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Sex Differences in Cardiovascular Disease – Impact on Care and Outcomes

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Globally, cardiovascular disease (CVD) is the number one killer of women; one third of female deaths are due to ischemic heart disease and stroke (WHO 2013). Historically considered a 'man's disease', the basic research and clinical trial evidence that underpins our treatment of CVD is largely based on males. The seminal publication from the Institute of Medicine – Exploring the Biological Contributions to Human Health: Does Sex Matter [1] – laid the foundation for the importance of examining sex and gender in order to better understand human health. Incorporating sex and gender into research leads to better science, and better science has the potential to improve the diagnosis, treatment and outcomes of both women and men. Funding organizations like the National Institutes for Health require the inclusion of women in clinical trials that they fund[2], when the disease is relevant to

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women; the Canadian Institutes for Health (CIHI) asks applicants to indicate how they are taking sex and/or gender into account in the research project[3]. These initiatives have the potential to improve the science that informs care, but more work needs to be done.

In this review, we predominantly focus on an examination of sex differences, which is evolving into a mature science with a body of knowledge that can inform the prevention, diagnosis and treatment of CVD. When available, the impact of gender is also addressed. The definitions of sex and gender, from the CIHI Research, are provided in Figure 1. As research and clinical practice move towards precision medicine, sex and gender differences are a critical component. As an example, sexual dimorphism in drug metabolism impacts both drug effectiveness and adverse drug reactions [4, 5], which directly inform the practice of precision medicine.

1 Cardiac Risk Factors

1.1 Traditional Risk Factors

In the early 1940's, the seminal, prospective, community-based Framingham Heart Study began following 2,489 men and 2,856 women between the ages of 30 and 74, to examine the epidemiology of CVD and identify patient characteristics that contribute to the development of heart disease. Over the years, the Framingham Heart Study identified age, sex, smoking, high blood pressure, high blood cholesterol, and diabetes as major cardiac risk factors. A more recent global case-control study of risk factors for acute myocardial infarction (AMI) in 52 countries, the INTERHEART study, extended these prior findings. The INTERHEART study identified nine modifiable risk factors, which collectively were shown to explain more than ninety percent of the population-attributable risk (PAR) for AMI in men and women, indicating that the risk of AMI could be reduced by more than ninety percent if all these nine risk factors were eliminated[6]. These modifiable risk factors include: smoking, hypertension, abnormal lipids, diabetes, abdominal obesity, high-risk diet, psychosocial factors, lack of physical activity and absence of alcohol use compared to moderate use[7].

These established cardiac risk factors play an important role in development and progression of CVD in both men and women. However, there are important sex differences in some of these factors[8, 9]. In particular, diabetes and smoking have a stronger association with development of CVD in women than in men, and they are the focus of our review in this section.

1.1.1 Diabetes—The WHO has estimated that the global prevalence of diabetes has increased continuously over three decades, with 422 million adults affected in 2014[10]. In many regions, including Canada and the United States, the prevalence of diabetes is higher among men than in women (7.5% vs. 5.8% in Canada[11] and 13.6% vs. 11.2% in the U.S.[12]); however, risk of developing CVD is much greater among women with diabetes than men. The Framingham data showed the relative risk of CVD in diabetics as compared to non-diabetics was 1.93 in men and 3.57 in women (Figure 2). This finding of excess risk in women was consistent for risk of heart failure, intermittent claudication as well as overall CVD[13, 14]. The INTERHEART study also found that diabetes was more strongly associated

with risk of AMI in women [OR= 4.26 (95% CI: 3.68, 4.94)] than in men [OR= 2.67 (95% CI: 2.43, 2.94)][6].

In more recent years, several studies have also shown that the impact of diabetes on development of coronary heart disease (CHD) is greater in women than in men. A meta-analysis by Peters et al. which included 858,507 individuals and 28,203 incident CHD events, found that the relative risk (RR) of developing incident CHD, comparing individuals with diabetes to those without diabetes, was 44% higher in women than in men [(RR= 1.44 (95% CI: 1.27, 1.63)][15]. Furthermore, the diabetes-related risk of fatal CHD was higher in women than in men. Huxley et al. also documented a 154% excess risk of fatal CHD among women with type 1 diabetes than their male counterparts [SMR=2.54 (95% CI: 1.80, 3.60)][16].

Our understanding of the mechanism for the observed excess risk of CVD in women with diabetes as compared to men with diabetes is still evolving. A more adverse cardiac risk profile in women with diabetes, as well as greater worsening of cardiac risk status during transition from normoglycemia to diabetes, may play an important role in the excess risk seen in women compared to men[17]. In a meta-analysis comparing diabetics and non-diabetics, the mean differences in systolic blood pressure, total cholesterol, HDL cholesterol, body mass index (BMI) and waist circumference were greater for women than for men[18]. Coupled with this, several studies have highlighted poorer management/treatment of diabetes and its associated risk factors in women as compared to men[19]. A national audit of diabetes care in the UK showed that women with diabetes were 15% less likely to complete all the recommended care processes, even after taking age, ethnicity, income and BMI into account[12]. Additionally, it has been reported that women with diabetes are less likely to receive lipid-lowering medication[19], despite evidence that statins reduce adverse vascular events[20].

Although the observed excess risk of CVD in women with diabetes may be primarily driven by biological factors, gender-related factors also play a role. A Canadian national health survey demonstrated an inverse association between SES and obesity, a major risk factor for diabetes, with a stronger association observed in women than in men[21]. Gendered-based factors such as lower SES, lower levels of physical activity and higher stress levels due to greater family responsibilities are all interrelated and often more prevalent among women than men[22–24]. The combination of these unfavorable factors could also contribute to the excess risk of CVD in women with diabetes.

1.1.2 Smoking—Smoking is a key cardiac risk factor for development of CVD in both women and men. Based on 2014 statistics, the prevalence of smoking is higher in men than in women, both in Canada (21.4% vs. 14.8%) and the U.S. (16.7% vs. 13.6%), with highest rates observed among younger age groups (20–34 years). A recent study, based on four nationwide French registries [including the French Registry of Acute ST-Elevation Myocardial Infarction (STEMI) or non-ST-Elevation Myocardial Infarction (NSTEMI)] indicated that the proportion of young patients (<60 years), particularly women, who present with smoking and/or obesity as their sole risk factors at the time of their hospitalization for STEMI, has continuously increased between the years 1995 to 2010[25]. Based on this study,

approximately 45% of young French women and 40% of young men presented with smoking and/or obesity as their only risk factors. The Framingham Heart Study[26], the INTERHEART Study[6] and a more recent study by Oliveira et al. [27] have reported three-fold to eight-fold increased risk of AMI, when comparing [27]current smokers to never smokers.

Similar to diabetes, the risk of development of CHD due to smoking is greater among women than men. Decades ago, the findings of a large prospective cohort study of 11,472 women and 13,191 men in Copenhagen found that the relative risk of MI was 50% higher in female smokers than male smokers across all ages, but the largest sex gap was observed among younger adults (Figure 3)[28]. More recently, in a meta-analysis of 17 cohort studies, the relative risk of CHD in smokers compared to non-smokers was 25% greater in females [RR=1.25 (95% CI: 1.12, 1.39)] compared to males[25].

The reason for the differential impact of smoking on development of CVD in women versus men is not fully understood. Some have speculated that the use of oral contraceptives may be a contributing factor as it has been shown that the combination of oral contraceptive use and smoking increases CVD risks[29, 30]. It has been suggested that the negative impact of smoking on HDL level, may be greater in women than in men and could contribute to the observed excess CVD risk among women[31]. Furthermore, increased levels of hormones including fasting insulin, free testosterone as well as neuroendocrine hormones such as arginine vasopressin AVP have been observed in female smokers, which can potentially lead to higher risk of cardiovascular disease[32–34]. These findings are based on small studies and as such our current understanding of the more pronounced negative impact of smoking in females remain largely speculative.

1.2 Psychosocial Risk Factors

It has long been observed that acute and chronic emotional stress, and stress-induced physiological perturbations, predict future cardiovascular disease events[35, 36]. The large INTERHEART study used an aggregate exposure of psychosocial and mental health factors, including depressive symptoms, perceived home/work stress, low locus of control, and major life events, some of which are driven by both biological (sex-based) as well as socially-constructed (gender-based) factors. The INTERHEART study found that this measure was significantly associated with a 3.5 increased odds of MI in women and 2.6 in men, with a population attributable risk of 40% in women and 25% in men[37]. Not all psychosocial risk factors may affect the two sexes equally. Among women, depression, early-life adversities, and posttraumatic stress disorder (PTSD) are especially prevalent and have shown some of the most robust associations with CVD[38, 39]. Unifying features of these factors include a link with severe stress, chronic dysregulation of neuroendocrine stress systems, and an average onset at young age, possibly resulting in protracted perturbations affecting women many years before CVD becomes manifest[40]. Depression affects approximately 7% of the population and is about twofold more common in women than in men, with a one-year prevalence of 8% and 5%, respectly[41].

Depression in women is also on average more severe than in men and has an earlier age of onset. Among cardiac patients, depression rates are doubled in females compared with males[42–44]. The condition is especially common in young women who have survived an

MI[42, 43]; about half of women < 55 years old with a previous MI have a history of major depression[43, 44].

Depression is a recognized risk factor for incident MI and cardiac death[45, 46]. Among women, depression approximately doubles their cardiovascular risk[47, 48]. Two recent follow-up studies of young adults (< 40 years old) found that the impact of depression on CVD risk was higher among women than men[49, 50]. Even among patients referred for coronary angiography depression has been shown to be more predictive of adverse cardiovascular outcomes in young women than in other groups[51]. There are insufficient data on whether these sex-related differences in outcome also apply to patients post-MI. Overall, however, depression seems to affect post-MI prognosis similarly in women and men[52].

Severe childhood adversities, such as physical and sexual abuse and child neglect, are unfortunately common in the population, especially among girls, and are emerging risk factors for CVD[53], in addition to being frequent precursors of major depression and PTSD. In the Nurses' Health Study II, childhood abuse was associated with approximately a 50% increased risk of CVD, independent of other risk factors[54]. Early life trauma appears to be a stronger predictor of CVD in younger women than it is in similarly aged men[55, 56]. Sexual abuse, in particular, was associated with a fivefold higher rate of self-reported CVD events in the previous 12 months in a national survey of adult women < 55 years of age[57], with no association observed among men. In a Finnish community sample of 23,916 individuals < 55 years at baseline, CVD risk among women (but not among men) tracked with the number of childhood adversities[56]; three or more adverse childhood experiences was associated with a threefold increased CVD risk in women, after adjusting for demographic and behavioural factors.

General symptoms of anxiety, measured with a variety of scales, have been associated with incident CVD in a number of studies, although individual study results are heterogeneous and effect sizes in general modest[58]. In contrast, symptoms of PTSD, a condition previously classified among anxiety disorders, have been consistently related to increased risk of CVD[59]. PTSD affects 9.7% of women (past year prevalence), vs. 3.6% of men[60]. In a prospective study, women with ≥ 5 PTSD symptoms had over threefold higher risk of ischemic heart disease compared with those without PTSD symptoms, independent of CVD risk factors and depression[61]. In the Nurses' Health Study II, women who reported ≥4 PTSD symptoms had a 60% higher risk of CVD. However, those with a history of trauma but no PTSD symptoms also showed an elevated CVD risk (45% higher)[62]. Thus, women exposed to psychological trauma may experience an increased risk of CVD even in the absence of PTSD, although the presence of the disorder likely has an additive effect.

There are multiple possible mechanisms linking depression, PTSD, and psychological trauma to CVD. Health behaviors are clearly implicated, such as smoking, poor dietary habits, and physical inactivity. However, lifestyle behaviors do not appear to explain entirely the connection between psychosocial factors and CVD. Alterations in neurobiological stress response pathways, leading to increased inflammation, chronic autonomic dysregulation, endothelial dysfunction and hypercoagulability are all plausible mechanisms that have been demonstrated in human and animal studies[40].

In addition to the chronic stressors and mental health disturbances described above, acute stressful events can contribute to CVD morbidity and mortality. Sudden, intense emotions can cause ACS and death in susceptible individuals[63–65]. However, because these events are unpredictable, it is difficult to study them rigorously. In patients with CVD, mental stress can induce transitory coronary perfusion deficits, known as mental stress-induced myocardial ischemia (MSIMI). MSIMI occurs in approximately one third to half of patients with CVD and is associated with approximately a doubling of subsequent CVD events and mortality; similar to ischemia induced by conventional stress testing[66].

Although studies of MSIMI were performed predominantly in men, emerging data suggest that MSIMI is more common in women than in men. In a study of stable CVD patients, women had a 39% higher incidence of MSIMI compared with men[67]. Recent studies using myocardial perfusion imaging revealed that young women (≤50 years) with a recent history of MI or stable CAD had 2–3 times the rate of MSIMI compared with men of the same age, while older men and women showed no difference[43, 68]. These results were not explained by factors such as severity of disease or traditional CVD risk factors.

