CONTEMPORARY REVIEW

State of the Science in Women's Cardiovascular Disease: A Canadian Perspective on the Influence of Sex and Gender

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Cardiovascular disease (CVD) is the leading cause of premature death for women in Canada.[1] Although it has long been recognized that estrogen impacts vascular responses in women, there is emerging evidence that physiologic and pathophysiologic cardiovascular responses are uniquely affected across the spectrum of a woman's life. Despite a global understanding that manifestations and outcomes of CVD are known to differ between men and women, uptake of the recognition of sex and gender influences on the clinical care of women has been slow or absent.[2]

To highlight the need for better research, diagnosis, treatment, awareness, and support of women with CVD in Canada, the Canadian Women's Heart Health Alliance (CWHHA), supported by the University of Ottawa Heart Institute, and in collaboration with the Heart and Stroke Foundation of Canada (HSFC), undertook a comprehensive review of the evidence on sex- and gender-specific differences in comorbidities, risk factors, disease awareness, presentation, diagnosis, and treatment across the entire spectrum of CVD. The intent of this review was not to directly compare women and men on epidemiological and outcome measures of CVD, but to synthesize the state of the evidence for CVD in women and identify significant knowledge gaps that hinder the transformation to clinical practice and care that is truly tailored for women, a significant health challenge that has only been recognized in Canada relatively recently. This review highlights

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the scarcity of Canadian data on CVD in women as part of the ongoing struggle to increase awareness of and improve outcomes for women with CVD. Because of a paucity of published Canada-specific evidence, the purpose of this review is to provide an infrastructure to summarize world-wide published evidence, including knowledge gaps that must be understood to then make effective recommendations to alleviate the glaring "unders" of CVD for women in Canada: under-aware, under-diagnosed and under-treated, under-researched, and under-support.[3]

The Writing Group

The writing group comprised members of the Knowledge Translation and Mobilization and Health Systems and Policy Working Groups of the CWHHA, a volunteer professional organization whose vision and mission is to improve women's cardiovascular health across their lifespan by supporting clinicians, scientists, patients, and decision makers to work collaboratively to implement evidence and transform clinical practice and public policy related to women's cardiovascular health in Canada. The CWHHA membership identified as a high priority the need for an environmental scan of CVD in women in Canada from which a scientific statement could be developed to summarize critical sex- and gender-specific issues in CVD diagnosis, treatment, and outcomes.

As a key collaborator with CWHHA, HSFC staff complemented the writing group. HSFC is the Canadian counterpart to the American Heart Association (AHA) and is dedicated to policy and advocacy, system change, knowledge translation, public awareness and education, and CVD research. In recent years, HSFC identified women's heart and brain health as a priority, forming a Women's Research Network consisting of cardiovascular experts from across Canada and launching a women's cardiovascular awareness campaign in 2018.

All writing group members have in-depth expertise on CVD among women. After 2 national planning teleconferences of the 2 CWHHA working groups, a topic outline based on the scope of the problem was developed. Writers were selected on the basis of experience and expertise to complete evidence-based summaries of their assigned topic areas. The writing group members had opportunities to comment on and approve the report, which also underwent extensive peer review by members of Canadian Women's Heart and Brain Health Research Steering Committee and HSFC.

Administrative data were obtained from the Canadian Institute for Health Information (CIHI) and analyzed by HSFC authors. Components of the demographic material were based on comparative data and information obtained from CIHI for the most recently available years, 2016 to 2017.

