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Review

Canadian Women's Heart Health Alliance

The Canadian Women's Heart Health Alliance Atlas on the Epidemiology, Diagnosis, and Management of Cardiovascular Disease in Women — Chapter 5: Sex- and Gender-Unique Manifestations of Cardiovascular Disease

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ABSTRACT

This Atlas chapter summarizes sex- and some gender-associated, and unique aspects and manifestations of cardiovascular disease (CVD) in women. CVD is the primary cause of premature death in women in

RÉSUMÉ

Dans le présent chapitre d'Atlas sont récapitulés les aspects et les manifestations uniques, associés au sexe et certains associés au genre, des maladies cardiovasculaires (MCV) chez les femmes. Les

Chapter 5 reviews current and evolving knowledge regarding sex- and some gender-unique manifestations of cardiovascular disease (CVD), including symptom presentation, pathophysiology, and outcomes, from clinical trial data, when available, and observational reports. Figure 1 summarizes the Chapter's key concepts.

Sex refers to biological constructs that are primarily associated with physical and physiological features, including hormones, genes, and anatomical and physiological characteristics, and is usually categorized as female or male. Gender refers to socially constructed roles, behaviours, expressions,

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Canada and numerous sex-specific differences related to symptoms and pathophysiology exist. A review of the literature was done to identify sex-specific differences in symptoms, pathophysiology, and unique manifestations of CVD in women. Although women with ischemic heart disease might present with chest pain, the description of symptoms, delay between symptom onset and seeking medical attention, and prodromal symptoms are often different in women, compared with men. Nonatherosclerotic causes of angina and myocardial infarction, such as spontaneous coronary artery dissection are predominantly identified in women. Obstructive and nonobstructive coronary artery disease, aortic aneurysmal disease, and peripheral artery disease have worse outcomes in women compared with men. Sex differences exist in valvular heart disease and cardiomyopathies. Heart failure with preserved ejection fraction is more often diagnosed in women, who experience better survival after a heart failure diagnosis. Stroke might occur across the lifespan in women, who are at higher risk of stroke-related disability and age-specific mortality. Sex- and gender-unique differences exist in symptoms and pathophysiology of CVD in women. These differences must be considered when evaluating CVD manifestations, because they affect management and prognosis of cardiovascular conditions in women.

MCV sont la cause principale de décès prématurés chez les femmes au Canada. De nombreuses différences quant aux symptômes et à la physiopathologie existent entre les sexes. Nous avons réalisé une revue de la littérature pour déterminer les différences entre les sexes dans les symptômes et la physiopathologie, et les manifestations uniques des MCV chez les femmes. Bien que les femmes atteintes d'une cardiopathie ischémique puissent éprouver des douleurs thoraciques, la description des symptômes, le délai entre l'apparition des symptômes et l'obtention de soins médicaux, et les symptômes prodromiques sont souvent différents de ceux des hommes. Les causes de l'angine et de l'infarctus du myocarde non liées à l'athérosclérose telles que la dissection spontanée de l'artère coronaire sont principalement observées chez les femmes. La coronaropathie obstructive et non obstructive, l'anévrisme aortique et la maladie artérielle périphérique montrent de plus mauvaises issues chez les femmes que chez les hommes. Des différences entre les sexes sont observées dans la cardiopathie valvulaire et les cardiomyopathies. Le diagnostic d'insuffisance cardiaque avec fraction d'éjection préservée est plus souvent posé chez les femmes qui présentent un meilleur taux de survie après un diagnostic d'insuffisance cardiaque. L'accident vasculaire cérébral (AVC) pourrait survenir tout au long de la vie des femmes, qui sont exposées à un risque plus élevé d'incapacités liées à l'AVC et de mortalité par âge. Il existe des différences uniques entre les sexes et les genres pour ce qui est des symptômes et de la physiopathologie des MCV chez les femmes. Lors de l'évaluation des manifestations des MCV, il faut tenir compte de ces différences puisqu'elles influencent la prise en charge et le pronostic des maladies cardiovasculaires chez les femmes.

and identities, and is often categorized as women and men. At times, throughout the Atlas chapters, we use the categorization that was used in the study being cited, although we recognize that these categorizations do not, in all cases, align with the sex and gender definitions described herein.

Symptoms of Ischemic Heart Disease

In Canada, ischemic heart disease (IHD) is a leading cause of mortality in women.[1] Annual mortality rates for IHD in women in Canada exceed rates for breast cancer by 3 times, and rates for breast and all gynecological cancers combined by more than 2 times.[2] The term, IHD, describes a group of clinical syndromes characterized by myocardial ischemia, including acute coronary syndrome (ACS), unstable angina, stable angina, non−ST-elevation myocardial infarction, and ST-elevation myocardial infarction (STEMI).[3] Women are more likely than men to have angina (47% vs 32%) and less likely to have acute myocardial infarction (AMI) (32% vs 46%) as their first manifestation of IHD.[4] The age-standardized prevalence of IHD and occurrence of AMI for women and men in Canada are presented in Figure 2, and age-standardized mortality rates for IHD and all major CVD in Figure 3.

Clinical presentation and characteristics of IHD differ among the sexes, with women presenting a varied pattern and distribution of cardiac symptoms that are distinct from that of men. Figure 4 summarizes the most common as well as additional and prodromal symptoms described by women presenting with IHD.[5,6]

Most women aged 18-55 years diagnosed with AMI present with chest pain, similar in proportion to men (87.0% of women vs 89.5% of men).[7] They also experience a greater number and variation of symptoms (ie, type, frequency, and quality), including prodromal symptoms (ie, fatigue, shortness of breath, and sleep disturbance),[6] which might delay evaluation and diagnosis. Others report chest symptoms that are common in all patients diagnosed with ACS but women experience more nausea, shoulder and upper back pain, and diaphoresis.[5] This varied pattern and distribution of symptoms makes it difficult for health care providers and women themselves to interpret pain/symptoms as cardiac-specific.[8-10]

Sex differences in the clinical presentation of IHD are more pronounced in younger women (younger than 45-55 years) with AMI, who are more likely to present without chest pain and have higher in-hospital mortality.[11,12] In older women (older than 65 years), sex differences are less pronounced; however, it is important to note that 50% of women aged older than 75 years who are diagnosed with AMI present without chest pain.[9] Longer prehospital delays have been reported in women with chest pain who are older than 75 years and shorter prehospital delays reported in women younger than 55 years who have additional or associated symptoms (eg, shortness of breath, fatigue).[12] Prehospital delay times are shorter in women who have an abrupt vs a gradual onset of symptoms,[13] making one wonder if delays are related to symptom recognition and/or interpretation, or the actual decision to seek care.[12] Women are generally older than men when diagnosed (mean 20 years older), and have a higher prevalence of comorbid conditions.[14] Nevertheless, women aged 20-74 years are more likely to die within 1 year of AMI (60.0-194.7 per 1000 in women vs 20.9-175.0 per 1000 in men).[15] Women post-AMI are also more likely to have heart

failure (HF) or stroke.[4] Poorer prognosis has been reported in younger women (younger than 55 years) with STEMI compared with their male counterparts.[14,16,17]

Defining chest pain as typical, atypical, and noncardiac according to its relation to exertion, rest, or emotional stress was derived from predominantly male cohorts and is less predictive of obstructive coronary artery disease (CAD) in women, especially those younger than 65 years.[18] Improving symptom evaluation tools for women could improve detection of obstructive CAD; however, definitive data are lacking.[18] Shifting the focus from the "culprit lesion," where only obstructive CAD is considered to be diagnostic, and where nonobstructive CAD, more prevalent in women, is very often overlooked, to the "culprit patient," where the focus on detection of adverse prognostic indicators, such as the presence of ischemia on noninvasive testing or presence of atherosclerosis on radiologic imaging, might improve the diagnosis, appropriate treatment, and prognosis of IHD and ACS in women.[19] Of note, the diagnostic accuracy to detect IHD/ACS in Black, Hispanic, and Asian and/or young women might improve if gender (socially constructed with identified roles and expectations), psychosocial stressors, clustering of > 3 cardiac risk factors, and other comorbidities are considered in addition to cardiac pain symptoms.[16]