Possible mechanisms for the higher rates of MSIMI in women include abnormal coronary vasomotion and peripheral vasoconstriction. MSIMI is at least in part caused by coronary microcirculatory dysfunction, due to a failure of small coronary arteries to dilate during stress[69–73]. As noted in section 4, women have a tendency towards abnormal vasomotion and microvascular dysfunction. Thus, it is possible that women exhibit enhanced microvascular dysregulation with mental stress due to their propensity to vasomotor reactivity[74]. Stress-induced vasoconstriction could be accentuated in young women given their higher baseline levels of inflammation[75]. Overall, these studies have uncovered vulnerability for adverse effects of emotional stress on cardiovascular function in women.

1.3 Risk Factors Unique to Women

In addition to the traditional risk factors discussed in section 1.1, a growing number of cardiovascular risk factors unique to women are being identified[76]. In this section we highlight the importance of these risk factors and focus on disorders related to pregnancy and reproduction, specifically hypertensive disorders of pregnancy, gestational diabetes and menarche/menopause. Factors that have been studied, but not yet shown to be strongly associated with an increase in CVD morbidity/mortality include spontaneous preterm delivery, giving birth to a small for gestational age neonate, recurrent miscarriage, polycystic ovarian syndrome and premature ovarian insufficiency[77]. These remain the focus of ongoing study, but will not be reviewed here.

1.3.1 Hypertensive Disorders of Pregnancy (HDP)—HDP can be divided into gestational hypertension and preeclampsia, both of which the American Heart Association considers major risk factors for the development of CVD[76]. Gestational hypertension is associated with development of hypertension later in life, and possibly associated with development of CVD, hyperlipidemia, chronic kidney disease and diabetes mellitus. A prospective study of over 15,000 women showed that women with gestational hypertension

in consecutive pregnancies had significantly higher blood pressure later in life than women who remained normotensive[78].

Women who develop preeclampsia during pregnancy have a twofold or greater risk of developing CVD later in life[79–83]. This increased risk is strongly supported by two systematic reviews that evaluated the risk of late cardiovascular events in women with and without a history of preeclampsia[79, 84]. Women with preeclampsia were at increased risk of developing hypertension [RR= 3.70 (95% CI: 2.70–5.05)] at mean follow-up of 14 years), ischemic heart disease [RR= 2.16 (95% CI: 1.86–2.52)] at mean follow-up of 11.7 years) and stroke [RR= 1.81 (95% CI: 1.45–2.27)] at mean follow-up of 10.4 years[79]. Prospective cohort studies have also reported similar findings[85–87].

It is important to consider whether gestational hypertension and preeclampsia are indeed independent risk factors for CVD or if they act predominantly through traditional risk factors. It is clear that women with HDP are at increased risk of developing hypertension later in life. It may also be that pregnancy unmasks an individual's predisposition to developing hypertension. Some epidemiologic data suggest that the increased risk of late CVD may be attributed to underlying genetic and other cardiac risk factors that are common to both disorders[78, 88–90]. It may also be that HDP induces physiologic and metabolic changes that remain after delivery leading to late CVD[91–100].

1.3.2 Gestational Diabetes (GDM)—Although most women with GDM are normoglycemic after delivery, they are at high risk for recurrent GDM, pre-diabetes, overt diabetes and/or CVD in the future. In a meta-analysis of 20 cohort studies (675,455 women, of whom 10,859 had type 2 diabetes), women with GDM were at significantly higher risk of developing subsequent type 2 diabetes (RR=7.43 (95% CI: 4.79–11.51)[101]. The relative risk was 4.69 within the first five years after delivery and 9.34 more than five years after delivery. Women with GDM are at greater risk of developing CVD than women with no history of GDM[102–105]. Even mild glucose impairment identifies women at increased risk of future development of CVD[106].

1.3.3 Menarche/Menopause—Early menarche appears to be associated with an increased risk of future CVD. A cohort study of 1.2 million women with no known CVD at baseline showed that early menarche (age 10 years or younger) was significantly associated with an increased risk of developing CVD as compared to menarche at age 13[107]. Subsequent meta-analysis has shown that every one year increase in age at menarche is associated with a 3% reduction in CVD related mortality[108].

In the absence of traditional CVD risk factors, CVD is unusual in premenopausal women. There is a definite shift in the post-menopausal state, which is recognized as a CVD risk factor equivalent to male sex[109]. Early natural menopause (≤ 44 years of age) has been shown to be associated with an increased CVD risk [110]. A recent meta-analysis of 32 studies (310,329 women) showed that early onset menopause before age 45 is associated with a 50% higher risk of CVD and nearly a 25% higher risk of CVD death as compared to women in whom menopause occurs later[111]. Among women aged 45 to 49 at the onset of

menopause as compared to those aged 50 or older there was no increased risk of CVD or death.

Menopause at usual age may not be directly responsible for the increased CVD risk after menopause. Although the CVD incidence rises over time following menopause, there is similarly an increase in risk among men with increasing age[112, 113]. An important contributing factor is that postmenopausal women who develop CVD have an increased burden of risk factors compared with those who do not. A large, prospective population based study in Norway (51% women) showed that the gender gap in risk of MI persists through life but declines with age in part due to levelling off of differences in risk factors between post-menopausal women and middle-aged men with increasing hypertension and dyslipidemia in post-menopausal women [114]. It is unclear whether the increased incident risk of CVD when moving from the pre-menopausal to postmenopausal state, is related to changes in in hormone levels specifically a decline in estrogen levels. There are multiple purported biologic mechanisms for the benefits of estrogen including: 1) decreased LDL and increased HDL cholesterol levels; 2) endothelium dependent vasodilation; 3) enhancing the release or bioavailability of nitric oxide from endothelial cells, resulting in increased vasorelaxation and 4) positive hemostatic effects. Consistent with the notion that menopause may not be directly responsible for the increase in CVD risk after menopause is the lack of benefit from hormone replacement therapy in the Women's Health Initiative primary prevention study and in the HERS trials of secondary prevention[115–117].

2 Acute Ischemic Heart Disease

Ischemic heart disease refers to a spectrum of pathological changes or events that results in myocardial ischemia or actual myocardial injury. The acute presentations of ischemic heart disease include acute coronary syndromes (ACS), myocardial infarction, unstable angina, coronary vasospasm, spontaneous coronary artery dissection, and Takotsubo's Syndrome, as illustrated in Figure 4. Furthermore, evidence supports the role of coronary microvascular dysfunction in ACS due to existing endothelial and non-endothelial dysfunction[118].

2.1 Acute Coronary Syndromes (ACS)

To facilitate immediate treatment, such as reperfusion therapies, it is common to designate ACS based on ischemic symptoms, ECG findings and elevated biomarker values. Patients who develop ST elevation in two contiguous leads are designated as ST elevation MI (STEMI); patient without ST elevation are designated as non-ST elevation MI (NSTEMI); and patients without elevated biomarker values are usually diagnosed as unstable angina (UA). In addition to these categories, MI is also classified into one of 5 types, based on pathological, clinical and prognostic differences. In this section, we will focus on MI type 1, which is related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection, with resulting intraluminal thrombus in one or more coronary arteries leading to decreased myocardial blood flow or distal emboli with ensuing myocyte necrosis. While patients frequently have severe underlying CAD, 5–20% may have non-obstructive or no CAD on angiography. This is particularly true in women[119].

2.1.1 Presentation—It is well documented that women are more likely than men to present with NSTEMI [120, 121] and with non-obstructive (i.e. defined as >50% disease in any epicardial artery) or normal coronary artery disease (CAD). However, one of the enduring controversies is whether women and men with ACS present with different symptoms. The GRACE registry reported similar proportions of chest pain in men (94%) and women (92%), but significantly more atypical symptoms, like jaw pain and nausea in women than men[122]. The GENdEr and Sex determInantS of cardiovascular disease: From bench to beyond-Premature Acute Coronary Syndrome (GENESIS-PRAXY) study also reported a high proportion of young adults with ACS reporting chest pain, 86.3% of men and 81.0% of women, and again, women reported significantly more non-chest pain symptoms, especially jaw pain, nausea, and back pain. In contrast, patients from the National Registry of Myocardial Infarctions (NRMI), a registry of consecutive AMI patients admitted to 1,658 participating U.S hospitals, reported significantly less chest pain overall, and significantly less in women than men (58.0% vs 69.3%)[123]. This study also demonstrated a significant effect of age on the prevalence of chest pain. Among those 45 years of age or less, 85.8% presented with chest pain; among those 75 years of age or older only 51.3% presented with chest pain.

The divergent rates of chest pain may, therefore, be due to age difference in these cohorts. The median age in GENESIS-PRAXY was 49 years in both women and men, while in the NRMI cohort 55.1% of the female subjects were 75 years of age or older, compared to 31.8% of the males. Given the different findings reported in the literature, definitive conclusions about sex-differences in ACS symptom presentation are lacking, but chest pain is the predominant presentation in both sexes; chest pain presentation declines markedly with age; and there is evidence to suggest women present with more symptoms, generally atypical symptoms, compared to men.

2.1.2 Pathophysiology—Our classic understanding of the pathophysiology of ACS, namely thrombus formation on a ruptured plaque, has evolved over the past two decades[124]. Importantly, this mechanism does not adequately describe the pathophysiology of ACS in women or why women presenting with ACS demonstrate significantly less atherosclerotic burden in the epicardial vessels. In an analysis of data pooled from 11 ACS trials, women were significantly more likely to have non-obstructive CAD disease (15% vs 8%). The more recent Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study also demonstrated less extensive CAD in women with ACS, both by coronary angiography and intravascular ultrasound.

The PROSPECT study also demonstrated less plaque rupture in women with ACS (6.6% vs 16.3%, p= 0.002)[125]. The intravascular ultrasound (IVUS) sub-study of the Relationship Between Intravascular Ultrasound Guidance and Clinical Outcomes After Drug-Eluting Stents (ADAPT-DES) confirmed these findings in their ACS patients by demonstrating both less plaque rupture and lower prevalence of thin cap fibroatheroma (TCFA), in women compared to men. This sex difference was attenuated by age. While overall plaque rupture was less common in women (23.0% vs 36.3%, $p < 0.01$) a significant sex difference was observed in those < 65 years of age (19.0% vs 42%), but not in those ≥ 65 year of age.

Similarly, while TCFA was less common in women than men overall, (44.7% vs 53.3%, p = 0.026), the sex difference was again observed in younger adults (39.2% vs 53.8%, p = 0. 04), but not in those > 65 years of age[126]. TCFAs are known to be vulnerable to rupture, whereas the thrombi overlying eroded plaques reflect more organization, suggesting longer duration (up to 7 days) prior to presentation with clinical symptoms[127]. Also, the degree of stenosis resulting from plaque erosion is less than from ruptured plaques. The longer thrombus duration seen in plaque erosion also provides greater risks for distal embolization. Microvascular embolization and microvascular occlusion have been shown to cause focal myocardial necrosis[128].

In a study of atheroma burden and endothelial function in young adults (mean age 49.3 ± 11.7 years) presenting with early atherosclerosis, a lower burden of atheroma was observed in women compared to men undergoing IVUS of the left main artery (14.1% vs 23.0%, p = 0.002) and the left anterior descending artery (29.3% vs 40.1%, p = 0.001). While men had longer segments of endothelial dysfunction (39.2 [0.0 – 71.6] mm vs 11.1 [0.0 – 38.5] mm, p = 0.002) in women, maximal coronary flow reserve (CFR) was lower in women than men (2.8 vs 3.3, p < 0.001). The authors concluded that in the setting of early atherosclerosis men had more functional and structural abnormalities in the epicardial vessels, while women had more microvascular dysfunction, independent of endothelial dysfunction in the epicardial vessels[129].

Coronary vasospasm (CS) can involve the epicardial coronary vessels but it can also occur in microvasculature[130]. It manifests as a sudden, intense vasoconstriction of an artery causing complete or partial vessel occlusion. The pathogenesis of CS is likely multifactorial and appears to vary based on whether it is focal or diffuse in nature. Hyper-reactivity of the coronary vascular smooth muscle has been noted[131] and is thought to be due to a loss of balance between vascular myosin light chain kinase and phosphatase activity, resulting in a predominance of myosin light chain phosphorylation leading to excessive vascular smooth muscle contraction[132]. Endothelial cell dysfunction also plays an important role as these cells act as paracrine regulators of vascular tone responding to shear stress, myogenic constriction, and bioavailable vasoactive substances[133, 134].

A key trigger of CS is the autonomic nervous system. Noradrenaline, the neurotransmitter of the efferent sympathetic neurons, triggers vasoconstriction of the vascular smooth muscle cells (VSMC). Clinical studies have demonstrated that CS is induced by catecholamines and by stimuli that increase sympathetic activation, like exercise or stress. Acetylcholine, the neurotransmitter of the parasympathetic neurons, causes vasodilation under physiologic conditions, but can cause vasoconstriction at high doses through the stimulation of the VSMC muscarinic receptors. When the VSMC are hyper-reactive, even low concentrations of acetylcholine may trigger CS. Attacks often occur at night, when vagal tone is higher, supporting the role of parasympathetic activity in vasospasm. However, angina attacks at night occur more frequently during REM sleep, when vagal outflow is reduced[134]. Thus the relationship between sympathovagal balance and coronary vasospasm is complex and not completely understood. There are also environmental factors that contribute to the pathogenesis of this presentation, including smoking, impaired glucose tolerance, and alcohol consumption[130].

