techniques, medication and preventive strategies being optimised for men. Dedicated randomised trials enrolling women with established or at risk of CAD are needed to close the sex gap in evidence. Further, sex-specific risk stratification tools and diagnostic pathways for women with chest pain should be developed and implemented into clinical practice.

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Conflict of Interest Statement

No financial support and no other potential conflict of interest was reported.

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