Pathophysiology

IHD

Ischemia in the setting of nonobstructive epicardial CAD (INOCA) is especially prevalent in women and up to two-thirds of angiograms performed for suspected ischemia show no obstructive epicardial disease (defined as absence of $\geq 50\%$ stenosis in any epicardial artery).[20] More than half of women with INOCA will have evidence of underlying coronary microvascular dysfunction (CMD) on invasive coronary reactivity testing and these women are at elevated risk of adverse cardiovascular events.[21] The pathophysiology of INOCA is complex and might include endothelial dysfunction (epicardial or microvascular), inflammatory processes, smooth muscle cell dysfunction, arteriolar remodelling, and/or sympathetic activation. Causes of increased afterload and decreased oxygen supply, including aortic stenosis, severe hypertension, and anemia are often evident.[21] Further, endothelial and nonendothelial pathways contribute to reduced myocardial perfusion.[20] Traditional cardiovascular risk factors for developing CMD include hypertension, diabetes, dyslipidemia, and smoking; there is an association with inflammatory diseases including systemic lupus erythematosus.[20] Diffuse nonobstructive coronary atherosclerosis is identified in most women with INOCA, and inflammatory processes might play a role.[20] Abnormal coronary flow reserve (CFR) in response to adenosine, and abnormal coronary blood flow (CBF) to acetylcholine, which indicates abnormal microvascular function, using either invasive intracoronary measurement or noninvasive positron emission tomography, are diagnostic and prognostic indicators of CMD.[20,22] β-Blockers, calcium channel blockers, nitrates, and/or ranolazine can be used for symptomatic relief, and statins and angiotensin converting enzyme inhibitors have been associated with improvement of symptoms and CFR in clinical trials.[23] The Coronary Microvascular Angina (CorMicA) randomized

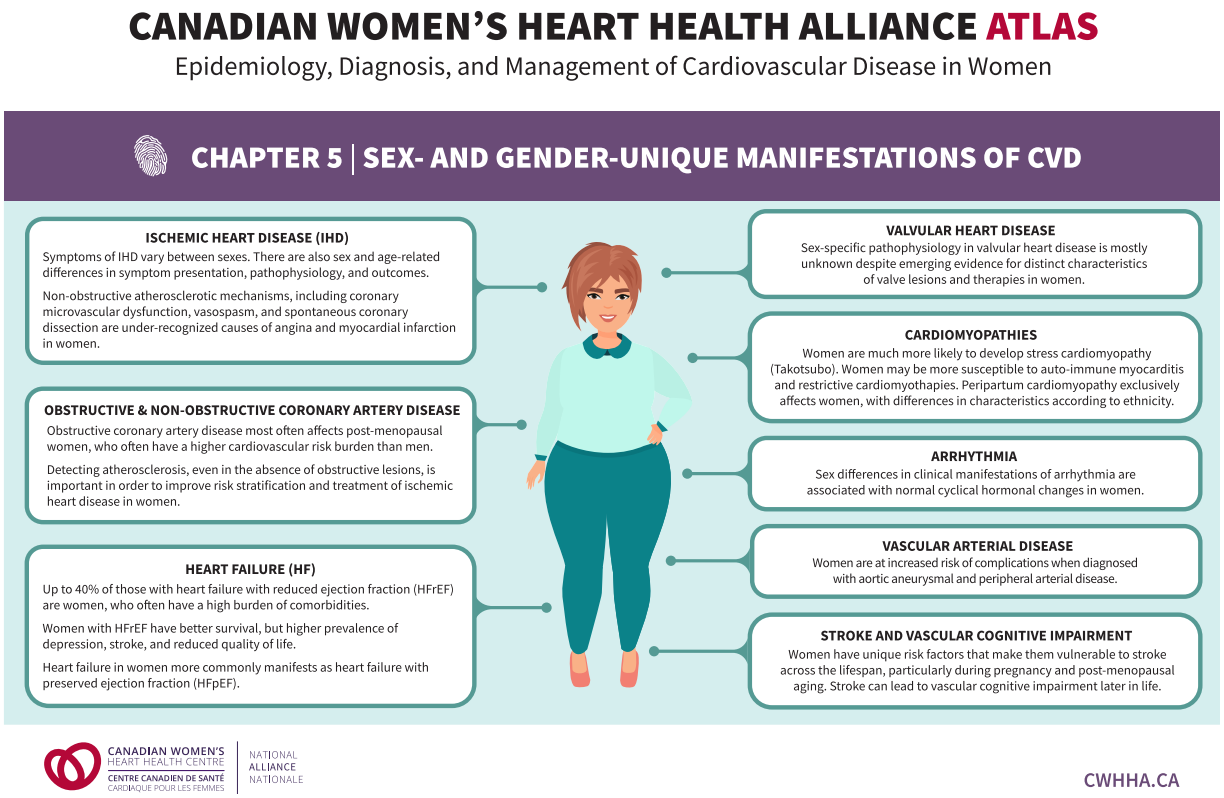

Figure 1. Summary of sex-unique manifestations of cardiovascular disease (CVD).

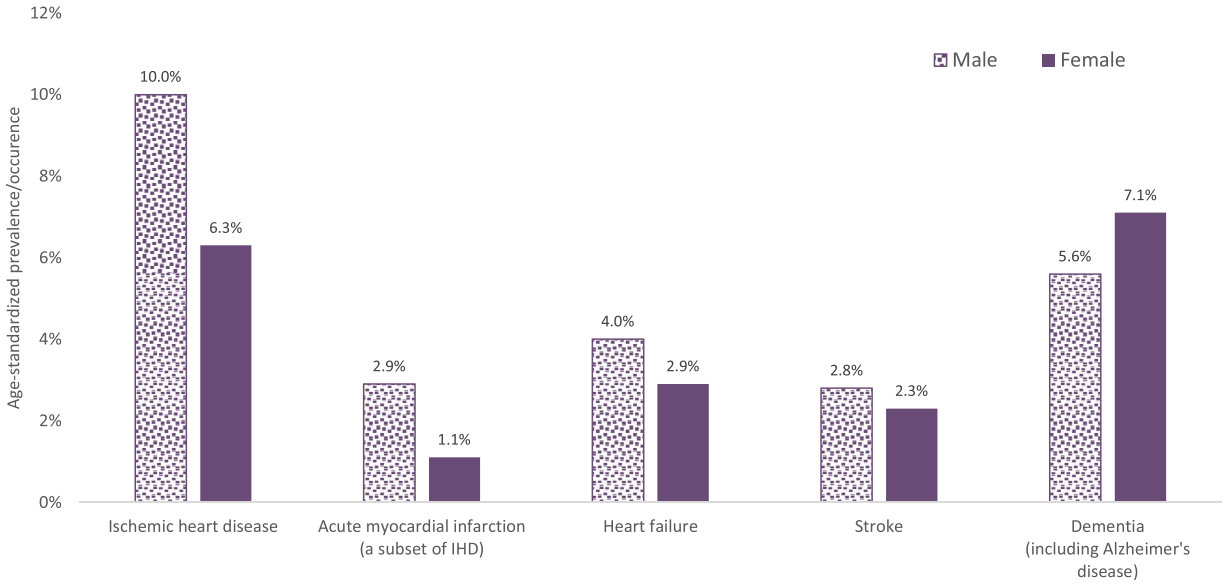

Figure 2. Age-standardized prevalence/occurrence of major cardiovascular diseases in Canada, according to sex. Age-standardized prevalence/occurrence calculated among Canadians aged 20 years or older for ischemic heart disease (IHD), acute myocardial infarction, and stroke; 40 years and older for heart failure; and 65 years and older for dementia. Data are from: (1) Report from the Canadian Chronic Disease Surveillance System: Heart Disease in Canada, 2018[1]; (2) Stroke in Canada: Highlights from the Canadian Chronic Disease Surveillance System (https://open.canada.ca/data/en/dataset/29c7e1d2-f6c1-4eb3-89dc-f36a3c7f53f3); and (3) Dementia in Canada, including Alzheimer's disease: Highlights from the Canadian Chronic Disease Surveillance System (https://www.canada.ca/en/public-health/services/publications/diseases-conditions/dementia-highlights-canadian-chronic-disease-surveillance.html).

controlled trial recruited 151 patients (73.5% female) with signs and symptoms of INOCA. Invasive coronary function testing, including measurement of CFR, CBF, and epicardial coronary vasospasm testing with acetylcholine were performed. In the intervention group, medical therapy was tailored according to the results: in addition to lifestyle changes, those with abnormal CFR or CBF were treated with β-blockers and statins, and angiotensin converting enzyme inhibitors were considered; those with evidence of vasospasm were treated with calcium channel blockers and nitrates. For the blinded control group, invasive CFR and CBF was performed but results were not disclosed; standard care medical therapy was provided according to physician preference. The intervention group had a significant improvement in Seattle Angina Questionnaire (SAQ) score and quality of life at 6 months over the control group.[24] The currently recruiting Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR) trial will investigate intense medical therapy including high-intensity statin, aspirin, and angiotensin converting enzyme inhibitor, on longer-term outcomes.[25]

Epicardial vasomotor dysfunction and vasospasm causing ischemia is the underlying mechanism in vasospastic angina, also known as Prinzmetal, or variant angina. Vascular smooth muscle hyper-reactivity, and endothelial and autonomic nervous system dysfunction are involved in its pathogenesis.[26] Cigarette smoking is an established risk factor.[27] The Japanese population are at higher risk, particularly Japanese women.[26] Diagnostic criteria include: (1) angina—typically occurring at rest and often nocturnally that is responsive to nitrate therapy; (2) transient ischemic ST changes; and (3) coronary artery spasm on coronary angiography.[27] Provocative invasive testing in the cardiac catheterization laboratory including ergonovine and/or acetylcholine can be used in patients with suspected but not confirmed vasospasm. Treatment is comprised of smoking cessation, calcium channel blocker therapy, and/or long-acting nitrates.[27] The long-term prognosis is good although there is a small risk of sudden cardiac death.[28]