2.1.3 Diagnosis—Diagnosis of ACS generally includes the elevation of cardiac biomarkers plus evidence of acute myocardial ischemia, including symptoms of ischemia, ischemic ECG changes, or other evidence of myocardial necrosis. The diagnosis of ACS may be missed more frequently in women than men, especially those younger than 60 years[135, 136]. Prior ACS studies have shown that cardiac troponin and CK-MB levels are on average lower in women than in men and that sex-specific cut-off points for high-sensitivity troponin assays may improve the diagnosis of ACS in women[137, 138]. When a high sensitivity cardiac troponin I with sex specific diagnostic thresholds (women 16 ng/L and men 34 ng/L) as opposed to a single threshold (50 ng/L) is used, the sex specific threshold doubles the diagnosis of MI in women and identifies those at high risk of recurrent MI and death[139]. Further investigation is needed to determine whether sex specific biomarker thresholds and subsequent reclassification can improve morbidity and mortality in women.

Risk scores for the assessment of ACS clinical severity include Killip class, which classifies patients according to signs of heart failure, as well as the Thrombolysis In Myocardial Infarction (TIMI) risk score and the GRACE score, which predict in-hospital and 6-month mortality risk[140]. There may be sex differences, however, in the interaction of the risk scores on post-ACS prognosis. For example, in a prospective cohort study of 557 patients admitted with ACS, women with low Killip class (Class 1) or normal left ventricular ejection fraction (LVEF) had higher cardiovascular mortality risk than men with the same Killip class or LVEF. Conversely, women with high Killip class (Class3–4) or low LVEF had lower cardiovascular mortality risk than men with the same Killip class or LVEF[141]. Women with ACS and a high TIMI risk score, which includes clinical, ECG criteria, and biochemical markers, have historically had lower rates of angiography and reperfusion and increased rates of refractory angina and rehospitalization for unstable angina, compared to men[142]. In a more contemporary Belgian cohort of STEMI patients who receive primary PCI, the TIMI risk score was effective in predicting in-hospital mortality for both women and men but performed slightly better in men[143]. Although the GRACE score also does not use sex as a parameter because it was not shown to be a statistically significant predictor of hospital mortality during score development[140], it may improve risk discrimination in women with the additional parameters of creatinine and cardiac arrest at admission, which may reflect sex differences[144]. Recently the GRACE score was studied in a contemporary Spanish cohort with ACS; the discriminative capacity of the GRACE score was significantly lower in women with STEMI compared to men, but inclusion of female sex did not substantially improve the discriminative ability of GRACE score for STEMI patients[145]. The development of new sex specific scores may be considered for adequate risk prediction in women with STEMI.

Since sex differences exist in the risk assessment and diagnosis of ACS, these may contribute to the sex disparity in reperfusion delays, decreased guidelines-based therapy and increased ACS mortality for young women[146, 147]. The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study, a prospective cohort study of women and men younger than 55 years hospitalized for acute MI, sought to characterize phenotypes of acute MI beyond the taxonomy outlined by 2012 Third Universal Definition of MI. The 2012 Third Universal Definition of MI does not provide categories for 1 in 8

women with acute MI but no obstructive CAD who do not have identifiable mechanisms for myocardial oxygen demand and supply imbalance[148, 149]. The VIRGO taxonomy was developed to provide clinicians with a better tool to describe the diverse acute MI phenotypes that occur in young women, such as coronary microvascular dysfunction, vasospasm, spontaneous coronary artery dissection, and embolism[149]. The VIRGO investigators found that young women with acute MI present with more cardiovascular risk factors, comorbidities, and higher clinical risk scores on average then men, but men present with higher levels of cardiac biomarkers and more classic ECG findings of ischemia[150]. These results are consistent with other studies of women with ACS and highlight the importance of understanding sex differences in the risk assessment and diagnosis of ACS.

2.1.4 Treatment—Overall, the evidence demonstrates less use of evidence-based medications and less invasive interventions in women compared to men. Guidelines for the management of ACS in women are largely based on evidence from randomized clinical trials, but those trials often failed to include sufficient women and/or failed to conduct sub-group analyses to identify potential sex differences in efficacy. While there have been marginal improvements in the proportion of women in clinical trials, rising from 20% in studies from 1966–2000 to 25% in studies from 1991–2000, this still falls far short of the proportion of women in the US population (43%) presenting with ACS[151].

2.1.4.1 Delay in Seeking Treatment: Women continue to delay seeking treatment for ACS, despite the favourable impact of early treatment on both survival and clinical outcomes[152]. This delay, defined as the time from symptom onset to presentation for treatment of those symptoms, is often attributed to the differences in women's symptoms of ACS or women's interpretation of those symptoms[153]. While significant reductions in delays within the healthcare system have been noted, delays in accessing the healthcare system remain, especially for women[154]. This delay in treatment-seeking by women appears to cross cultures, and has been observed in Saudi Arabia, China, Brazil, and Norway, and across racial groups, including both white and black women in the US[154].

2.1.4.2 Invasive Treatment: The most recent Scientific Statement from the American Heart Association on AMI in Women[155] outlines the evidence for the treatment of women presenting with ACS. In STEMI, primary PCI is the preferred revascularization treatment, if readily available, over thrombolysis[156]. Both women and men derive greater benefit from primary PCI over thrombolysis, but given the higher event rate in women the absolute benefit is greater in women than men, with a reduction of 56 deaths per thousand women treated with PCI compared to a reduction of 42 deaths per thousand men[157].

In NSTEMI, the role of early invasive management is more complex. The guidelines recommend early invasive management of NSTEMI in women with high-risk features, including elevated troponin levels[158], based on the results from two meta-analyses[159, 160] and several post-hoc analyses[161–163]. Despite the evidence for the benefit of primary PCI in the setting of STEMI and an early invasive strategy in high-risk women with NSTEMI, these interventions are used less in women than men with ACS[124]. Contemporary data demonstrates lower rates of reperfusion therapy (primary PCI or thrombolysis) in women than men with STEMI (56.3% vs 73.0%, $p < 0.001$) which was not explained by differences

in baseline characteristics[164]. Timely reperfusion is also less common in women than men with STEMI, irrespective of modality – door to needle time < 30 minutes: 28.3% vs 35.2%, p< 0.001; door to balloon time < 90 minutes: 39.0% vs 44.8%, p < 0.0001[164]. A similar picture emerges in the setting of NSTEMI, where women are less likely to undergo revascularization. In some studies, the lower rates of revascularization were observed irrespective of angiographic findings[165], while in the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes (CRUSADE) registry there was no difference in the rate of PCI after accounting for the severity of CAD on angiography [(adjusted OR=0.97 (95% CI:0.91, 1.03)][166].

The risk of bleeding is greater in women than men, following PCI[167]. While a radial approach has been shown to reduce the incidence of peri-procedural bleeding[168], this approach is more challenging in women, given the smaller size of their radial arteries. Despite more failures with a radial approach in women than men, and more bleeding, the longer term clinical outcomes do not appear to differ between women and men undergoing PCI with radial access[169].

2.1.4.3 Pharmacological Treatment: The core medications for secondary prevention following an ACS event include: anti-platelet agents; beta-blockers (BB); angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB); and statins. The efficacy of these medications for the reduction of morbidity and mortality has been demonstrated in numerous randomized controlled trials, however, evidence of sex differences in efficacy, if any, are limited, especially for the older medications, as few women were enrolled in these trials.

BB therapy post-MI demonstrates reductions in death, re-infarction, and recurrent ischemia. Treatment with BB is associated with a 21% reduction in death, a 30% reduction in sudden death, and a 25% reduction in re-infarction[170]. Meta-analyses show comparable benefits in both sexes[171].

Numerous randomized clinical trials have demonstrated improved survival and reduced heart failure and MI with ACE-I use[172–174]. ARBs have been shown to be equally effective and are considered an alternative to ACE-I therapy[175]. Women were under-represented in the trials of ACE-I and ARBs, but meta-analyses of ACE-I trials report similar relative reductions in death, HF or MI in the range of 21%–29%[176, 177].

The Scandinavian Simvastatin Survival Study demonstrated a 30% reduction in CHD mortality, but the study did not enrol enough women to show a significant reduction in women. Subsequent trials, including the Cholesterol and Recurrent Events (CARE) trial and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), enrolled sufficient women to demonstrate the benefit of lipid-lowering with statin therapy. Meta-analyses have also demonstrated the efficacy of statins, irrespective of sex[178, 179]. A more recent evaluation of six randomized clinical trials looking at the impact of sex on lipid-lowering, cardiovascular events, and adverse events, demonstrated similar changes in lipid levels, but higher rates of discontinuation of therapy due to adverse events in women[180].

Meta-analyses of aspirin for secondary prevention demonstrate similar reductions in cardiovascular events in both women and men[181, 182]. In ACS patients undergoing PCI, clopidogrel reduces the risk of adverse events in both women and men[183, 184]. In a pre-specified subgroup analysis of the Clopidogrel and Aspirin Optimal Dose Usage (CURRENT-OASIS 7) trial, the treatment effects did not vary by sex, p-interaction = 0.59[183]. However, women and men respond differently to glycoprotein IIb/IIIa inhibitors, an intravenous antiplatelet therapy. While glycoprotein IIb/IIIa inhibitor treatment reduced the risk of death or MI at 30 days among men with ACS, women actually exhibited worse outcomes[185]. However, similar to what was seen with an early invasive strategy for NSTEMI, once the analysis was limited to those with elevated troponin levels, both women and men benefited from the use of glycoprotein IIb/IIIa inhibitor therapy. The benefit of anti-platelet therapy in ACS must be balanced against the risk of bleeding, which has consistently been shown to be higher in women[186, 187]. The more recent ACC/AHA NSTEMI-ACS guidelines advise careful attention to weight and renal function, when dosing anti-platelet agents to reduce the risk of bleeding in women[158].

Despite compelling evidence of efficacy for anti-platelet agents, BBs, ACE-I/ARBs and statins, women are less likely to receive these evidence-based medications. Among patients hospitalized for ACS and undergoing PCI, fewer women received aspirin [(adjusted OR=0.86 (95% CI=0.83, 0.86)] and glycoprotein IIb/IIIa inhibitors [(adjusted OR=0.90 (95% CI: 0.88, 0.92)][188]. Similar disparities have been noted in the use of BB, ACE-I/ARBs, and statins[136, 166, 189]. The GRACE study determined that even when women presented with obstructive CAD, there was less use of aspirin (95% vs 96%), beta blockers (87% vs 89%), and statins (75% vs 77%) compared to men[122]. While the absolute differences in treatment are small, the sex difference consistently trends in the same direction, with women receiving less aggressive management than men.

2.1.5 Outcome—While the incidence of ACS has declined markedly over the past few decades, and survival post-MI has improved significantly, sex differences in outcomes post ACS persist, and vary by age[190]. Young women (<50 years of age) were shown to have a two-fold higher risk of death than men in the same age group based on data from the large NRMI database[136]. Similarly, a Canadian study of 70,628 AMI hospitalizations between 2000–2009 found a significantly higher 30-day mortality rate in women compared to men, but only among those 55 years of age and younger, [OR= 1.61 (95% CI: 1.25, 2.08)[191]. Emerging evidence regarding the impact of gender, suggests that gender may have a more important role with respect to long-term health-related QoL, than sex[192], and feminine gender was also shown to be independently associated with recurrent ACS over 12 months, in a cohort of young adults[193].

Short-term mortality post ACS has been shown to be higher in women, especially after STEMI. In a meta-analysis of 11 randomized clinical trials of ACS, which included over 136,000 patients, the 30-day outcomes in women with STEMI were worse than in men [(adjusted OR= 1.15 (95% CI: 1.06, 1.24)], but in women with NSTEMI [(adjusted OR= 0.77 (95% CI: 0.63, 0.95)] or unstable angina [(adjusted OR= 0.55 (95% CI: 0.43, 0.70)], the outcomes were better in women than men[194]. In another study of 78,254 patients post MI, in-hospital mortality did not differ by sex, after adjustment for baseline differences,

however, in the STEMI patients mortality in women remained higher (10.2% vs 5.5%, p< 0.0001)[120].

Among STEMI patients, treatment with fibrinolysis is associated with a significantly higher risk of bleeding in women than men. In the The Global Utilization of Strategies to open Occluded Coronary Arteries-V (GUSTO V) study, moderate to severe bleeding was seen in 25.2% of women compared to 14.4% of men, p<0.001. Adjustment for differences in comorbid conditions did not eliminate the higher risk in women, [OR=1.31 (95% CI: 1.18, 1.46), p< 0.001][195]. Intra-cranial haemorrhage (ICH) also occurred significantly more in women (1.2%) than men (0.4%), p < 0.01. Even after adjustment for baseline differences the risk of ICH remained significantly higher in women, [OR=1.9, (95% CI: 1.2, 2.8, p = 0.004][195]. A recent evaluation of six randomized controlled trials of fibrinolysis in the treatment of STEMI, reported similar findings, with a 1.9 fold higher risk of moderate to severe bleeding in women than men, 1.3% vs 7.1%, p<0.001[196].