In this comprehensive review, CVD refers to diseases, disorders, syndromes, and conditions that affect the heart and blood vessels. Canadian vital statistics and hospitalization administrative data were extracted using *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes (Data S1; Tables S1 and S2). When available, studies with Canadian data were prioritized for inclusion in this review to provide a Canadian perspective. When unavailable, studies with data from outside of Canada were included. Because of the lack of Canadian data covering the full scope of topics included, it is not intended for this to be a systematic literature review. On the basis of the specific subject matter and the available evidence, various search strategies were used. Please see Table S3 for a detailed list of the sources and keywords used for literature searches. Quality of studies searched was appraised by authors' expert opinions, with top prioritization for those studies reporting data from high-quality systematic reviews or meta-analyses and/or primary data from randomized controlled, prospective, or retrospective observational cohort, or case-control studies; studies published within the past decade were also given priority. Although the terms sex and gender are often used interchangeably in the available literature, we recognize that they have distinct definitions and attempted to clarify when the differentiating information was available. 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 woman or man. Gender refers to socially constructed roles, behaviors, expressions, and identities.

Scope of the Problem

The stunning lack of research specifically oriented to women and the under-representation of women in CVD research studies are significant contributing factors to the under-recognition, under-diagnosis, under-treatment, and under-support of women with CVD in Canada. To illustrate the full scope of the problem, this review begins with an appraisal of the currently inadequate evidence to support female-specific clinical guidelines and recommendations for CVD in Canada. This is followed by an assessment of the present burden of CVD on women in Canada and an analysis of how sex- and gender-specific differences in comorbidity, risk factors, and a lack of awareness on the part of women and their healthcare providers all contribute to the slow progress made in advancing the cardiovascular health of women in Canada. A thorough examination of the multitude of sex- and gender-specific differences in presentation, diagnosis, and treatment across the full spectrum of CVD highlights the urgent need to drive more research and transform clinical practice to

improve the cardiovascular health of women. The authors conclude with a discussion of future directions and the action needed on multiple fronts to achieve sex and gender equity for women's cardiovascular health to correct the glaring "unders" of CVD for women in Canada.

Clinical Practice Guidelines and Recommendations

An inadequate evidence base to support the development of comprehensive sex- and gender-specific guidelines or recommendations for the treatment of CVD is a global problem; there are few Canadian, United States, or international CVD guidelines that are women specific. This speaks to the importance of stratifying research results by sex so as to discern sex-specific implications. Health Canada recommends that women be included as participants in health research and clinical trials, to provide evidence for the crucial impact of sex and gender. Organizations such as HSFC, Canadian Cardiovascular Society, and Hypertension Canada have developed CVD clinical practice guidelines and position statements, but they contain limited information on sex-specific care. The Canadian Institutes of Health Research and HSFC recognize the importance of women's participation by mandating sex- and gender-based analysis and reporting in funded research.

In 2018, the Canadian Cardiovascular Society led an initiative to determine the feasibility of developing a process to consider sex and gender in guidelines, specifically to manage ST-segment–elevation myocardial infarction (STEMI) in short-term care. Despite concluding that implementing a systematic process to appraise sex-specific evidence for clinical practice guidelines was feasible, inadequate enrollment and reporting by sex hindered a comprehensive assessment of the quality of evidence and strength of recommendations.[2]

In the United States, women-specific CVD prevention guidelines were published in 2004 and updated in 2007 and 2011. Recent guidelines, scientific statements, and advisories addressing CVD in women include the following:

1. 2014: Guidelines for the prevention of stroke in women: A statement for healthcare professionals from the AHA/American Stroke Association;
2. 2014: Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease (IHD): A consensus statement from the AHA;
3. 2016: Acute myocardial infarction (MI) in women: A scientific statement from the AHA;
4. 2018: Spontaneous coronary artery dissection (SCAD): current state of the science: A scientific statement from the AHA;
5. 2018: Promoting risk identification and reduction of CVD in women through collaboration with obstetricians and gynecologists: A presidential advisory from the AHA and the American College of Obstetricians and Gynecologists.

The 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice[4] provided some recommendations tailored specifically to women, using evidence from 8 risk estimation systems (Framingham, SCORE, ASSIGN-SCORE, QRISK1 and QRISK2, PROCAM, Pooled Cohort Studies Equations, CUORE, and Globorisk). Several sex-specific cutoffs for CVD risk factors were recommended.