Myocardial infarction in the setting of nonobstructed coronary arteries (MINOCA) represents 6% of all AMIs and is diagnosed more frequently in women, younger patients, and African-American patients.[21,29] Despite better survival than patients with obstructive CAD, 12-month mortality rates of 4.7% have been reported.[21] Table 1 summarizes the underlying mechanisms for MINOCA.[30,31]

Identification of such unique pathophysiologic mechanisms requires a high index of suspicion on viewing coronary angiograms, and if inconclusive, additional invasive imaging including intracoronary vascular ultrasound (IVUS), or optical coherence tomography might be helpful. IVUS can be used to assess coronary artery plaque and plaque burden, disruption, and ulceration.[25] Intracoronary optical coherence tomography imaging is useful in identifying high-risk plaques as well as characteristic intramural hematoma seen in spontaneous coronary artery dissection (SCAD),[27,28] and cardiac magnetic resonance imaging can provide insight on etiological mechanisms.[31] A recently published study on coronary optical coherence tomography and cardiac magnetic resonance imaging in the workup of MINOCA revealed a cause in 84.5% of patients when one or both imaging modalities were used. An ischemic etiology was identified in 63.8% of women (most commonly plaque disruption such as plaque rupture) whereas a nonischemic cause was found in 20.7%.[30] It should be

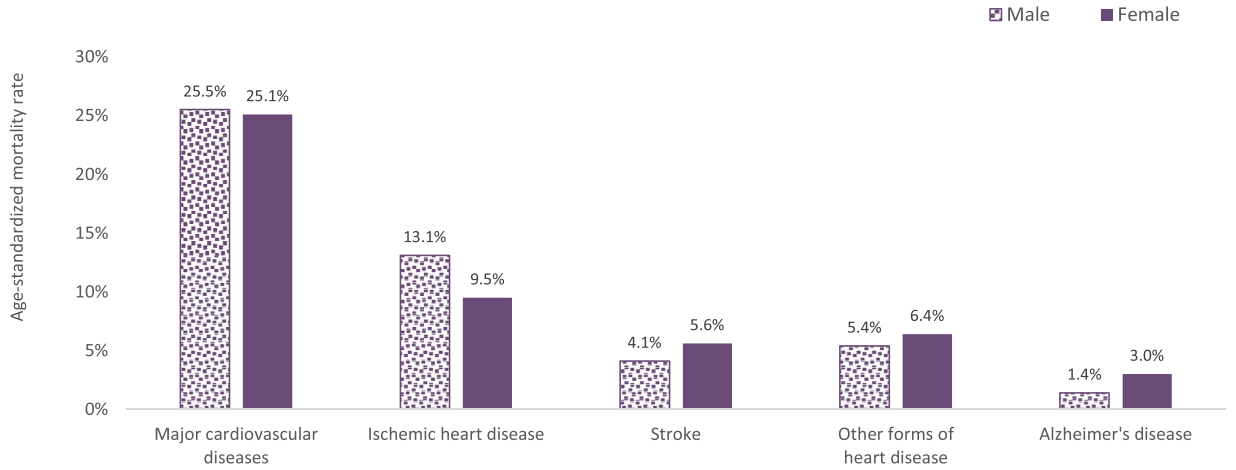

Figure 3. Age-standardized mortality rates for major cardiovascular diseases in Canada, according to sex. Age-standardized mortality calculated among Canadians aged 20 years and older for major cardiovascular diseases, ischemic heart disease, stroke, and other forms of heart disease; and, for 65 years and older, for Alzheimer's disease. Other forms of heart disease includes International Classification of Diseases-10th Revision codes I30-I51 (including heart failure, heart valve diseases, cardiomyopathies, and arrhythmias). Data are from: (1) Statistics Canada: Deaths and age-specific mortality rates, 2019, by selected grouped causes, Table: 13-10-0392-01 (https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039201); (2) Statistics Canada: Deaths, by cause, Chapter IX: Diseases of the circulatory system (I00 to I99), 2019, Table: 13-10-0147-01 (https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310014701); and (3) Statistics Canada: Population estimates on July 1st 2019, by age and sex, Table: 17-10-0005-01 (https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501).

emphasized that MINOCA is a "working diagnosis," and if any of the foregoing etiologies are identified, then the ACS is attributed to that specific entity.

SCAD is an increasingly recognized condition that primarily affects women (89% of new SCAD cases in British Columbia, Canada) and refers to the spontaneous separation of the coronary arterial wall creating a false lumen filled with intramural hematoma.[32] Angiographically, there are 3 types of SCAD, the most common being type 2 (diffuse long and smooth stenosis), with no differences in baseline characteristics or outcomes according to subtype.[33] Symptoms and signs are those of ACS; myocardial ischemia, ventricular arrhythmias, and sudden cardiac death can ensue.[33] SCAD presents most frequently in younger women (younger than 55 years of age); however, studies have also reported its occurrence in older and postmenopausal women.[34] Figure 5 summarizes the principal factors and conditions associated with SCAD. It is associated with fibromuscular dysplasia (in up to 63% of cases), peripartum state, multiparity ($\geq$ 4 births), connective tissue disorders, systemic inflammatory conditions, hormonal therapy, stress, and intense exercise.[35] Although definitive data are lacking, the predominance of female sex and relationship to pregnancy suggest that female sex hormones might play a role in SCAD pathophysiology.[16] SCAD comprises 1%-4% of AMI patients,[34] accounts for 35% of AMI in women younger than the age of 50 years,[34] is the main cause of AMI in women younger than age 40 years, and the main cause of pregnancy-associated AMI.[36] Emotional stressors (eg, death of family member) appear to be more common in women compared with physical stressors (eg, extreme isometric exercise) in men[34]; however, approximately one-third of patients cannot recall any significant emotional or physical stress before their SCAD event.

Correct diagnosis and recognition of SCAD as the underlying cause of the ACS is imperative—conservative management of stable patients is warranted in most cases.

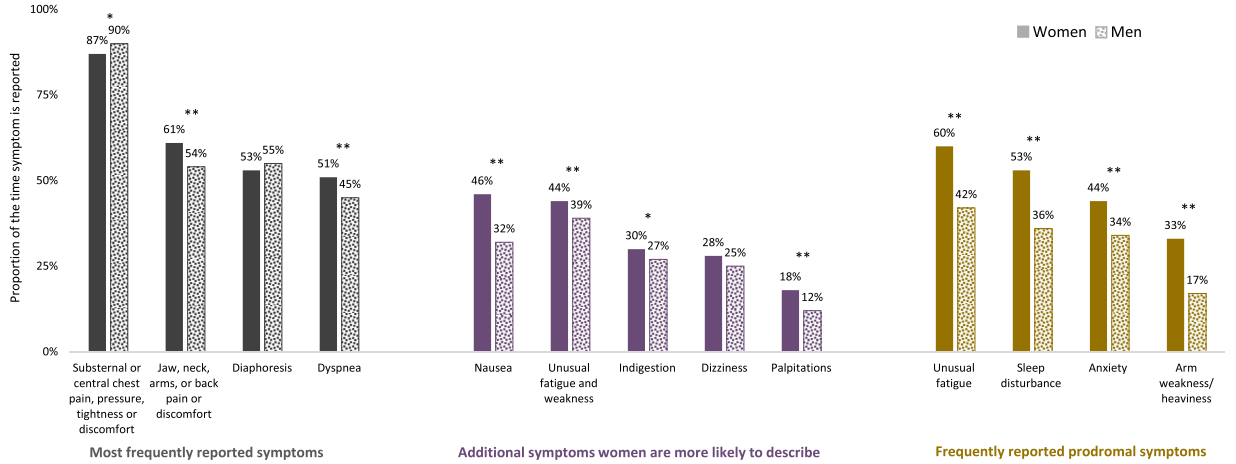

Figure 4. Symptoms commonly reported by those presenting with ischemic heart disease, women vs men. * $P < 0.05$; ** $P < 0.01$.