After elective PCI contemporary outcomes no longer differ by sex, though the older data demonstrated worse outcomes in women[197]. Both 30-day and longer-term outcomes are similar in women and men post PCI. However, women still appear to have worse outcomes than men, both in the short term and the longer term, following CABG, though the gap appears to have narrowed over time[198, 199]. In the setting of NSTEMI, women undergoing CABG tend to have more post- and peri-operative complications, but the long-term risk of death, MI or stroke does not vary by sex[155]. Women have been shown to have poorer health-related quality of life and less functional improvement post-CABG than men[200, 201].

2.2 Spontaneous Coronary Artery Dissection (SCAD)

SCAD is an important cause of MI particularly in young women. SCAD is defined as a spontaneous separation of the coronary artery wall that is not iatrogenic or due to trauma, and the contemporary usage of the term is reserved for non-atherosclerotic variant of SCAD. SCAD had been under-diagnosed, however, there has been a surge in SCAD diagnosis in recent years due to increased utilization of coronary angiography for patients presenting with ACS, and increased utilization of high-resolution intracoronary imaging (especially optical coherence tomography [OCT]) that improves diagnosis[202–204]. About half of the ~1500 reported SCAD cases to-date were published in the past five years[202, 205–214]. It is estimated that SCAD is the underlying cause for 1.7–4% of overall ACS presentation based in contemporary series[212, 215], and accounts for 0.5% of sudden cardiac death[216]. In young women <60 years of age, SCAD accounts for 22–35% of the ACS presentations[208, 212, 214]. Indeed, 92–95% of SCAD cases are women[202, 209, 211–213, 217], with mean age of patients ranging from 44 to 55 years, reflecting a young to middle-aged population[202, 208, 209, 211–214].

2.2.1 Pathophysiology—SCAD can occur within or between any of the 3 arterial layers (intima, media, or adventitia) of the coronary artery. The two proposed mechanisms for the initiation of the arterial tear were (1) primary intimal dissection of the intimal-luminal interface, and (2) spontaneous haemorrhage into the media such as through rupture of vasa vasorum, both of which results in intramural hematoma within the false lumen of the arterial

wall[218]. Compression of the true lumen by the intramural hematoma can then result in myocardial ischemia and infarction.

The underlying cause of SCAD appears to be multifactorial. In most cases, there is an underlying predisposing arteriopathy that weakens the arterial wall, increasing the susceptibility for dissection. This arterial fragility may be compounded by a precipitating stressor, either an emotional or physical stressor, which then potentiates the arterial tear. Many predisposing non-atherosclerotic arteriopathies have been associated with SCAD, with the most prevalent being fibromuscular dysplasia, which was reported in 50–80% of SCAD patients[217, 219, 220].

2.2.2 Diagnosis—Early and correct diagnosis of SCAD is paramount since the management is different from atherosclerotic coronary disease. Despite the limitations of coronary angiography, it remains the first-line imaging tool for SCAD given its widespread availability. However, since it does not image the arterial wall, dedicated intracoronary imaging [e.g. OCT and IVUS may be required to confirm the presence of intramural hematoma and/or intimal tear. Contemporary SCAD angiographic classification has been proposed by Saw: type 1 describes the appearance of arterial wall contrast staining with multiple radiolucent lumens; type 2 describes diffuse stenosis of varying severity and length (typically >20mm); and type 3 describes focal or tubular (typically <20mm) stenosis mimicking atherosclerosis, thus requiring intracoronary imaging to confirm diagnosis[221]. Utilizing this classification in a series of 203 dissected arteries, type 2 SCAD was observed in 67.5% of cases, type 1 in 29.1% of cases, and type 3 in 3.4%[221]. Several series have reported diffuse smooth stenosis to be the most common angiographic manifestation [207, 212, 214]

2.2.3 Treatment—The ideal management of SCAD is yet to be determined since there are no published randomized trials, and current management recommendations are based on expert opinions from observational studies[155, 202, 208, 222]. As shown in Figure 9, conservative approach is preferred based on published data that revascularization is associated with high failure rates, and SCAD arteries tend to heal spontaneously in the vast majority of cases. However, a small proportion of patients may require revascularization, such as those with ongoing or recurrent ischemia, hemodynamic instability, ventricular arrhythmias, or left main dissection. In such cases, coronary stenting is preferred if the anatomy is suitable, otherwise coronary artery bypass surgery should be considered.

Generally, aspirin and beta-blockers are administered acutely and long-term. Beta-blockers may reduce coronary arterial shear stress such as with aortic dissection[223], furthermore they reduce ventricular arrhythmias and improve long-term survival in post-MI patients[126, 158]. Some authors advocate a short duration of clopidogrel in addition to aspirin, to counteract the prothrombotic milieu of intimal disruption, and to reduce false lumen thrombus[224]. However, heparin and thrombolytic therapies are generally avoided, because of the risk of extension of dissection[225, 226]. Angiotensin converting enzyme inhibitor or angiotensin receptor blocker may be administered for those with significant left ventricular dysfunction[227]. Statins may be used in patients with underlying dyslipidemia and calcium channel blocker and nitrate therapies may be administered in patients with recurrent chest

pain post-SCAD who are unresponsive to BB. Cardiac rehabilitation has been demonstrated to be safe and effective post-SCAD event, and is highly recommended to improve the psychosocial and physical wellbeing of survivors[228].

2.2.4 Outcome—In contemporary series, the acute outcomes with SCAD are relatively good with in-hospital mortality <5%, and recurrent MI or need for urgent revascularization in 5–10%[206, 208, 210]. Subacute MACE within 2 year follow-up were reported in 10–20% of patients, with recurrent SCAD event-rate ~15%[217, 224]. Although long-term survival is >95% in SCAD patients, long-term MACE rates were reported to be high at 15–37% at 5–7 years, and estimated at ~50% at 10 years[206, 210, 214, 221, 229]. Recurrent SCAD rates at 4–5 years may be as high as 27%[209, 214]. Such high follow-up event-rates emphasize the importance of cardiovascular follow-up of SCAD survivors.

2.3 Takotsubo's Syndrome (TTS)

TTS is an acute and typically reversible HF syndrome that is increasingly recognised since the first published case in 1990. The name "Takotsubo" was derived from the left ventricle at end-systole having the appearance of the octopus pots of Japanese fisherman in the Hiroshima fish markets. Many alternatives names have been used, such as stress-induced cardiomyopathy, apical ballooning syndrome, and "broken heart syndrome". Since the diagnosis is based on several clinical observations, there is consensus that the description as a "clinical syndrome" is more appropriate than "cardiomyopathy"[230]. TTS is distinct from ACS, although the presenting features are very similar to MI presentations with chest pain and ischemic ECG changes. However, it probably represents a form of acute catecholaminergic myocardial stunning. It is estimated that 50,000 – 100,000 cases occur annually in the US, accounting for 1–2% of patients with suspected ACS[231]. It is often triggered by emotional or physical stress, and occurs predominantly in post-menopausal women in ~90% of cases[231].Several diagnostic criteria have been proposed in the past decade, including those from the Mayo Clinic, the Japanese Takotsubo Cardiomyopathy Group, the Gothenburg Group, and the Takotsubo Italian Network. The Heart Failure Association of the European Society reviewed and adapted these criteria, which was published in the position statement in 2016[230]. The key diagnostic features for TTS are: (1) transient regional wall motion abnormalities of the left or right ventricle often preceded, but not always, by a stressful trigger; (2) regional wall motion abnormalities usually extend beyond a single epicardial artery distribution; (3) absence of culprit atherosclerotic/non-atherosclerotic CAD or other pathological conditions to explain the ventricular dysfunctional pattern (e.g. myocarditis, cardiomyopathy); (4) new and reversible ECG abnormalities during the acute phase (3 months); (5) significant elevation of serum natriuretic peptide during the acute phase; (6) relatively small elevation in cardiac troponin level in disparity to the amount of dysfunctional myocardium present; (7) recovery of ventricular systolic function on cardiac imaging at 3–6 months follow-up.

Patients typically present with acute chest pain, breathlessness, and palpitations. And in more severe cases, they may present with pre-syncope or syncope from ventricular arrhythmias, severe left ventricular outflow tract obstruction, or cardiogenic shock[80]. The typical apical ballooning appearance is observed in 75–80% of cases, and the remaining

atypical variants include mid-ventricular, basal, and focal akinesis variants[230]. Although this is typically a reversible disorder, it is associated with major complications in ~50% of cases. These include acute HF, left ventricular outflow tract obstruction, mitral regurgitation, cardiogenic shock, atrial and ventricular arrhythmias, apical thrombus formation, pericardial tamponade, and ventricular rupture[230]. Treatment consists predominantly of supportive HF therapy, and repeat imaging should be performed to assess for recovery of ventricular function in 3–6 months[230]. The reported in-hospital mortality ranges 1–5%, with subsequent recurrence rate of 5–22%, 30-day MACE of ~7%, and 5-year mortality of 3–17%[80, 230].

3 Stable Ischemic Heart Disease (SIHD)

The conventional paradigm that flow-limiting atherosclerosis of one or more epicardial vessels underlies stable ischemic heart disease, fails to recognize many other mechanisms that may alter determinants of myocardial oxygen supply-demand and result in ischemia. In this section we review both obstructive and non-obstructive etiologies of SIHD and we examine both the coronary microvasculature and epicardial vessels.

3.1 Stable Angina

Stable angina pectoris is more common in women than men[232, 233]. Normal or non-obstructive CAD is observed more frequently in women with angina than in men[234]. Women have more diverse symptoms than men. Cardiovascular risk evaluation and diagnosis of ischemic heart disease is thus more difficult in women. Angina pectoris is more debilitating in women than men[235].

3.1.1 Prevalence of stable angina—From population studies, it is apparent that unlike the male excess of MI, women have a similar or slightly higher prevalence of stable angina compared to men. In a systemic review and meta-analysis of prevalence of angina using the Rose Questionnaire in 31 countries, the pooled estimates for women were 6.7% compared to 5.6% in men[232]. This finding was consistent across countries and cultures (Figure 5). The Rose questionnaire, although a standardized instrument for diagnosing angina, was developed and validated in men and based on the assessment of typical chest pain associated with obstructive CAD. Studies using this questionnaire may therefore in fact underestimate the prevalence of angina in women who suffer from symptoms other than those described as typical.

In a prospective ambulatory cohort study from Finland, the age-standardized annual incidence of angina was similar in both sexes[236]. Angina in this study was defined as “nitrate prescription angina,” (i.e. physician diagnosed angina and prescribed nitrate drugs) or “test-positive angina” (i.e. physician diagnosed angina based on an abnormal noninvasive test indicative of myocardial ischemia). These inclusion criteria may also underestimate the prevalence of angina in women, as women in general are less likely to undergo non-invasive and invasive testing and be treated according to guidelines.

In the National Heart and Lung and Blood Institute survey, the prevalence of angina in women < 65 years was 5–7% and in men 4–7%, and in the age group 65–84 years, 10–12% in women and 12–14% in men[233]. The higher prevalence of angina in younger and middle-

aged women compared to men may reflect the higher rate of microvascular angina. In the Swedish Coronary Angiography and Angioplasty Register (SCAAR) study in 12,200 patients undergoing diagnostic coronary angiography for stable angina, almost 80% of women < 65 years with stable angina had either no CAD or non-obstructive CAD (Figure 6)[237]. In older age groups, obstructive CAD is more common in both men and women.

A higher prevalence of angina in women is also reported for different ethnic groups. In the United States the estimated age-adjusted prevalence of angina in women age ≥20 years is 4.1% for non-Hispanic white women, 4.5% for Mexican-American women, and 6.7% for non-Hispanic black women[233]. Rates for men in these three groups were 4.1%, 3.5%, and 4.4%, respectively. The higher rates of angina in the non-Hispanic black female population may in part be explained by the high prevalence of cardiovascular risk factors[238].

3.1.2 Pathophysiology—Angina pectoris is the medical term for chest pain due to ischemic heart disease. It occurs when the supply of oxygen to the myocardium is less than the demand. The most common cause of angina is narrowed or blocked coronary arteries. In women, angina with normal or non-obstructive CAD occurs more often than in men as reported in several studies in patients undergoing diagnostic coronary angiography for stable angina. In the Coronary Artery Surgery Study (CASS) registry, in approximately 25,000 patients, 39% of women compared with 11% of men had normal coronary arteries[239]. Data from 375,886 patients in the American College of Cardiology-National Cardiovascular Data Registry (NCDR) showed that no obstructive CAD was significantly higher in women than in men (51% vs. 32 %)[240]. In the Swedish SCAAR report non-obstructive CAD was more common among women than men in all age groups (Figure 6)[237]. This high prevalence in women has also been confirmed by the WISE study, in which 62% of women referred for coronary angiography had no obstructive CAD[241].