Although CVD risk factor and population prevalence may differ across the globe, evidence suggests that there are similarities in the unique aspects of pathophysiological characteristics of CVD in women globally. Thus, although a united effort would benefit development of strategies to accelerate the improvement of cardiovascular outcomes for women, individual populations must study and understand their specific CVD burdens.

Burden of CVD among Women in Canada

Although some progress has been made in raising awareness of women's cardiovascular health, CVD continues to be a major leading cause of death for women in Canada.[5] The top 3 CVD-related causes of death for women in Canada are IHD, stroke, and heart failure (HF), as shown in Table 1. Overall, female CVD mortality is proportional to the populations in individual provinces and territories (Table S4) without a clear disproportion for any geographic region.

In 2016, women in Canada sought emergency care and/or were admitted to inpatient short-term care for a wide range of CVDs. Aside from IHD, the most common CVD diagnoses that led women in Canada to seek emergency (Table 2) or inpatient (Table 3) short-term care were HF, stroke, and atrial fibrillation (AF).

Since 2016, there have been several publications summarizing CVD differences in women, derived primarily from US data resources.[6] Unfortunately, there is a paucity of such data pertaining specifically to women in Canada, and it is the purpose of this review to focus attention on the need to examine the underlying sex-specific aspects of CVD in women in Canada, by summarizing what is currently known in the broader North American context and highlighting knowledge gaps specifically for women in Canada. Thus, as described in The Writing Group, the remainder of this review will present a synthesis of sex- and gender-unique aspects of CVD in the published literature, including Canadian-specific data when available, while underscoring their paucity and the need for additional research.

Table 1. Number of Women in Canada With Mortality Caused by CVD, 2016

Province/Territory	IHD including MI	MI only	Stroke	Heart Failure	Vascular Disease	AF	Valvular Heart Disease	Arrhythmia	PAD	Congenital Heart Disease
Newfoundland and Labrador	255	80	120	50	30	30	35	5	5	10
Prince Edward Island	80	15	20	10	15	10	10	. . .	. . .	. . .
Nova Scotia	460	175	270	70	55	85	40	15	15	. . .
New Brunswick	305	140	170	90	35	40	20	20	15	. . .
Quebec	5600	2080	2420	800	620	675	550	120	210	60
Ontario	510	200	275	125	50	80	40	15	20	20
Manitoba	460	140	220	155	45	75	35	10	15	. . .
Saskatchewan	1475	445	510	240	170	155	100	20	30	15
Alberta	1705	810	1050	390	195	340	255	75	70	20
British Columbia	. . .	. . .	10	5	. . .	. . .	. . .	. . .	. . .	. . .
Yukon	10	5	5	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Northwest Territories	5	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Nunavut	2890	1600	1520	895	265	325	500	370	35	20
TOTAL	13 755	5690	6590	2830	1480	1815	1585	650	415	145

Data source: Statistics Canada, 2016. Deaths by province for selected *International Classification of Diseases, Tenth Revision, With Canadian Enhancements* (*ICD-10-CA*), codes (see Table S1), custom tabulation January 1, 2016, to December 1, 2016. Received May 2019. Only sample sizes of ≥5 are shown. A sample size of <5 is indicated by a "..." and does not necessarily mean that no woman died from CVD in that province or territory. AF indicates atrial fibrillation; CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; PAD, peripheral artery disease.