Percutaneous coronary intervention has been observed to result in an increased risk of procedural complications, and generally poorer outcomes in SCAD patients, especially those with distal disease. Most patients are managed conservatively, unless they are at high risk, defined as severe proximal disease in 2 or more vessels and/or the presences of ongoing ischemia or hemodynamic instability.[34,37] Expert consensus suggests 3-5 days of in-hospital monitoring after presentation; extension of the dissection or new recurrent SCAD have been observed in approximately 5%-10% of SCAD patients.[34] Later recurrence of SCAD has been reported in 10%-30% of resolved cases and ongoing surveillance is required.[38] Good blood pressure control is paramount and β-blocker therapy has been associated with reduced SCAD recurrence in an observational study.[39] Less clear is the use and duration of dual antiplatelet therapy with aspirin and clopidogrel in the setting of medical therapy without percutaneous coronary intervention. Statin therapy should be reserved for those with hyperlipidemia.[38] Concomitant noncoronary fibromuscular dysplasia is highly prevalent in patients with SCAD (42%-86% depending on the number of territories, renal, iliac, or cerebrovascular),[35] and should be pursued with dedicated imaging. A history of migraines, anxiety, and depression is also common (20%-33% prevalence) in SCAD patients.[40,41]

Atherosclerotic disease

Obstructive CAD. CAD, including AMI, is the leading CVD-related cause of emergency department visits, hospitalizations, and death among Canadian women, resulting in nearly 14,000 deaths per year.[42]

Sex-specific pathophysiological mechanisms exist in the development of coronary atherosclerosis. In most women who present with ACS, the underlying mechanism is due to the formation of thrombus caused by a rupture of atherosclerotic plaque composed of accumulation of infiltrating macrophages and low-density lipoproteins, with subsequent limitation of blood flow to the myocardium.[43,44] However, women, especially younger women, are more likely to present with plaque erosion, where a discontinuation of the endothelium is identified, without evidence of plaque rupture of the fibrous cap.[44] Sex differences in atherosclerosis formation and plaque instability are not completely understood. Estrogen might play a role in slowing lesion progression, through decreased inflammatory activation, increased vasodilation, and decreased low-density lipoprotein oxidation and binding,[45] potentially explaining the lower prevalence of obstructive CAD and plaque rupture in premenopausal women.[16] Beyond sex-based physiological differences, feminine gender, which reflects social norms and expectations ascribed to women, was found to increase risk of recurrent AMI at 1-year follow-up in younger patients, independent of biological sex.[46]

Women who present with obstructive CAD are generally older than men and have a higher cardiovascular risk factor burden, with diabetes and smoking disproportionately affecting the risk of obstructive CAD in women, as well as an increased mortality.[47] Women presenting with STEMI due to obstructive CAD experience longer door-to-balloon delays,[48] which might be improving over time.[49] Prehospital STEMI diagnosis systems, including automated systems, might attenuate this sex gap,[50] but confirmatory studies are needed. Importantly, findings from a recent single-centre study suggest that a systems-based approach to STEMI care might reduce sex disparities and improve care and outcomes in women.[51] Recent data from Alberta, Canada, show that women are at higher risk of in-hospital mortality and of HF and mortality in the 5 years after their myocardial infarction.[52] Women are less likely to achieve key quality indicators after AMI, and are less often discharged after a cardiac event with an optimal medical regimen, even when age and renal function are considered.[53]

Nonobstructive CAD. Plaque erosion is more frequently diagnosed in women.[21,29] Women exhibit positive remodelling, which results in concealment of atherosclerosis and fewer lumen-occluding lesions.[19,21] IVUS in women enrolled in the Women's Ischemia Syndrome Evaluation (WISE) cohort identified coronary atherosclerosis with positive remodelling in 73/92 (79%) of women with no obstructive CAD.[54] Total plaque burden is associated with adverse cardiovascular events in women.[55] Overall burden of calcification measured using the **C**oronary **A**rtery **C**alcification score is a marker of cardiovascular risk, with scores > 300 predicting higher risk of events in women.[56] These findings underline the importance of accurately diagnosing the pathophysiologic mechanism of IHD in women; differentiation of atherosclerotic CAD, obstructive or nonobstructive, and/or CMD, is important to improve risk stratification and treatment of IHD in women.

HF

HF is the second leading CVD-related cause of hospitalization and third leading CVD-related cause of death among Canadian women.[57] Age-standardized prevalence of HF according to sex is presented in Figure 2.

Although the lifetime risk of developing HF is 1 in 5 for female and male individuals, risk factors including previous AMI, hypertension, and diabetes differ in their importance according to sex, and some risk factors—hypertensive disorders of pregnancy, gestational diabetes, peripartum cardiomyopathy (PPCM), and early menopause—are unique to women.[58,59] It is not yet known whether the increased risk for HF in women (compared with men) post-AMI is because women present at an older age, with higher prevalence of diabetes/renal dysfunction, experience delays in diagnosis and treatment for AMI, or due to an inherent feature of IHD in women.[60] HF in women manifests more commonly as HF with preserved left ventricular (LV) ejection fraction ([LVEF] $\geq 50\%$; HFpEF) rather than HF with reduced LVEF (LVEF $< 50\%$; HFrEF).[61] In the Swedish HF Registry (SwedeHF), which included 42,937 patients with HF, 55% of those with HFpEF were women, compared with only 29% of those with HFrEF.[62] Although a large proportion of women who develop HF (more often HFrEF) have CAD, the risk factors for progression from CAD to HF have not been well investigated. In women in the Heart and Estrogen/Progestin Replacement Study (HERS), diabetes was the strongest predictor of HF, especially in the setting of concomitant renal insufficiency or morbid obesity.[63] Patients presenting with symptoms suggestive of HF (edema, fatigue, and dyspnea) should undergo a clinical history and physical exam.[64-66] In the 2017 comprehensive update of the Canadian Cardiovascular Society (CCS) guidelines for management of HF, Ezekowitz et al. noted that

Table 1. Mechanisms and diagnosis of MINOCA

Potential underlying mechanisms of MINOCA*	Diagnostic testing
Coronary plaque disruption (eg, plaque rupture, or ulceration, erosion, calcific nodules)	Coronary angiogram IVUS OCT
Epicardial coronary vasospasm	Coronary vasoreactivity testing (acetylcholine, ergonovine)
Coronary microvascular dysfunction	Coronary function testing (CFR, IMR) Myocardial PET
Spontaneous coronary artery dissection	Coronary angiogram IVUS OCT
Hypercoagulable disorders	Hypercoaguable work-up
Coronary emboli Paradoxical emboli	TTE, TEE, bubble contrast echocardiography
Takotsubo or other cardiomyopathy†	Cardiac MRI TTE
Myocarditis†	Cardiac MRI TTE

CFR, coronary flow reserve; IMR, index of myocardial resistance; IVUS, intravascular ultrasound; MINOCA, myocardial ischemia with non-obstructive coronary artery disease; MRI, magnetic resonance imaging; OCT, optical coherence tomography; PET, positron emission tomography; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

*MINOCA is defined according to the fourth universal definition of myocardial infarction with no lesions $\geq$ 50% in an epicardial coronary artery, with an ischemic basis, after excluding overt noncardiac causes of elevation in troponin (sepsis, pulmonary embolism, tachyarrhythmias, hypertensive crisis, etc), or nonischemic cause of myocardial injury, such as myocarditis.[34]

†Takotsubo or other cardiomyopathy/myocarditis are considered non-ischemic causes of myocardial injury diagnosed in up to 21% of cases of MINOCA and must be considered in the differential diagnosis.[35]

atypical presentations (cognitive impairment, delirium, nausea, abdominal discomfort, oliguria, anorexia, and cyanosis) should also be recognized, particularly when evaluating women.[67]

Transthoracic echocardiography is the imaging modality of choice in a patient suspected of having HF. Assessment should include LVEF, LV mass, presence of valvular disease, and markers of diastolic dysfunction. It is important to note that there are normative gender-based values for echocardiographic measures of chamber volumes.[68]

HFrEF. HFrEF, defined as an LVEF $\leq$ 40%,[59] accounts for approximately half of all cases of HF.[69] In an American midwestern epidemiologic study conducted more than a decade ago, the age- and sex- adjusted incidence of HF had decreased over the decade by 37% (95% confidence interval [CI], −30% to −44%), more so for HFrEF (−45%; 95% CI, −33% to −55%) than HFpEF (−28%; 95% CI, −13% to −40%).[70] It is estimated that women account for 40% and men 60% of patients with HFrEF[71]; overall, women are approximately 65% less likely to develop HFrEF than men.[72] Women with HFrEF live longer with the condition than men, likely because of sex-related differences in etiology. Although prevalence of diabetes is similar, women with HFrEF are more often obese and have a higher prevalence of hypertension, valvular heart disease (VHD), and nonischemic cardiomyopathy than men.[72,73] Women with HFrEF are less likely than men to smoke cigarettes or drink alcohol, and less likely to have preexisting cardiovascular comorbidities such as CAD, atrial fibrillation (AF), AMI, or stroke.[73]

HFrEF-related rehospitalizations are less common in women (8.48 events per 100 person-years [95% CI, 7.89-9.11] for women vs 11.40 events per 100 person-years [95% CI, 11.04- 11.79] for men), with an age-adjusted incident rate ratio of 0.69 (95% CI, 0.61-0.79).[73] Additionally, lower odds of in-hospital death has been independently associated with female sex (odds ratio, 0.88; 95% CI, 0.87-0.89).[74]

Implantable cardioverter defibrillator/cardiac resynchronization therapy. In current guidelines, similar recommendations for implantable cardiac device (ICD) therapy apply to women and men with HFrEF despite many differences established in subgroup analysis. The annual rate of sudden cardiac death in women is approximately half of that in men, and substudies of many large randomized controlled trials have consistently shown up to a 50% lower appropriate ICD shock rate in women, compared with men.[75,76] Women have a higher adverse event rate post-ICD implantation.[77] Sex-specific prospective studies on which patients will benefit from ICD implantation are ongoing.