The underlying mechanism of angina pectoris, in the absence of significant CAD, remains unclear[242]. Studies using IVUS or optical coherence tomography provide evidence that cholesterol deposition may be found in seemingly “normal” coronary arteries. T he epicardial coronary arteries are smaller in women, and smaller coronary arteries may be associated with ischemia at a lower plaque burden. Other causes include coronary microvascular dysfunction and coronary artery spasm as discussed in further detail elsewhere in this review.

3.1.3 Diagnosis—Current guidelines recommend a stepwise approach for decision making in patients with suspected stable angina[243]. The first step is to assess the patient’s pre-test probability (PTP) of CAD. The major determinants of PTP include sex, age and symptom description as typical, atypical or non-anginal. Typical chest pain is defined as substernal chest pain provoked by exertion or emotional stress and relieved by rest and/or nitrates. The second step is non invasive or invasive testing to establish the diagnosis of CAD after which treatment is initiated.

The use of PTP has its limitations, particularly in women. PTP is based on studies performed several decades ago and it assesses the likelihood of obstructive CAD based on typical symptoms[244]. Women more often than men have symptoms described as atypical and

normal or non-obstructive CAD, on angiography. Hence categorical use of PTP in women may lead to an under-diagnosis and subsequent under-treatment of ischemic heart disease in women not caused by obstructive CAD. These limitations are important to acknowledge and PTP, especially in women, should be used in the context of other clinical information (i.e. cardiovascular risk).

There are many different CVD risk assessment tools available to physicians[245]. They are often easy to use and establish a common ground for lifestyle and medical intervention. However, these scores focus on the10-year risk for coronary heart disease rather than long-term risk for CVD. A woman's risk for stroke and HF through middle and older age typically exceed their risk for coronary heart disease, which contrasts with the pattern observed in men.

These scores are also limited to the major traditional risk factors and may not fully quantify risk in women, especially in younger women and those with non-obstructive CAD. The Reynolds risk score is an example of a novel attempt to more accurately classify risk in women by adding biomarkers reflective of the complex biological process underlying ischemic heart disease[246]. However, this score is not endorsed as there are no data to support the association between a reduction in hsCRP and improved clinical outcomes.

As outlined in the 2011 CVD prevention guidelines for women, history of pregnancy complications (e.g. gestational diabetes mellitus, preeclampsia, preterm birth, or birth of an infant small for gestational) should be routinely included[76]. These guidelines also recommended heightened awareness of conditions more common in women such as depression and autoimmune diseases. Further studies are needed on how inclusion of female-specific factors may improve women's risk classification.

3.1.3.1 Diagnostic Modalities: Symptomatic women with suspected SIHD should undergo initial non-invasive diagnostic testing for myocardial ischemia and prognosis depending on their risk. The 2014 AHA consensus statement for the role of noninvasive testing in the clinical evaluation of women with suspected SIHD outlines an algorithm for diagnostic testing (Figure 7)[247]. Low-risk women generally should not undergo any diagnostic testing, but low-intermediate risk or intermediate-risk women should be considered for exercise ECG if she has a normal or interpretable ECG and able to exercise. Intermediate-risk women with resting ST-segment abnormalities or high-risk women should be considered for stress imaging (myocardial perfusion imaging [MPI], stress echocardiography, or stress cardiac magnetic resonance [CMR] imaging) or coronary computed tomography angiography (CCTA). Exposure to ionizing radiation should be discussed with the patient, including the test's effective radiation dose and estimation of cancer risk, and the lowest dose should be used for all patients.

If an intermediate-risk woman has a normal baseline ECG and can exercise, exercise ECG is the recommended initial non-invasive test of choice given its high negative predictive value, ability to assess functional capacity, and evidence from the WOMEN trial of similar 2-year clinical outcomes for women randomized to exercise ECG compared with exercise MPI while providing significant cost savings[248]. Calculation of the Duke Treadmill Score has

diagnostic and prognostic value in women and can help predict the risk of significant coronary stenosis[249, 250].

More recently for the assessment of low to intermediate -risk patients, the PROMISE trial showed that CCTA and functional testing had similar 2-year clinical outcomes when used as an initial diagnostic strategy[251]. Post-hoc analysis of the PROMISE study, however, identified sex-differences in risk assessment, noninvasive test outcomes and noninvasive test prognostic value, highlighting the importance of sex-specific approaches for the evaluation of CAD[124, 252]. For example, not only were women more likely to be characterized as lower risk by providers and by risk scores despite having a greater number of cardiac risk factors, women were also less likely to have a positive test[252]. The Diamond and Forrester risk score, which classifies chest pain as typical, atypical, and nonanginal, was predictive of a positive test in men but not in women. Finally, the PROMISE study concluded that women tend to derive more prognostic value from a CCTA than from traditional functional testing, whereas men tend to derive similar prognostic value from both functional testing and CCTA[124], which likely reflects the lower rates of obstructive CAD in women with SIHD and suggests that the detection of nonobstructive atherosclerosis is clinically important in women with SIHD[253].

3.1.4 Treatment—The aims of the management of stable angina are to reduce symptoms and to prevent future cardiovascular events. As with ACS patients, management includes lifestyle modifications, control of cardiovascular risk factors, pharmacological therapy and invasive therapy (PCI or CABG) when significant obstructive CAD is present[243]. These recommendations are similar for men and women. Medical therapy may include a combination of anti-hypertensive medications (BBs, calcium channel blockers, ACE-inhibitors, RAAS-inhibitors), lipid-lowering drugs, and nitrates (long and/or short-acting). Low-dose aspirin is recommended in the presence of obstructive CAD. Dual-antiplatelet therapy is prescribed for a restricted period of time after PCI and stent implantation. Although there are sex differences in the reported side effects of a number of cardiovascular drugs (e.g. calcium channel blockers) there are at present, no separate dosage recommendations for men and women.

3.1.5 Outcome—The prognosis of stable angina in women is difficult to assess. The difficulties lie in how angina is defined and confirmed in the different study populations, as well as which endpoints are evaluated. Much of the prognostic data available is on patients with ACS and hard endpoints such as MI and death. The pathophysiology of stable angina however differs from acute CAD. In patients with non-obstructive CAD functional testing for microvascular disease for example is not routinely carried out. Patients with microvascular disease have worse prognosis with an increased risk for cardiovascular events including death[254]. Inclusion of patients suffering from non-cardiac chest pain may dilute results and contributes to the misconception of a benign prognosis in women with stable angina.

An additional problem in interpreting studies of stable angina in women is that for every step in the referral cascade the proportion of women to men decreases. The worse prognosis observed for women compared to men in the Euro Heart Survey of Stable Angina may, as

the authors suggest, be a consequence of the selected nature of the population (Figure 8)[255]. In this survey women compared to men were less likely to undergo coronary angiography (31% vs 49%) despite a higher angina class. A worse prognosis for women compared to men who underwent PCI for stable angina or ACS was also observed in a Swedish-British registry study in 458,261 patients, in which women experienced higher all-cause mortality at 30-days and 1 year[256]. The excess mortality could partly be explained by higher rates of procedural complications (e.g. vascular complication and bleeding).

Another factor which may impact and contribute to a worse prognosis in women is less optimal medical treatment[255]. Under-treatment of angina is especially a problem in women with angina and normal coronary arteries who are often assured of the benign nature of their condition. Lack of appropriate medical treatment may contribute to the persistent chest pain, which is common in women with angina, both with or without obstructive CAD. Women with angina more often repeatedly seek healthcare contact, are hospitalized and undergo repeat coronary angiography, which impacts negatively on quality-of-life[235].

3.2 Coronary Microvascular Dysfunction (CMD)

Up to 30% of women and 5–10% of men with signs and symptoms of ischemia will have no obstructive CAD on invasive coronary angiography[234, 257, 258]. Further, among women presenting for evaluation of suspected ischemic symptoms, a diagnosis of normal coronary arteries is five times more common, as compared to men[259]. The WISE study suggests that more than half of these patients have CMD indicated by abnormal coronary blood flow (CBF) on invasive coronary reactivity testing (ICRT)[260]. Further up to 70% will have a pathological response to acetylcholine testing indicating abnormal coronary vasomotion[261].

3.2.1 Pathophysiology—A subset of these patients have microvascular angina due to CMD[262]. CMD refers to abnormalities in the vasomotor or metabolic regulators of the smaller resistance coronary arterioles (<500um), although structural abnormalities of the microcirculation (for example smooth muscle cell hypertrophy) have been described by some studies[263]. Suggested mechanisms of CMD include altered regulation of coronary microcirculation through autonomic dysregulatory and endothelial mechanisms, generalized vascular disorder and abnormal subendocardial perfusion[264]. Other suggested contributing factors include inflammation, hyperinsulinemia, enhanced sodium-hydrogen exchange, hormonal deficiency, abnormal pain perception and inherent pathogenetic pathways. Endothelial dysfunction in particular is supported by various studies of the pathophysiology of the condition. In CMD, endothelium-dependent, but not endothelium-independent, vasodilatation is thought to be impaired. Elevated endothelin activity[265] blunted nitric oxide (NO) and endothelin responsiveness to intravenously infused insulin[266] in patients with angina and normal coronary arteriograms provides a pathophysiological basis for the demonstration of endothelial dysfunction in such patients. Interestingly, an NO-dependent vasodilatation mechanism appears to be suboptimal and defective in patients with CMD[267].

3.2.2 Diagnosis

3.2.2.1 Non-invasive Testing: Non-invasive testing such as exercise treadmill testing, nuclear myocardial perfusion imaging, and stress echocardiography for CMD remain

insensitive[268, 269] although positron emission tomography (PET) is a gold standard[270], and newer imaging modalities such as adenosine cardiac magnetic resonance imaging (CMRI) hold promise. CMRI allows evaluation of subendocardial perfusion, fibrosis and microinfarction, assessment of left ventricular function and mass and measurement of myocardial flow reserve using a myocardial perfusion reserve index (MPRI). In a recent study from the WISE of 128 women with signs and symptoms of ischemia but no obstructive CAD, 11% of women had myocardial scar by late gadolinium enhancement (LGE) and 69% had an abnormal MPRI on CMRI (≤1.8)[155]. Future research is needed to determine sensitivity and specificity of CMRI in the clinical setting as MPRI is not routinely measured outside the research field.

3.2.2.2 Invasive Testing: CRT is an alternate gold standard technique for evaluation of CMD. Intra-coronary infusion of adenosine, acetylcholine and nitroglycerin allows assessment of microvascular and macrovascular endothelial and nonendothelial pathways. The normal response to intra-coronary infusion of adenosine is a ≥ 2.5 increase in CFR. Therefore, a CFR of <2.5 defines CMD and examines the non-endothelial dependent microvasculature[271]. Acetylcholine uniformly dilates both the microvasculature and macrovasculature in an endothelial-dependent fashion. The normal response to acetylcholine is an increase in CBF of >50% above baseline and endothelial dysfunction may be manifest by a significant attenuation, no change or even a decrease in CBF[272]. Finally, nitroglycerin tests the non-endothelial macrovascular pathway and lack of a response to nitroglycerin may indicate smooth muscle dysfunction.

3.2.3 Treatment—Usual care for patients with angina and non-obstructive CAD is not well defined and rates of prescription use are low[237, 257, 259, 273]. An analysis of medication use for all patients ≥20 years with stable angina who underwent index coronary angiography in British Columbia, Canada, from 2008–2010 revealed that only 14% and 26% of patients with no CAD and non-obstructive CAD respectively were prescribed an ACE-I, a statin and an anti-anginal such as a BB within 90 days of angiography (manuscript in press).

Regarding non-pharmacologic techniques, exercise, cognitive behavioral therapy, spinal cord stimulation and enhanced external counterpulsation have been shown to increase coronary blood flow, reduce duration and frequency of anginal attacks and reverse ST segment depression during stress testing compared to controls[274].

Regarding pharmacologic management, prior studies have demonstrated improvements in chest pain with angi-anginals such as beta-blockers, nitrates and calcium channel blockers[275]. Further, studies have shown improvements in both angina scores and ICRT with statins[276, 277] and ACEI[260, 278]. Several recent studies have evaluated the effect of ranolazine in patients with CMD, with conflicting results. In a double-blind, placebo-controlled, cross-over design trial, Mehta et al randomized 20 women with ischemia but no obstructive coronary lesions to ranolazine 500 to 1000 mg BID versus placebo[196]. There was a significant improvement in the Seattle Angina Questionnaire (SAQ) in patients on ranolazine for 4 weeks. Villano et al. investigated the effects of 375mg BID of ranolazine for 4 weeks in CMD and demonstrated significant improvements in SAQ and quality of life (QoL) scores in the ranolazine arm[279]. More recently, however, Bairey Merz et al published the WISE

trial, which randomized 128 patients with CMD[155]. After a 2-week course of ranolazine, patients were evaluated with regards to SAQ, QoL and CMRI and there was no improvement in SAQ scores after this short time period.