Sex- and Gender-Specific Differences in CVD Comorbidity

Certain comorbid conditions affect women differently than men (Table 4).[7–32] Women with HF have a 24% higher risk of AF than men, whereas women with valvular heart disease (VHD) have a 47% higher risk of AF than men.[33] Canadian women, and especially those who are younger, are more likely than men to die within 1 year after an acute MI.[34]

Risk Factors

Traditional

Smoking, hypertension, diabetes mellitus, obesity, unhealthy dietary patterns, sedentary behavior, excess alcohol consumption, plasma apolipoproteins, and psychosocial factors account for 96% of the population-attributable risks of MI among women.[35] The sex-specific impacts of selected traditional CVD risk factors are shown in Table 5.[35–46]

Table 2. Most Responsible Diagnosis Reported in Women Admitted to Emergency Department in 2016

Variable	Ischemic Heart Disease	Stroke	Heart Failure	Atrial Fibrillation	Arrhythmia	Vascular Disease (Including Peripheral Artery Disease)	Valvular Heart Disease	Peripheral Artery Disease Only	Congenital Heart Disease
No. of female admissions to emergency department	26 355	25 672	21 969	19 110	11 025	3087	1729	971	260
Aged ≤51 y, %	8.6	11.1	2.8	5.5	33.3	23.6	7.5	34.7	77.3
Aged >51 y, %	91.4	88.9	97.2	94.5	66.7	76.4	92.5	65.3	22.7
Discharged home, %	42.0	42.0	34.0	69.0	72.0	57.0	76.0	88.0	72.0
Admitted to inpatient care from emergency department, %	56.0	57.0	66.0	31.0	27.0	41.0	24.0	11.0	25.0

Data source: Heart and Stroke Foundation of Canada's analysis of Canadian Institute for Health Information's National Ambulatory Care Reporting System data, April 1, 2016, to March 31, 2017. Data include all facilities in Ontario and Yukon and available facilities in Prince Edward Island, Nova Scotia, Manitoba, Saskatchewan, and British Columbia. Age 51 years stratification was selected as approximate average age of menopause, to characterize premenopausal and postmenopausal populations.

Table 3. Most Responsible Diagnosis Reported in Women Admitted for Inpatient Acute Care in 2016

Variable	Ischemic Heart Disease	Heart Failure	Stroke	Atrial Fibrillation	Arrhythmia	Vascular Disease (Including Peripheral Artery Disease)	Valvular Heart Disease	Congenital Heart Disease	Peripheral Artery Disease Only
No. of female admissions to inpatient acute care	32 969	24 604	19 183	9998	7124	4750	4506	1807	308
Those with comorbid hypertension, %	54.0	36.0	56.0	28.0	28.0	26.0	38.0	6.0	20.0
Those with comorbid diabetes mellitus, %	34.0	38.0	26.0	20.0	20.0	10.0	22.0	2.0	4.0
Aged ≤51 years, %	7.0	3.0	8.0	4.0	16.0	9.0	8.0	86.0	11.0
Aged >51 years, %	93.0	97.0	92.0	96.0	84.0	91.0	92.0	14.0	89.0
Discharged home, %	66.0	73.0	51.0	88.0	80.0	74.0	80.0	85.0	75.0

Data source: Heart and Stroke Foundation of Canada's analysis of Canadian Institute for Health Information's Discharge Abstract System data, April 1, 2016, to March 31, 2017. Only data from Quebec were not accessible and, therefore, are not included.

Sex Specific

An increasing body of evidence suggests CVD risk assessment in women should extend beyond the traditional CVD risk factor assessment to include a reproductive evaluation that considers age at menarche, menstruation, contraception use, pregnancy, ovarian health, menopause, and hormonal therapy use.

Early age at menarche has been shown to increase the risk of CVD among white women.[47] Women with irregular menstrual cycles, including polycystic ovary syndrome, have an increased risk of metabolic abnormalities and CVD risk factors, such as diabetes mellitus. Combined oral contraceptive therapy increases the risk of arterial thrombosis and predisposes women to MI and/or stroke, particularly those aged >35 years who have numerous cardiovascular risk factors, especially smoking.[48]

Pregnancy creates a natural stress on the cardiovascular system, with structural and hemodynamic changes to