Women are less likely than men to receive cardiac resynchronization therapy (CRT) and less likely to undergo CRT with defibrillator (CRT-D) implantation.[59,78] Slightly improved survival outcomes with CRT have been observed in women, compared with men.[79] Despite the greater benefit, women are less likely to receive device counselling than men, which might partly explain sex differences in CRT implantation.[79] In a retrospective study of New York Heart Association functional class III-IV patients (49.5% female) with left bundle branch block and nonischemic cardiomyopathy, women were more likely to experience a treatment response to CRT compared with men (84% and 58%, respectively).[80] Response rate was high in women regardless of QRS duration, whereas men had greater benefit with QRS $\geq$ 150 ms. In a meta-analysis of 3 CRT-D vs ICD trials, CRT-D led to greater reductions in HF events and death in women with a left bundle branch block QRS of 130-149 ms. Benefits were observed for both sexes at QRS > 150 ms.[81] Current guideline recommendations are identical for women and men; however, sex-specific indications for CRT-D on the basis of QRS duration might be warranted.

Heart transplantation. Women undergo heart transplantation less frequently than men.[82] Reasons might include: (1) fewer women listed for transplant; (2) more women die while waiting for transplant; (3) less aggressive HF treatment in women; and (4) increased sensitization in women limiting the transplant donor pool.[83-86] After receiving the transplant, women are more likely to experience moderate or severe allograft rejection resulting in acute rejection and hospitalization.[82] Fewer women have a LV assist device before transplantation; this might be because, historically, larger ventricular assist devices not thought to be ideal for implantation in women, and this trend might change with the new smaller devices.[87]

End of life care. In-hospital health care utilization is lower among women than men with HFrEF and HFpEF in the final months of life.[74] Specifically, a lower proportion of women

than men with HF presented to emergency departments, were hospitalized in the final month, and were admitted to the intensive care unit in the final month of life. Fewer women than men are mechanically ventilated, receive cardiac catheterization or coronary revascularization, and hemodialysis in the final month of life and female sex is an independent predictor of death outside a hospital setting.[74]

Clinical outcomes. In a large multicentre international study, including more than 15,000 participants (one-fifth women), and a participating Canadian site, women with HFrEF had better survival and lower hospitalization rates than men.[73,88] The 5-year mortality rate for patients with HFrEF is 75.3%, which is comparable with the rate for HFpEF of 75.7%.[69] Compared with men, women have significantly lower rates of cardiovascular death (age-adjusted hazard ratio [aHR], 0.70; 95% CI, 0.69-0.81), first hospitalization for HF (aHR, 0.80; 95% CI, 0.72-0.89), sudden death (aHR, 0.65; 95% CI, 0.56-0.76), and pump failure death (aHR, 0.67; 95% CI, 0.55-0.82).[73] Additionally, women with HFrEF have lower rates of noncardiovascular death (aHR, 0.66; 95% CI, 0.52-0.83), all-cause death (aHR, 0.68; 95% CI, 0.62-0.74), and fatal/nonfatal myocardial infarction (aHR, 0.79; 95% CI, 0.63-1.00), compared with males.[73]

Events of fatal/nonfatal stroke appear to be more common among women than men with HFrEF (aHR, 1.22; 95% CI, 0.99-1.50).[73] This might be because of the lower rate of anticoagulation in the setting of AF and higher prevalence of hypertension experienced in women vs men.[73] The odds of AF in women with HFrEF appears to be lower than that of men (adjusted odds ratio, 0.69; 95% CI, 0.64-0.75).[89] However, women with AF report more severe symptoms, worse quality of life, and increased risk of complications (ie, mortality, stroke, myocardial infarction) than men.[90]

Despite fewer recurrent events and better survival rates, women with HFrEF often report a greater prevalence of anxiety and depression; more severe symptoms affect their psychological and physical health with associated lower quality of life, and reduced 6-minute walk distance, compared with men.[73,91-93]

Representation in clinical trials. Relative to men, women have pharmacokinetic differences such as lower oral drug absorption rate, larger distribution for lipophilic drugs, smaller distribution for hydrophilic drugs, and differences in metabolic activity due to menopause, which mighty affect the female response to HFrEF drugs.[72] Sex-specific HFrEF guidelines for medical management are lacking because of the underrepresentation of women in HF trials.[59,94]

Women are recruited into clinical trials at disproportionately lower rates than the HFrEF prevalence.[72] For example, female enrollment in β-blocker trials, angiotensin receptor blocker trials, aldosterone antagonist or mineralocorticoid receptor antagonist trials, hydralazine or isosorbide dinitrate trials, angiotensin receptor-neprilysin inhibitor trials, and ivabradine trials ranges from 0% to 29%.[92] The underrepresentation of women in HFrEF trials limits the generalizability of results and limits statistical power required to test for sex as an effect modifier of treatments.[94,95] Factors independently associated with underenrollment relative to female:male disease distribution include trial leadership by men and sex-specific eligibility criteria, a majority of which are not justified in the context of their individual clinical trials.

HFpEF. Women with HFpEF are responsible for > 30% of HF cases in women in Canada.[96] The most common risk factors for HFpEF include older age, obesity, hypertension, smoking, diabetes, VHD, and AF.[97]

Long-term prognosis after HFpEF onset is poor; however, women have better survival than men overall.[72] The cause of death in patients with HFpEF is often noncardiac, often associated with older age and comorbidities. The CCS guidelines emphasize that management should include identification and treatment of underlying etiologies and comorbid conditions that might exacerbate HF.[67]

There are few randomized clinical trials to guide pharmacological therapy for HFpEF treatment. Although trial results have not consistently been stratified according to sex, treatment efficacy remains to be confirmed in women; however, the Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF), a trial of angiotensin-neprilysin inhibition in patients with HFpEF, was associated with lower rates of the composite primary outcome of death or HF hospitalizations specifically in women.[98]

VHD

VHD affects 0.6% of the general population and its prevalence increases with age, affecting 5%-10% of adults older than the age of 65 years, with a slight majority being men.[99] Approximately 6% (n = 1995) of CVD-related deaths and 4.6% (n = 6126) of CVD-related hospitalizations among Canadian women are due to VHD.[57,100] The most common VHD is aortic stenosis (55%) followed by mitral regurgitation (28%).[99] Most (93%) of the VHD were diagnosed in women older than 52 years of age. VHD hospitalizations were frequently complicated by hypertension (46%) and diabetes (26%). Despite women representing 47.5% of patients with VHD, most studies on VHD pathophysiology include a large proportion of men or male animals. Nevertheless, distinct characteristics of valve lesions and therapies in women are emerging.

Aortic stenosis. Women reach the same hemodynamic severity of aortic stenosis as men with a lower amount of aortic valve calcification, even after accounting for aortic annulus size.[101] When analyzing explanted aortic valves from matched patients who received surgery for severe aortic stenosis, valves explanted from women had less calcification and more fibrosis compared with valves from men. Interestingly, in young women with stenotic bicuspid aortic valves, the quantity of calcium can be minimal and does not represent the severity of the stenosis.[102] These sex-specific valve lesions might be explained by the effect of sex hormones on aortic calcification/fibrosis. Indeed, androgens have been shown to induce the calcification pathway of smooth muscle cells via the androgen receptor,[103] whereas estrogen seems to inhibit valvular interstitial cells, but only in female cells.[104] Thus, aortic valve lesions might also be linked to sex specificity at the cellular level.