Other possible therapeutic targets in CMD involve phosphodiesterase-5 inhibition with Sildenafil, a phosphodiesterase inhibitor that may target the nitro oxide pathways in CMD[280]; low dose tricyclic anti-depressants (TCAs) such as imipramine and amitriptyline which may be useful in patients with cardiac nociceptive abnormality and uncontrolled chest pain despite traditional use of anti-anginals[281]; and L-arginine which is a precursor of nitric oxide and mediates vascular smooth muscle cell relaxation and inhibits platelet aggregation[282]. Finally, Nicorandil and Ivabradine, two drugs only available in Europe, improved angina, but these were small studies[283, 284].

3.2.4 Outcome—Early studies reported angina with non-obstructive CAD as a benign condition[285, 286]. However, more recent and larger studies have shown an adverse prognosis with a 2.5% per year major adverse cardiovascular event rate including hospitalization for MI, HF, stroke, or cardiovascular death[234, 254, 257, 259]. In addition, these patients have high rates of recurrent chest pain, poor QoL and higher rates of functional disability, angina hospitalizations and repeat angiography than patients with 1-vessel obstructive CAD[287]. In the absence of effective treatment, patients with angina and non-obstructive CAD continue to seek help in the emergency services and pose a substantial health care burden. For women with signs and symptoms of ischemia but non-obstructive CAD the average lifetime cost for ischemic heart disease is $ 767,288, comparable in magnitude to the more than $1 million dollars for obstructive CAD[287].

3.2.4.1 Sex Differences in Adverse Outcomes: Women with no obstructive CAD tend to have an adverse prognosis compared to men. A study by Humphries *et al.*, in a large population-based setting, assessed the outcomes (re-hospitalization for ACS or chest pain) of 3,647 patients undergoing coronary angiography for stable angina or ACS, but had angiographically normal coronaries and found that women were 4 times more likely to be re-hospitalized with a diagnosis of ACS or chest pain requiring angiography within the first 6 months[235]. Further, Sedlak *et al.* evaluated the outcomes of 4,184 women and 9,511 men with chest pain and normal or non-obstructive CAD and reported that as compared to patients with no CAD, women with non-obstructive CAD had a 3.5 times greater hazard of MACE (i.e. hospitalization for MI, HF, stroke, or all-cause mortality) within the first year post angiography [HR=3.58 (95%CI: 1.87, 6.86)] [234]. In contrast, the hazard of MACE in men with non-obstructive CAD was similar to men with no CAD [(HR=0.82 (95%CI: 0.35, 1.93)].

4 Heart Failure (HF)

HF is a clinical syndrome that can result from many different processes. The European Society of Cardiology (ESC) defines HF as “a clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress”[288]. Etiologies, or the structural and/or functional cardiac

abnormalities, vary widely and include hypertension, CAD, and valvular disease, among others.

HF is a worldwide epidemic, affecting almost six million adults in the United States and over 20 million adults worldwide[289, 290]. Some data suggest that the incidence is increasing[291, 292], while other suggests decreasing incidence[293, 294]. While definitions vary between studies, HF is consistently associated with older age. The Rotterdam Study, which used physician review to define HF, showed that prevalence increased from 0.9% among 55 to 64 year olds, to 17.4% among those aged 85 years and older[295]; other observational studies echo this finding[291]. Given the longer life expectancy of women, we can expect continued population growth of older women with HF.

4.1.1 Pathophysiology

Left-sided HF can broadly be classified as HF with preserved ejection fraction (HFpEF) or HF with reduced ejection fraction (HFrEF), with EF of ≤40% to ≤50% typically used as the cut point for HFrEF. Compared to patients with HFrEF, patients with HFpEF are more likely to be women, representing almost two-thirds of the HFpEF population[294]. In reality, HFpEF is distinctly different from HFrEF, with a different set of risk factors. Hypertension, diabetes, and obesity have all been associated with HFpEF[296]. In fact, while the association between hypertension and HF is weak compared to other risk factors, hypertension is highly prevalent and accounts for over a fourth of HF cases among women. In other words, hypertension has the highest population attributable risk for HF among women. Conversely, the association between diabetes and HF is stronger, yet diabetes accounts for 10% of HF among women[296, 297]. In the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE trial), hypertension was present among 91% and obesity was present among 46% of women, with lower rates for both among men. Diabetes prevalence was similar between sexes[298].

HFrEF can be classified as having an ischemic or non-ischemic etiology. Ischemic etiology is associated with epicardial CAD and/or MI and/or small vessel/microvascular disease. In the Framingham Heart Study, women accounted for 40% of the patients with HFrEF, compared to 65% of the patients with HFpEF[299]. This analysis found that CAD strongly favors the development of HFrEF (compared to HFpEF). Women are less likely to experience MI, which may contribute to the lower prevalence of women in the HFrEF population.

HFrEF from non-ischemic etiologies deserves special attention because of risk factors that are specific to women: pregnancy and cancer treatment for breast cancer. Peripartum cardiomyopathy (PPCM) presents as HFrEF late in a pregnancy, or soon after delivery. This condition affects about one in one thousand live births in the United States, with higher rates in other countries. The pathophysiology of PPCM is most likely different than other forms of HF and may be related oxidative-stress related cleavage of prolactin, a hormone unique to the pregnancy state, into a fragment that causes endothelial damage and myocardial dysfunction. Unique genetic variants may play a role, as well[300]. Still, as with HFpEF, hypertension may be associated with PPCM[301].

Breast cancer is the most common cancer among women and the treatment is associated with cardiomyopathy, with or without HF symptoms. Broadly, chemotherapy toxicity can be grouped as type I, irreversible damage most often caused by anthracyclines, or type II, potentially reversible toxicity[302]. Many breast cancer-specific treatments fall into one of these categories. Anthracyclines are type I agents that are often used to treat breast cancer, and are associated with left ventricular dysfunction in a cumulative dose dependent fashion. At higher doses (≥700 mg/m^2 of doxorubicin), HF incidence may be as high as 18%. Trastuzumab, a type II agent, is used to treat HER2 positive breast cancer, but has cross-reactivity with HER2 receptors in the heart[303]. Using administrative billing data to identify HF, Bowles et al. found a four-fold increase in incident HF among women treated with trastuzumab alone, and a seven-fold increase in incident HF among women treated with doxorubicin plus trastuzumab[304].

4.1.2 Diagnosis

Guideline based diagnosis and therapy in HF does not differ between women and men. Gender specific comorbidities and living conditions should be assessed, e.g. history of inflammatory or psychiatric diseases, malignancies, depression and other potentially related comorbidities, stress, socioeconomic and working conditions, gynecological and andrological history with number of children, still births, sexual activity and hormone therapy[305, 306]. Women exhibit a worse quality of life after diagnosis of HF and exhibit depression more frequently. Because of the high prevalence of depression in women with HF, systematic screening may be considered[305].

Clinical investigation and echocardiography are the gold standards. When assessing ventricular size in HFrEF, care should be taken to normalize ventricular diameters and ventricular diameters to body size. This is not trivial and different normalization algorithms may lead to different results[307]. It has been documented that HF diagnosis was less frequently based on objective diagnostic tests in women than in men[305]. In the Euro Heart Survey echocardiography was used less frequently in women than in men, even in patients with identical clinical indications. Physicians should be informed about this potential bias in order to reduce it.

4.1.3 Treatment

4.1.3.1 HFrEF—HF treatment has been more successful in HFrEF, compared to HFpEF. The mainstays of HFrEF treatment include BBs and ACE-Is. Five randomized-controlled trials have compared BBs to placebo among patients with HFrEF, including metoprolol, carvedilol, bisoprolol, bucindolol, and nebivolol. Roughly one-fifth of participants in these trials were women, with the exception of the nebivolol trial (37%), a reflection of the older age inclusion criteria. The carvedilol and metoprolol trials both included subgroup analyses, with non-significant interactions between sex and treatment effect. In addition, a meta-analysis of the beta-blocker trials suggested a similar mortality benefit for men and women with HFrEF[308]. Seven randomized clinical trials have compared ACE-Is to placebo among patients with HFrEF. Similar to beta-blockers, the proportion of women included in these trials was low, ranging from 7% in the enalapril prevention trial to 28% in the trandolapril trial. Several of the original trial results did not include subgroup analyses, but a subsequent

meta-analysis suggested similar mortality benefit in men and women: the relative risk of mortality was [RR=0.82 (95% CI:: 0.74 to 0.90)] for men and [RR=0.92 (95% CI: 0.81 to 1.04)] for women.

Like BBs and ACE-Is, aldosterone receptor antagonists also have mortality benefit among patients with HFrEF. Spironolactone and eplerenone have been tested in randomized placebo controlled trials, and both included subgroup analyses. While the proportion of women included was small, non-significant interaction terms between treatment effect and sex suggest similar efficacy among women.

Digoxin and chronic resynchronization therapy (CRT) may have more sex-specific efficacy compared to BBs, ACE-Is, or ARBs. The original digoxin trial demonstrated lack of mortality benefit in HFrEF and subsequent analyses suggested an increased mortality among women. A post-hoc analysis found that death from any cause was 5.8% higher in women, and digoxin was associated with a higher rate of death in women, but not in men. While these findings may have been due to higher drug levels in women[309], the results are still alarming and highlight the need for sex-specific attention to medical treatment. CRT, on the other hand, may have greater efficacy in women compared to men with HFrEF. One study used a large, observational registry of over 75,000 patients to examine mortality differences among men and women with CRT-defibrillator versus defibrillator alone. Among patients with a left-bundle branch block (LBBB), women with CRT-defibrillator compared to defibrillator alone had a more pronounced mortality benefit than men [(HR 0.74 in women versus HR 0.84 in men, with a significant sex-efficacy interaction (p=0.025)][310]. Subsequently, the Food and Drug Administration undertook a patient-level pooled analysis to address the same question. The study included data from three clinical trials and, again, showed significantly greater mortality benefit among women with LBBB compared to men, despite the small number of women included in the CRT clinical trials[311]. On the heels of these results, Biotronik has launched the Biowomen trial—which may be the first HF trial that explicitly aims to enroll equal numbers of men and women—to examine sex-specific response to CRT treatment[312].

Only one randomized-controlled trial for treatment of peripartum cardiomyopathy has been published to date. In this study of 21 women randomized to bromocriptine had greater recovery of left ventricular ejection fraction at six months, as well as a lower rate of the composite end point defined as death, New York Heart Association (NYHA) functional class III/IV, or left ventricular ejection fraction <35% at 6 months[313]. A larger trial of bromocriptine treatment has been completed and the results are forthcoming[314].

4.1.3.2 HFpEF—Clinical trial data to support the treatment of HFpEF, the predominant form of HF among women, are scarce and generally neutral. While beta-blockers are a key part of HFrEF treatment, the same is not true for HFpEF. A small trial from Sweden randomized 113 patients with HFpEF (EF ≥45%) to carvedilol or placebo. The primary outcome of the trial was echocardiography-based diastolic function parameters and carvedilol treated patients had improved estimated left-sided filling pressures[315]. A registry based study, however, found no clinical benefit (defined as mortality and hospitalization) for beta-blockers among patients with HFpEF[316]. One clinical trial tested an ACE inhibitor,

perindopril, against placebo among older patients with HFpEF. Low enrolment and high cross over, however, limit the utility of this negative trial[317]. Finally, a randomized placebo controlled trial failed to show a benefit of spironolactone over placebo among HFpEF patients[318].

4.1.4 Outcome

With comparable treatment, women with HF have better clinical outcomes than men[305]. This remains true even if HFrEF and HFpEF are analyzed separately. In most cases of HF due to inherited cardiomyopathies, women appear to do better, independent of therapy. Thus it has been suggested that women have more efficient compensatory mechanisms that may overcome an insult at the molecular or at cellular level.

Worldwide, fewer women than men undergo heart transplantation. In a large dataset of consecutive patients with idiopathic non-ischemic DCM referred for heart transplantation to the German Heart Institute only 15.6% were women, suggesting a referral bias against women[305, 319].

Women present more frequently in NYHA III-IV than men, have lower exercise tolerance, respiratory efficiency and kidney function. Women also have significantly less diabetes than men. Thus, women were referred at a more advanced disease state and relative contraindi cations such as diabetes appear to be taken more seriously in women. An international multicenter prospective study on referral for heart transplantation, organ allocation and survival appears mandatory.

5 Conclusions and Future Research

CVD remains the leading cause of morbidity and mortality in women, worldwide. To reduce the burden and improve outcomes in women, sex differences in diagnosis, treatment and outcomes must be explored and understood. This is an essential as we move towards the era of precision medicine. While significant progress has been made, as outlined in this review, much more needs to be done. At a minimum, more women need to be enrolled in clinical trials, and the results of those trials need to be reported by sex. While legislation in the US and policy recommendations in Canada and Europe are moving in that direction, policies to increase research into sex differences at the basic research level are also required to close the knowledge gap.

The social and psychosocial (gendered) reasons for the under-treatment of women require urgent attention. Greater engagement of women patients in the design, conduct of studies, as well as their input to guide knowledge translation and implementation deserves greater consideration. This may be particularly relevant in younger women, who have benefitted the least from the significant improvements in survival from CVD experienced by the rest of the population. Improved awareness among women and their healthcare providers regarding the burden of CVD and its implications for morbidity and mortality also needs to be addressed. Ideally, CVD risk factors should be reviewed at each encounter with a woman’s healthcare provider. We encourage healthcare providers to increase their index of suspicion for heart disease when they encounter women with vague symptoms (e.g. atypical pain/discomfort,

indigestion, extreme fatigue). We also encourage individuals, women's groups, heart health charities, colleges and universities, ethnic organizations, and the media, to increase awareness about heart disease among women.

Research areas that merit special attention include research into optimal methods to diagnose and treat coronary microvascular dysfunction; research to standardize the diagnosis of SCAD and to identify and test treatments for SCAD; and research to identify and evaluate efficacious treatments for HFpEF. There is also an urgent need to better understand women's risk over the lifespan, from menarche, to pregnancy, through menopause.

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Abbreviations and Acronyms

ACE-I	Angiotensin Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
BB	Beta Blocker
CABG	Coronary Artery Bypass Grafting
CBF	Coronary Blood Flow
CFR	Coronary Flow Reserve
CHD	Coronary Heart Disease
CIHI	Canadian Institutes for Health
CMD	Coronary Microvascular Dysfunction
CMRI	Cardiac Magnetic Resonance Imaging
CRT	Chronic Resynchronization Therapy
CS	Coronary Vasospasm

GDM	Gestational Diabetes
HF	Heart Failure
HFpEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
ICH	Intra-Cranial Haemorrhage
ICRT	Invasive Coronary Reactivity Testing
IVUS	Intravascular Ultrasound
MACE	Major Adverse Cardiac Events
MPRI	Myocardial Perfusion Reserve Index
NSTEMI	Non-ST-Elevation Myocardial Infarction
OR	Odds Ratio
PCI	Percutaneous coronary intervention
PTP	Patient's Pre-test Probability
QoL	Quality of Life
RR	Relative Risk
SAQ	Seattle Angina Questionnaire
SIHD	Stable Ischemic Heart Disease
SCAD	Spontaneous Coronary Artery Dissection
SES	Socioeconomic Status
SMR	Standardized Mortality Ratio
STEMI	ST-Elevation Myocardial Infarction
TCAs	Tricyclic Anti-depressants
TCFA	Thin Cap Fibroatheroma
TTS	Takotsubo's Syndrome
WHO	World Health Organization
WISE	Women's Ischemic Syndrome Evaluation

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Highlights

- Cardiovascular disease is the major cause of death in women worldwide
- Women under-represented in clinical trials and results often not reported by sex
- Women and men share most risk factors, but several are unique to women
- Coronary microvascular dysfunction may be present if no obstructive lesions found
- Women are more likely to have heart failure with preserved ejection fraction.

Figure 1.
Infographic of Sex and Gender from Canadian Institutes of Health Research

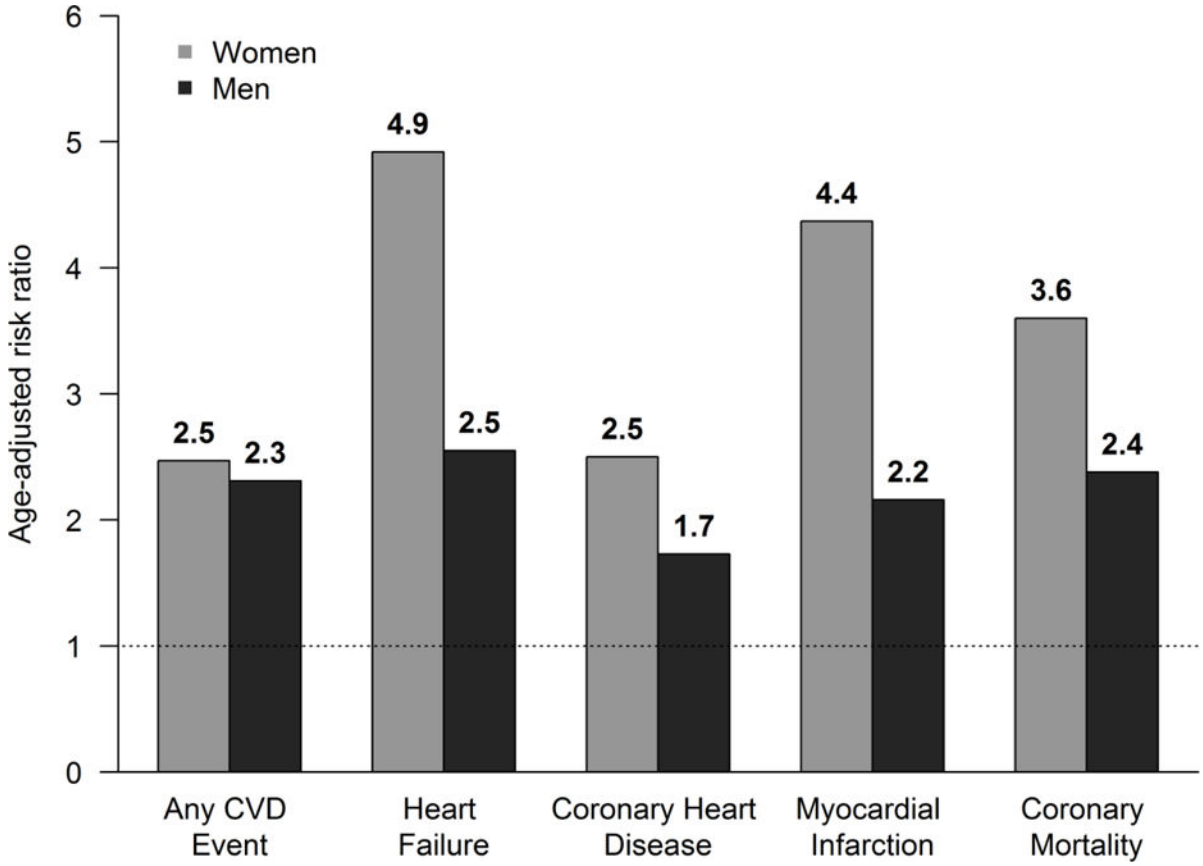

Figure 2. Relative risk of cardiovascular events in men and women with diabetes
Note: Adapted from Kannel et al[320], with permission.

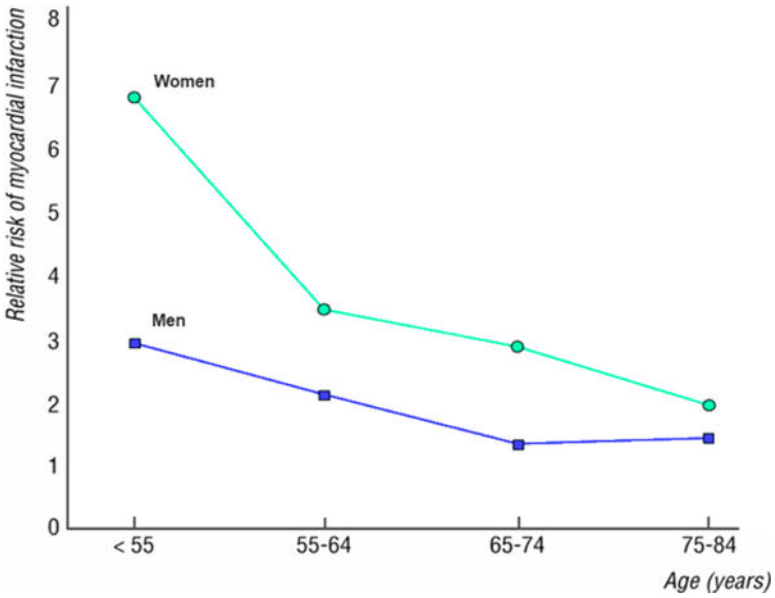

Figure 3. Relative risk of myocardial infarction for current smokers compared with never smokers

Note: Adapted from Prescott et al[28], with permission.

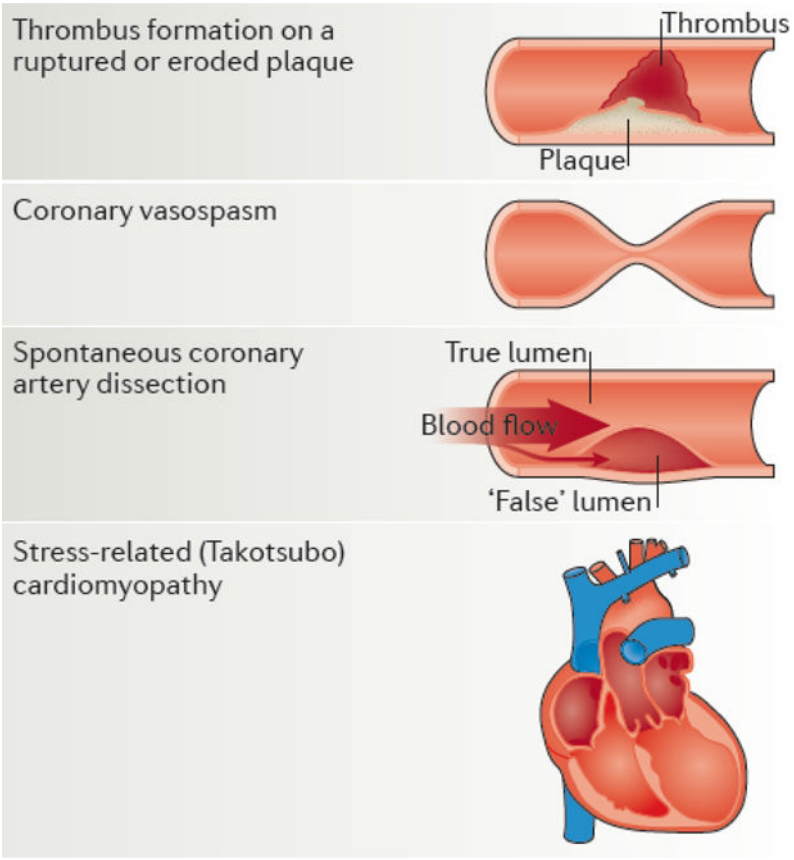

Figure 4. Sex-specific differences in the pathophysiology of acute coronary syndrome

Note: Although Coronary vasospasm, spontaneous coronary artery dissection (SCAD) and stress-related (Takotsubo) cardiomyopathy do occur in both males and females, these presentations are much more common among females. With respect to thrombus formation, males are more likely to present with ruptured plaque while females are more likely to present with eroded plaques. Adapted from Pagidipati et al[124]., with permission