In normal swine aortic valves, 183 genes were identified as significantly different; females exhibited extracellular matrix remodelling genes, and males displayed more calcification/osteoblastic pathway genes.[105] These observations led to 2 hypotheses in the sex-specific aortic stenosis pathophysiology: disease development is sex-specific from the beginning with fibrosis in women and calcification in men, or both sexes have a common fibrotic pathway at the initiation of the disease and due to androgens, but calcification becomes preponderant in men.[106]

VHD should not be considered just as valvular disease; the effect on the ventricles must also be considered. Interestingly, ventricular remodelling is sex-specific and in aortic stenosis, women will most often present with concentric remodelling/hypertrophy, which can lead to paradoxical low flow aortic stenosis (ie, HFpEF associated with aortic stenosis).[107] Moreover, for a given level of aortic stenosis, women present with more myocardial fibrosis,[108] which might explain the deleterious effect of concentric hypertrophy in women compared with men.[109]

Mitral valve disease. Women are more likely to present with rheumatic mitral VHD than men, despite an overall decrease in recent decades of this condition in industrialized countries.[99,110] This might be linked to differences in fibrotic valve remodelling modulated by the effects of androgens and estrogen; however, further mechanistic studies are warranted.[99] Mitral valve prolapse involving both leaflets is diagnosed more frequently in women, who present with thicker leaflets, representative of a generalized myxomatous degenerative process. Women less often present with flail leaflets, a phenomenon thought to be related to X chromosome-linked genetic determination of mitral valve prolapse properties.[111] Posterior leaflet prolapse, which is associated with a more successful surgical repair, is less frequent in women, and thus their postoperative outcomes are poorer compared with men.[111] Similarly, in the presence of severe mitral regurgitation, delays in surgical intervention, and associated poorer outcomes can occur due to failure to index LV enlargement to the smaller body size of women.[112] Sudden cardiac death associated with mitral valve prolapse is more frequent in women with bileaflet prolapse, mitral annular disjunction, and frequent and repetitive premature ventricular contractions.[113,114]

Mitral annulus calcification develops more often and more extensively in women and could lead rarely to degenerative mitral stenosis or regurgitation. Despite being mostly without hemodynamic consequences, severe mitral annular calcification might have important consequences for surgical and catheter-based therapeutic interventions.[115]

Tricuspid and pulmonic valve disease. Despite being rare, isolated tricuspid regurgitation is more prevalent in women than in men. In-hospital mortality after surgical repair is high (approximately 9%), but comparable for both sexes.[116]

Cardiomyopathies

Takotsubo or stress cardiomyopathy. Takotsubo syndrome, also known as stress cardiomyopathy, apical ballooning syndrome or, in the lay literature, "broken heart syndrome," is characterized by chest pain, HF symptoms ranging from dyspnea to cardiogenic shock, elevated serum troponin levels, and electrocardiogram changes, in the absence of acute obstructive CAD, and often occurs in response to an emotional or physical trigger.[117] Nearly 90% of patients affected are postmenopausal women.[117] Proposed pathophysiological mechanisms involve excess catecholamine stimulation of the myocardium, possibly associated with acute multivessel epicardial coronary artery spasm, and not infrequently observed, acute LV outflow tract obstruction.[117,118] Although atypical patterns exist, characteristic findings include transient LV dysfunction with akinesis of the apical and mid ventricular wall segments, and hypercontractility of the basal segments.[117,118] Patients diagnosed with this condition are at higher risk of in-hospital complications, including acute HF (12%-45%), AF (5%-15%), malignant arrhythmias (3%-10%), LV thrombus (2%-3%), cardiac arrest (4%-6%), ventricular rupture (< 1%), and death (1%-5%).[117,118] Risk of recurrence is estimated to be between 5% and 22% over 10 years, and might be reduced by the administration of angiotensin converting enzyme inhibitors or β-blockers.[117,118] The mean age at presentation for patients with stress-induced cardiomyopathy is older than for SCAD (67 years vs 48 years, respectively); however, the age ranges do overlap and it is important to note that stress-induced cardiomyopathy and SCAD might have similar clinical presentation characteristics. Both diagnoses require coronary angiography with careful examination of the coronary appearance; additional investigations including optical coherence tomography might be required to differentiate SCAD.

Dilated cardiomyopathy. Dilated cardiomyopathy (DCM) has numerous genetic or acquired origins,[119] which result in myocardial dysfunction leading to systolic dysfunction and clinical HF. DCM is less frequently diagnosed in women,[120] who are less often diagnosed with HFrEF. Up to 30% of cases of DCM have a familial basis, and sex differences in phenotype are likely due to genetic variations, including gene mutations, differences in penetrance, and modifier genes. Mutations such as the troponin *TA171S* and *TTN* mutations have been associated with sex differences in phenotype of DCM.[120]

PPCM. PPCM is a cause of HF affecting women toward the end of pregnancy or in the postpartum period. Diagnosis is on the basis of women presenting with signs and symptoms of HF, including systolic LV dysfunction, and an LVEF < 45%, in the absence of other causes of HF.[121] Risk factors for developing PPCM include multiparity, twin pregnancies, African American ethnicity, and advanced maternal age.[121] Concomitant preeclampsia increases the risk of adverse events in women with PPCM, namely the risk of clinical HF and pulmonary embolism.[122] Indigenous women in Canada presenting with PPCM have lower ejection fraction and greater LV dilatation on diagnosis.[123] A protein resulting from cleavage of the lactation hormone prolactin, 16-kilodalton, has anti-angiogenic properties, and has been linked to myocyte damage and HF in animal models.[124] Higher LV end diastolic diameter, low LVEF on presentation, and African

American ethnicity have been associated with poor LV recovery.[125] In addition to standard HF goal-directed medical therapy, bromocriptine, an antagonist of prolactin production in the anterior hypothalamus, might be useful in improving LVEF and clinical outcomes at follow-up.[121,124] Anticoagulation is recommended in conjunction with bromocriptine, and might be considered in women with PPCM and very low LVEF.[121] Pregnancy after a diagnosis of PPCM should be avoided in women with any residual LV impairment (LVEF $\leq$ 50%-55%).[121]

Some data suggest a possible genetic link between PPCM and DCM. Cardiologic screening of family members of women diagnosed with PPCM have identified first-degree relatives with DCM and vice-versa.[120]

Myocarditis. Myocarditis is an inflammatory disease of the muscle cells of the myocardium, with or without necrosis.[120,126] It can be acute, subacute, or chronic, and can involve focal or diffuse areas of the myocardium.[126] In Canada and other developed countries, viral infections are the leading cause of myocarditis.[120] Presentation of myocarditis ranges from asymptomatic states with vague symptoms to severe chest pain, cardiogenic shock, and arrhythmias.[126] Despite myocarditis being more common in men, there are sex differences.[120] Women are able to clear infections and repair damage without high levels of inflammation and without long-lasting damage.[127] However, similar to atherosclerosis, the mechanisms by which women develop myocarditis that subsequently leads to HF is different than in men.[127] Women might be more susceptible to certain types of myocarditis, such as autoimmune myocarditis caused by immune-complex deposition in the heart, which might be promoted by estrogen.[128]

Restrictive/infiltrative cardiomyopathies. Characterized by diastolic dysfunction in a nondilated ventricle, restrictive cardiomyopathy is caused by either infiltrative diseases, storage diseases, or various systemic diseases.[129] Infiltrative diseases are caused by a build-up of a substance in the myocardium and include amyloidosis, sarcoidosis, hereditary hemochromatosis, and primary hyperoxaluria.[130] Storage diseases are congenital abnormalities in metabolism and include Anderson-Fabry disease.[130] Systemic diseases including scleroderma, which has an overall female-to-male ratio of 3:1 and whose incidence is highest in women of childbearing age,[43] can also lead to restrictive cardiomyopathy.[130]

Anderson-Fabry disease is a rare X-linked lysosomal storage disorder resulting from a deficiency of α-galactosidase A activity.[131] It is a multisystem disorder in which the substrate globotriaosylceramide is stored within many tissues such as vascular endothelium, renal glomeruli and tubules, dorsal root ganglia, cardiac myocytes, conducting tissue and valves, cornea, and skin.[131] Cardiac involvement, including LV hypertrophy, occurs in more than half of heterozygous female patients.[131] In contrast to men, who develop symptomatic manifestations of disease in the first to second decades of life, most symptoms of Anderson-Fabry in women develop in the third and fourth decades of life, or even later, with Fabry disease accounting for up to 12% of late-onset hypertrophic cardiomyopathy in women.[132] There often is a significant further delay between symptom onset and diagnosis in women.[131] One possible explanation for this delay is skewed X chromosome inactivation.[133] Early in embryonic development, 1 of the 2 X chromosomes in each somatic cell becomes inactivated, which results in patchy and variable expression of the defective gene, resulting in the variable degree of disease severity and its delayed onset relative to men.[133] Women develop fibrosis before evident hypertrophy, causing loss of myocardial function despite normal LV wall thickness, emphasizing the need for tissue characterization using cardiac magnetic resonance imaging; strain imaging with echocardiography might also have an emerging role.[134] Because women do often have some expression of α-galactosidase A, diagnosis using enzyme testing is not possible, and genetic diagnosis must be done if there is clinical suspicion. Plasma lyso-Gb3 represents a potential primary screening biomarker sensitive and specific for identifying Fabry disease in women and men, with more studies needed.[135,136]

Sarcoidosis. Cardiac sarcoidosis might be more common in women. A Finnish cohort study reported 65% of cardiac sarcoidosis cases to be in women, but recent data are lacking.[137] The exact mechanism for sarcoidosis is unclear, but is characterized by the development and accumulation of granulomas.[138] Granulomas usually develop to restrict pathogens, reduce inflammation, and protect surrounding tissue.[138] Granulomas are small, centrally organized collections of macrophages and epithelioid cells encircled by lymphocytes.[138] Because of the presence of chronic cytokine response, macrophages differentiate into epithelioid cells, develop secretory and bactericidal capacity, reduce phagocytic capacity, and fuse to form multinucleated giant cells.[138] As they mature, fibroblasts and collagen encase the granulomas into a ball-like cluster of cells, causing sclerosis and altering organ architecture and function.[138]