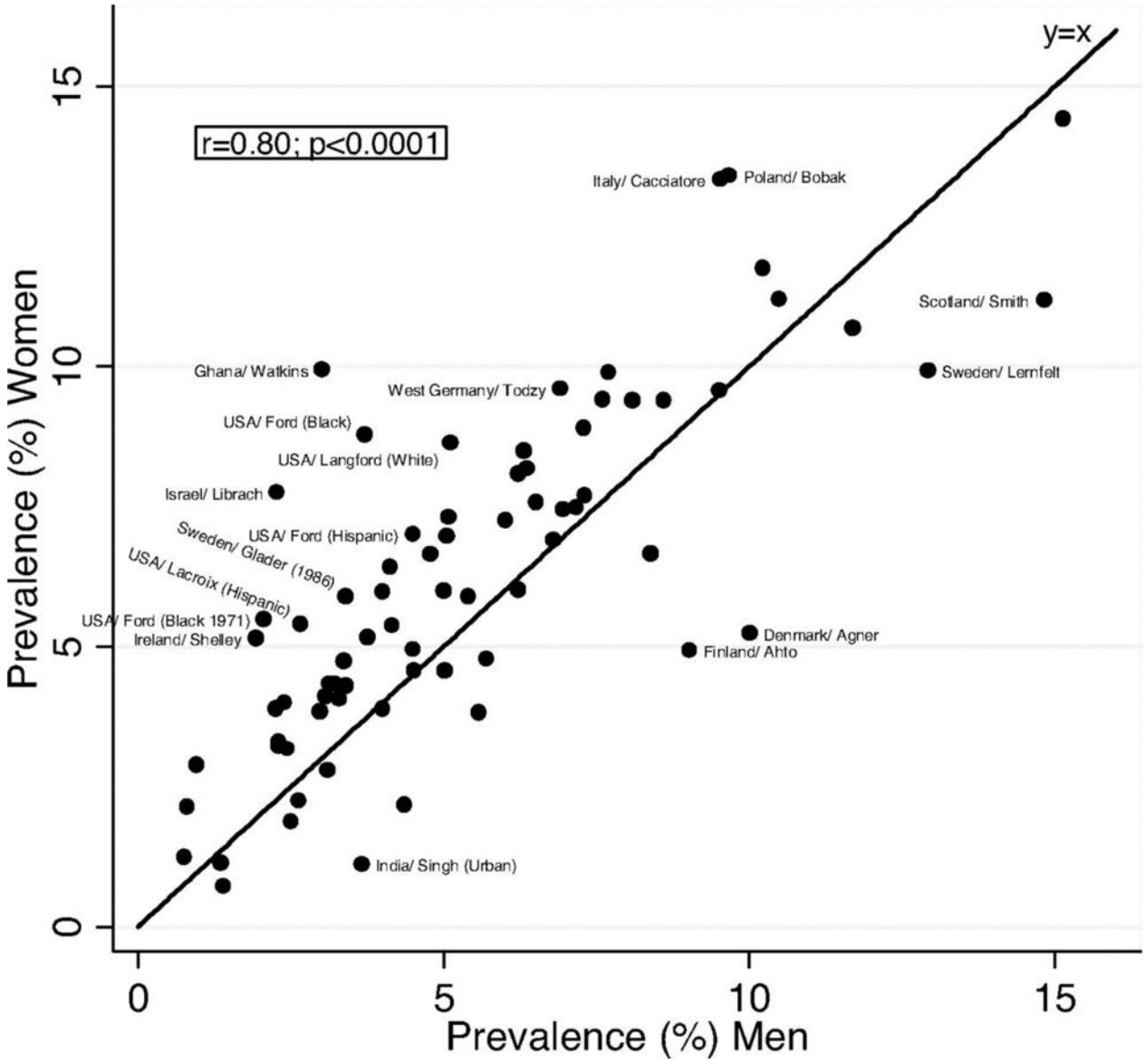

Figure 5. Angina prevalence in women vs men

Note: Adapted from Hemingway et al[232], with permission

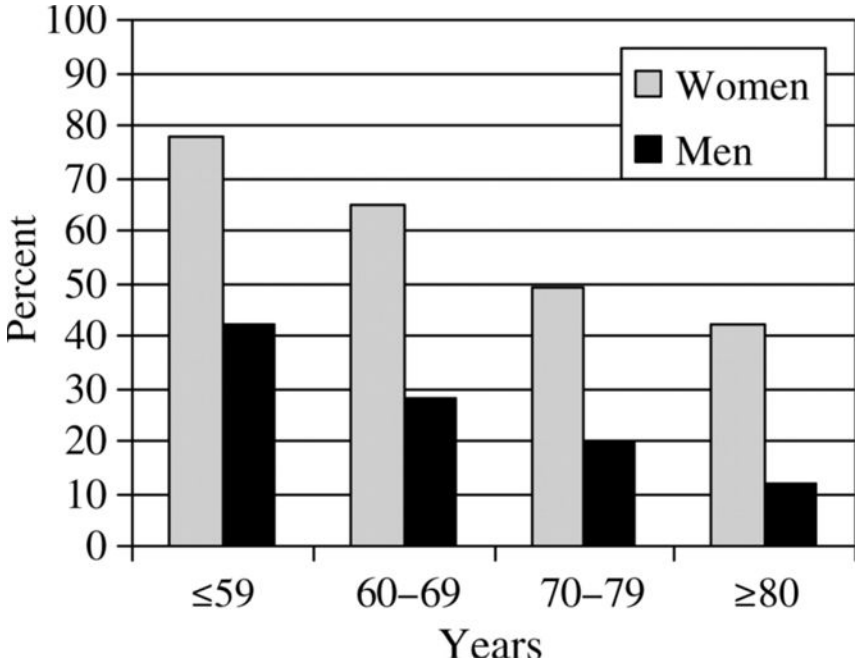

Figure 6. Proportion of patients (%) with normal findings at coronary angiography according to sex and age group

Note: Adapted from Johnston et al[237], with permission.

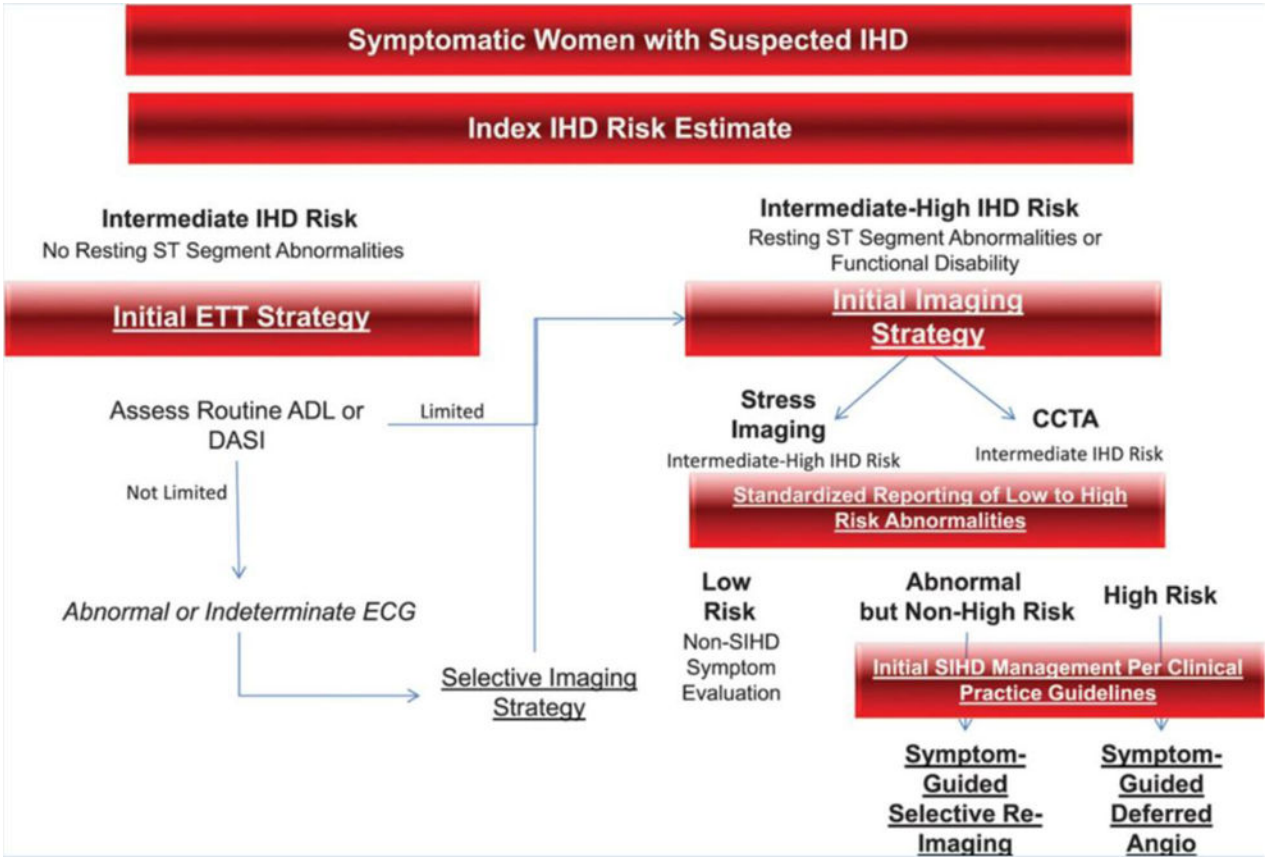

Figure 7. Diagnostic evaluation algorithm for symptomatic women with suspected ischemic heart disease and intermediate and intermediate-high risk

Note: ADL, activities of daily living; Angio, angiography; CCTA, coronary computed tomography angiography; DASI, Duke Activity Status Index; ETT, exercise treadmill testing; and SIHD, stable ischemic heart disease. Adapted from Mieres JH et al[247], with permission.

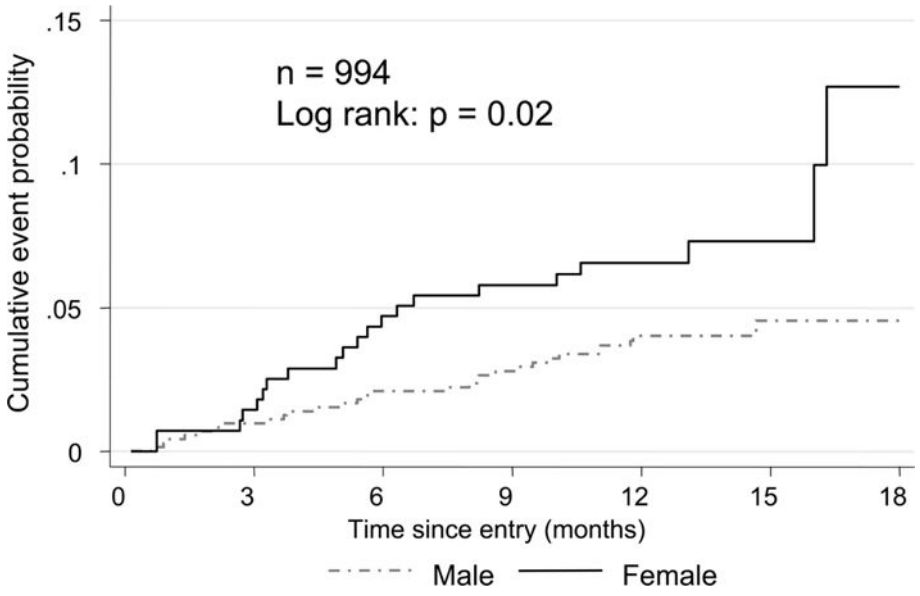

Figure 8. Cumulative probability of death or MI in patients with confirmed coronary disease and stable angina according to Sex

Note: Adapted from Daly et al[255], with permission

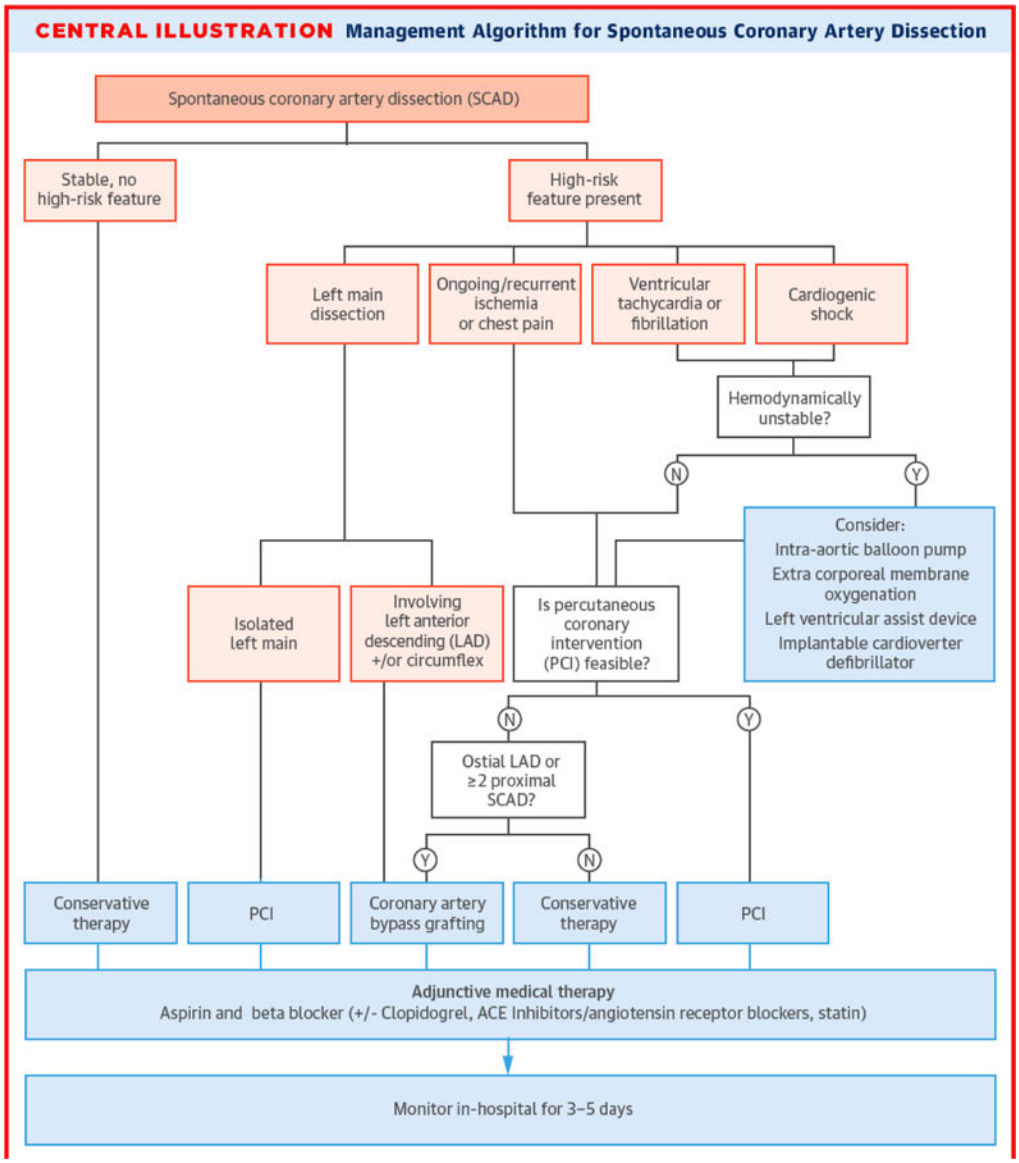

Figure 9. Management of Algorithm for spontaneous coronary artery dissection
Note: Adapted from Saw et al[224], with permission