Hypertrophic cardiomyopathy. Despite being an autosomal dominant genetic disorder, hypertrophic cardiomyopathy is more often diagnosed in men, potentially because of the under-recognition of the condition in women.[139] Contemporary cohorts have shown that symptomatic HF is more frequent in women with hypertrophic cardiomyopathy, who are twice as likely to progress to advanced HF and 3 times more likely to experience HFpEF.[140] Consequently, a higher proportion of women undergo myectomy and alcohol septal ablation.[140] Age-adjusted mortality is similar for men and women, with similar rates of sudden cardiac death and appropriate reference for primary prevention ICD.[140]

Arrhythmia

Arrhythmias are the fourth leading CVD-related cause of death among Canadian women, resulting in > 2600 deaths per year.[100] Arrhythmias are a leading cause of annual emergency department visits and CVD-related hospitalizations for Canadian women.[57] More than 74% of cases of arrhythmia are due to AF,[100] the most common sustained arrhythmia in clinical practice. Its prevalence is 1%-2% in the general population and is expected to double in the next 50 years. Up to age 75 years, AF is more commonly found in men[141]; however, after age 75 years, almost 60% of people with AF are

women, with concomitant higher rates of mortality.[141] Women with AF have a higher risk of stroke and all-cause mortality, greater symptom burden, and worse quality of life, including poorer functional outcomes.[142,143] Women with AF suffer larger strokes and have greater admission rates to long-term care.[141-143] AF is typically associated with obesity and VHD in women, and with CAD in men.[142-144] Women tend to be more symptomatic with AF and have higher recurrence rates,[141,143] and women with paroxysmal AF tend to have faster and longer heart rate responses compared with men.[145] In South Asian women, AF is less prevalent despite a high burden of traditional risk factors such as hypertension and CAD.[57,146,147] It has been hypothesized that genetic predisposition for South Asian women to have smaller left atrial volume size protects against the development of reentrant circuits and atrial fibrosis, thereby reducing structural and electrical remodelling.[143,146,148,149]

No ethnic or sex-specific differences in direct oral anticoagulation therapy efficacy has been determined although there is a significant reduction in major and nonmajor bleeding in female patients receiving direct oral anticoagulation therapy.[142,150,151] Symptom control in women with AF remains suboptimal in women compared with men, who experience symptoms more frequently and have poorer quality of life pre- and postablation.[152] Registry data show that women are less likely to undergo electrical cardioversion in clinical practice,[153] but more likely to be treated with pharmacological cardioversion. Female patients with AF are less likely to undergo ablation therapy, despite obtaining similar symptom relief, reduction in AF burden, and outcomes similar to those of men after ablation therapy.[152] Women are at a higher rate of complications after catheter ablation for AF, including phrenic nerve injury, although this difference is not statistically significant (3.5% in men vs 7.0% in women; $P = 0.18$).[152]

Women have a longer length of systole and a longer QT segment, compared with men.[154,155] It is believed sex differences in arrhythmias are related to sex hormones and their influence on cardiac electrophysiology.[141] Women's longer QT segments are thought to occur in the absence of testosterone, which suppresses the inward movement of calcium into cell membranes and enhances inward-rectifying potassium currents, thereby causing a net positive potential to the membrane, and shorter QTc intervals in men.[156] Although progesterone might have an effect similar to that of testosterone, estrogen prolongs the QT interval.[141,142,157]

The normally occurring increase in progesterone and the decrease in estrogen levels during a normal menstrual cycle correspond to an increased frequency, symptomatic burden, and duration of supraventricular tachycardia (SVT) in women.[158] Sick sinus syndrome, SVT, atrioventricular nodal reentry tachycardia (AVNRT), and postural orthostatic tachycardia syndrome are also more common in women.[159] The most common type of SVT in women is AVNRT. In a study on the sex-related differences in patients undergoing catheter ablation of AVNRT, women were twice as likely to have AVNRT, and were significantly younger at onset compared with men.[160]

Pregnancy is a proarrhythmic state and the risk of SVT increases with pregnancy, especially in women with a history of Wolff-Parkinson-White.[161]

Vascular arterial disease

Aortic aneurysms. Thoracic aortic aneurysm (TAA) is more prevalent in men, who account for nearly 70% of those with thoracic aortic dissections.[162] However, women with TAA have faster aneurysm expansion,[163] are 3 times more likely to dissect[164] (especially at smaller aneurysm sizes),[165] and are 40% more likely to die[162] than men with TAA.[163,165] Evidence from the Canadian Thoracic Aortic Collaborative identified that after aortic surgical repair women experience higher risk of mortality (81%) and stroke (90%), compared with their male counterparts.[166]

Prevalence of abdominal aortic aneurysm (AAA) is also higher in men,[167] but AAA-related outcomes are far worse in women. Current smoking yields twice the risk of AAA for women compared with men.[168] Women with AAA also experience twice as fast aneurysm growth,[169] and up to 4 times higher risk of AAA rupture[170] despite having smaller aneurysm sizes, compared with men. Women are less likely than men to be referred for AAA repair,[171] and more likely to experience surgical complications post repair.[172,173] Thus, although women appear to be "naturally protected" against thoracic aortic disease, for women who go on to develop the condition this might be a signal that their aortas harbor a greater burden of wall pathology, and/or are exposed to greater hemodynamic challenges—all of which might contribute to worse aorta-related outcomes in women.

A potential explanation for these sex differences lies in hormonal, molecular, and hemodynamic differences between women and men. Aortic stiffness (a robust marker of aortic health and arterial aging) correlates better with TAA expansion in women compared with men.[174] In a study of TAA specimens obtained during elective repair, higher levels of matrix metalloproteinase (MMP)-2 and MMP-9 (enzymes capable of degrading and remodelling the arterial wall) and decreased expression of the inhibitory enzymes TIMP metallopeptidase inhibitor 1 and -2 were found in women, compared with men.[175] This impairment of aortic wall homeostasis, resulting in enhanced extracellular matrix degradation, led to a higher aortic elastic modulus, increased aortic stiffness, and decreased aortic strength in women. This suggests that women with TAA have greater insults to aortic health and structure than men, potentially explaining women's faster aneurysm expansion and worse TAA-related outcomes. For AAA, evidence supports a role for estrogen in modulating inflammation and MMP activity, resulting in a protective effect on aortic matrix remodelling.[176,177] The amount of estrogen receptor α in the aortic wall is inversely associated with MMP activity and AAA expansion.[178] These findings help explain the lower prevalence of AAA among reproductive-age women, while highlighting links between loss of estrogen and worse AAA outcomes in older, postmenopausal women.

Despite worse TAA-related outcomes in women, guidelines do not propose sex-specific approaches for this condition. The CCS position statement on the management of thoracic aortic disease[179] recommends indexing TAA size to body surface area in shorter individuals and women, and surgery should be contemplated when the TAA size exceeds 2.75 cm/m^2. However, it remains unclear whether simple indexation

will eliminate the sex differences in TAA complications and outcomes among those undergoing regular surveillance. The Society of Vascular Surgery recommends elective AAA repair in women when the aneurysm reaches between 50 and 54 mm,[180] which is smaller than the 55 mm cutoff for men. Although AAA ultrasound screening recommendations are available, studies for AAA screening have notoriously underrepresented women, undermining the evidence to guide screening practices in women.[181] The CCS, Canadian Society of Vascular Surgery, and Society of Vascular Surgery recommend screening women for AAA if they have smoked, have heart disease, have a family history of AAA, and are between the ages of 65 and 80 years.[179]

Atherosclerotic lower extremity arterial disease ("peripheral arterial disease"). Similar to other atherosclerotic vascular diseases, peripheral arterial disease (PAD) tends to develop 1-2 decades later in women, compared with men.[182] After menopause, rates of PAD are at least similar, and possibly higher, in women than men.[183] Risk factors for PAD are similar for both sexes, except that hypertensive disorders of pregnancy increase future risk of PAD by threefold[184]; and diabetes appears to be more ominous for women, tripling the risk of occlusive vascular mortality.[185]

Women with PAD are more likely than men to be asymptomatic or have atypical leg symptoms.[186] Conversely, when disease is clinically manifest, women have more complex disease,[187] have greater functional impairment,[188] and, perhaps partially as a result, are 4 times more likely to be depressed[189] than men. Although it has been reported that women have slightly lower ankle-brachial index than men, this is not expected to affect diagnostic accuracy.[190] The sensitivity and specificity of advanced anatomical imaging techniques do not appear to be different for men and women.[190]

Sex differences have been reported in response to treatment and outcomes in PAD. Although walking rehabilitation is an integral component of claudication treatment, women with diabetes and PAD have a worse functional response to rehabilitation than men with diabetes.[191] However, other studies and clinical trials that have evaluated walking rehabilitation in patients with PAD either failed to recruit women or to report results according to sex, limiting our ability to draw conclusions about its overall efficacy in women. Women are less likely than men to be referred for elective lower extremity revascularization; however, they are more likely to be admitted emergently for PAD-related complications.[192] Women tend to be older and have more advanced disease at the time of surgical revascularization. Postprocedurally, women are more likely to have a bleeding complication and have longer hospital stays.[192,193] Postoperatively, women have a 31% higher 30-day mortality, 56% higher risk of early graft thrombosis, 64% higher risk of embolization, 7% higher risk of amputation, 21% higher risk of cardiac events, and 35% higher risk of stroke than men.[194] Outside of the postoperative period, non-PAD outcomes are worse in women, because they are 15% more likely to suffer AMI, compared with men.[195]

Despite disease prevalence that is at least as high as men's and worse outcomes, women remain under-represented in PAD studies. Women constitute < 35% of participants in PAD research; and 22% of participants in randomized trials of arterial revascularization.[196] As a result, present guidelines about PAD do not specifically address PAD in women.

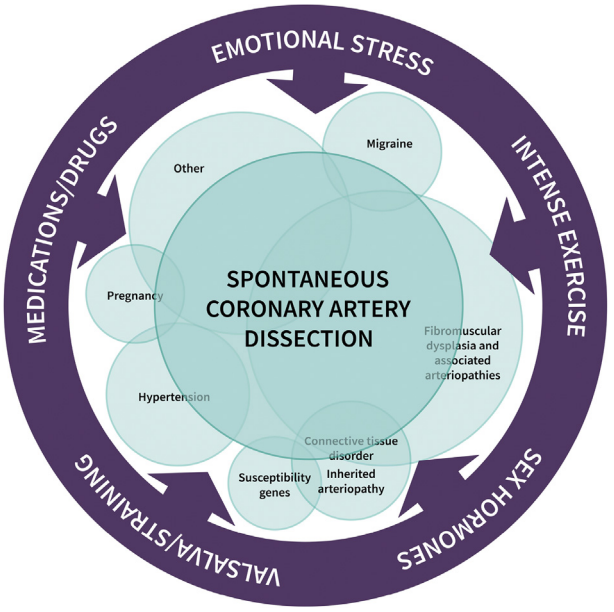

Figure 5. Associated conditions and risk factors for spontaneous coronary artery dissection. Modified from Hayes et al.[38] with permission from Elsevier.

Vascular cognitive impairment, dementia, and stroke

Stroke. Stroke is a major cause of all adult disability worldwide,[197] and is the second leading cause of CVD-related mortality in women in Canada, resulting in approximately 7000 deaths annually.[98] Stroke is a major driver of emergency room visits for Canadian women, responsible for more than 25,000, or 22% of CVD-related encounters in primarily women of postmenopausal age (89%), with 57% of visits resulting in an admission to inpatient care.[57] Just under 20% (n > 25,000) of CVD-related hospitalizations among Canadian women are due to stroke. The age-standardized occurrence rates of stroke according to sex are presented in Figure 2, and age-standardized mortality rates for stroke according to sex in Figure 3.

Although the overall incidence of stroke is higher in men, incidence in women rises sharply after age 75 years to rates exceeding those observed in men.[198] Because of the increased life expectancy of women, the lifetime risk of stroke is higher in women compared with men.[198] Women are disproportionately affected by stroke, demonstrating higher age-specific mortality after age 75 years,[199] greater stroke severity[200] (although this disparity might be confounded by older age at onset and premorbid functional status[201]), an increased likelihood of stroke-related disability,[202] reduced quality of life after stroke,[203] increased levels of post-stroke depression,[204] and higher rates of institutionalization compared with male stroke survivors.[199]

Although major vascular risk factors (eg, hypercholesterolemia, smoking, IHD, diabetes) are more prevalent among men

who present with stroke, hypertension and AF are more frequent among female stroke patients.[205] AF is a major preventable cause of stroke,[206] independently increasing stroke risk by fivefold[207] and accounting for more than 20% of all acute ischemic strokes.[208] Although they have a lower prevalence of AF, because of aging, women have a comparable lifetime risk.[143] Early population-based studies and clinical trials showed an increased risk of stroke for women with AF, especially after age 75 years,[209,210] and a more recent meta-analysis of more than 4 million participants reported a twofold increase in the pooled relative risk of stroke associated with AF in women vs men (Relative risk = 1.99; 95% CI, 1.46-2.71).[211] On the basis of these associations, female sex was included as a risk factor in the Congestive Heart Failure, Hypertension, Age (≥75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age (65-74 years), Sex (Female) (CHA_2DS_2-VASc) score for stroke risk stratification[212] and clinical guidelines for stroke prevention and the management of AF.[213,214] However, recent work suggests that this excess risk might be more dependent on age and the presence of comorbid risk factors[215] and a reanalysis of the prognostic value of female sex for stroke risk in AF patients identified sex as a "risk modifier," rather than independent risk factor.[216]

Women have several unique risk factors that make them vulnerable to stroke across the lifespan, particularly during pregnancy and postmenopausal aging. A recent meta-analysis (n > 10 million) of sex-specific stroke risk factors showed that hypertensive disorders of pregnancy, including gestational hypertension, preeclampsia, and eclampsia increase relative stroke risk by 81% and stroke mortality by 54%[217] and stroke risks were increased among women with oophorectomy, preterm delivery, and stillbirth.[217] Endothelial dysfunction and disruption of the blood brain barrier play a central role in cerebral injury related to preeclampsia/eclampsia, as suggested by the presence of microangiopathic hemolysis and subcortical edema in the occipital lobes in 28 women who underwent cerebral magnetic resonance imaging.[218] Estrogen, particularly 17b-estradiol, has multiple potential protective effects associated with enhanced endothelial nitric oxide synthesis and production, vasodilating prostanoids, and endothelium-derived hyperpolarizing factor, all of which promote tissue perfusion during and after a cerebral artery occlusion.[205] Other protective effects of estrogen might include reduced oxidative stress, increased neuro- and angiogenesis and the suppression of atherogenesis,[219] potentially contributing to increases in stroke risk associated with estrogen reductions at menopause. Differences in genetic factors and differential activation of apoptotic cell-cell signalling pathways and neuroinflammatory and immune responses might contribute to sex differences in stroke risk.[220]

Although some evidence of sex differences in acute stroke management exists, these findings are inconsistent and many studies did not account for treatment confounds such as age, stroke severity, and pre-stroke functional status.[221,222] Despite this variability, there remains consistent evidence that women might experience greater prehospital delays and longer door-to-imaging times,[221] undergo fewer lipid investigations,[222] and have reduced access to some preventive medications, including antiplatelet and anticoagulation therapy.[222] However, although some registries have shown that women with AF are less likely to receive oral anticoagulation after stroke,[223] others report no differences,[224] highlighting the need for more sex-stratified studies of treatment and outcomes post-stroke.

Vascular cognitive impairment and dementia. Two-thirds of the > 5 million Americans living with dementia due to Alzheimer disease are women.[225] Several population-based studies report comparable rates of incident dementia among men and women until age 80, at which point incidence increases dramatically among women and significantly reduces quality of life.[225] Although there is much less evidence characterizing sex differences and mechanisms of vascular cognitive impairment (VCI) and dementia than stroke, female sex has been shown to be an independent predictor of pre-stroke dementia.[226] Potential mechanisms of sex differences in the development of cognitive decline include genetic, neurochemical, and vascular risk factors.[225] Specifically, women with the apolipoprotein E genotype show higher age-specific odds of developing dementia and are more likely to convert from mild cognitive impairment to dementia.[225] Although midlife hypertension is more common in men, the onset of midlife hypertension is predictive of increased dementia risk in women only.[227] At menopause, reductions in estrogen might reduce neuroprotective effects and increase vulnerability to cognitive decline, and metabolic factors (eg, changes in glucose metabolism and insulin signalling) might also contribute to dementia risk.[225] Although there are limited available treatment options for VCI and dementia, future work on sex-specific vascular contributions to dementia risk and related biological pathways is urgently needed to identify potentially viable therapeutic targets for VCI and dementia.

Conclusions

Sex- and gender-unique differences in CVD affect symptom presentation, underlying pathophysiology, and clinical outcomes. These differences must be understood when evaluating women to determine optimal CVD management and improve patient outcomes. With a few notable exceptions in which women predominate in CVD manifestations, such as SCAD and stress-induced cardiomyopathy, there is a paucity of sex-disaggregated data to guide management and guideline development. Evaluation of women with cardiovascular disorders must be done through this sex- and gender-specific lens. Efforts must be made to increase enrollment of women into clinical trials, to build a solid evidence base for guideline-directed management.

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