Table 4. Comorbid Conditions Associated With an Increased Risk of CVD in Women

Comorbid Condition	Impact on Women's Heart Health
Polycystic ovary syndrome	• Associated with obesity, insulin resistance, hyperinsulinemia,[8] metabolic syndrome,[8,9] dyslipidemia,[10,11] impaired glucose tolerance, type 2 diabetes mellitus,[12] and obstructive sleep apnea.[13,14]
Autoimmune disorders (eg, rheumatoid arthritis and systemic lupus erythematosus)	• 2 to 10 times more common in women.[15] • Associated systemic inflammation increases the risk of premature atherosclerotic CVD, as well as many other cardiovascular disorders of the myopericardium, valves, and conduction system.[16] • Associated chest, jaw, neck, shoulder, or back pain; fatigue; dyspnea; and exhaustion can be difficult to differentiate from clinical CVD symptoms and may delay recognition of a CVD diagnosis.[17]
Breast cancer	• Breast cancer survivors are more likely to die from CVD.[19–21] • Cancer treatment–related cardiac toxicity can occur with anthracycline-based chemotherapy, trastuzumab-targeted therapy, and radiation therapy (left-sided breast cancer); noninvasive cardiac testing can be used to detect cardiovascular toxicity.[20]
Chronic kidney disease	• Women with reduced kidney function are at greater risk of CVD than men.[21] • Hypertensive disorders of pregnancy and gestational diabetes mellitus increase the risk of chronic kidney disease progression.[22] • Women on dialysis have a CVD mortality rate similar to age-matched men.[23]
Depression	• Incidence is 2 times higher in women than in men.[24,25] • Increases a women's risk for a cardiac event by 50% to 70%[26,27] and correlates with fatal cardiac events in postmenopausal women.[28] • Almost 2 times more women than men experience depression after cardiac diagnosis[29,30]; younger women are particularly susceptible.[31] • Post-MI depression increases by 2 to 3 times the risk of all-cause mortality, cardiac mortality, and cardiac morbidity.[32]

CVD indicates cardiovascular disease; MI, myocardial infarction.

Table 5. Traditional CVD Risk Factors and Their Impact on Women's Cardiovascular Health

Traditional Risk Factor	Implications for Women
Smoking	• Single-most modifiable risk factor for developing MI.[35] • Increases the risk of CVD in women aged <55 years by 7 times.[35]
Hypertension	• Prevalence and incidence higher in women than men aged >60 years.[36] • Poorer hypertension control in women than men aged >60 years.[37] • Women treated with antihypertensive medications have higher systolic blood pressures than men.[37] • Additive interaction between current smoking and hypertension on IHD incidence in women.[38]
Diabetes mellitus	• Women with diabetes mellitus are at a 2 to 4 times greater risk for IHD compared with men with diabetes mellitus.[39,40]
Obesity	• More women than men in Canada are overweight and obese.[41] • Metabolic effects of obesity are associated with increased CVD risk.[41]
Physical inactivity	• Across all ages, women are less physically active[42] and spend more time in sedentary activities.[43]
Cholesterol	• Low HDL cholesterol is a stronger predictor of IHD mortality in women than in men, especially in women aged ≥65 years.[44] • Elevated LDL cholesterol, a strong predictor of IHD risk in women aged <65 years, is less predictive in older women.[44]
Stress	• Women may be more vulnerable to the adverse effects of psychosocial stress, occupational stress, and sleep disturbances, increasing their risk of CVD.[45] • Disproportionately more unpaid housework and family responsibilities may exacerbate and sustain high stress levels because of conflicting demands.[45] • Discrimination and gender roles may further increase the environmental psychosocial stress, as may sex and gender differences in stress responses.[40,46]

CVD indicates cardiovascular disease; HDL, high-density lipoprotein, IHD, ischemic heart disease; LDL, low-density lipoprotein; MI, myocardial infarction.

accommodate increased blood volume and cardiac output. These normal physiologic changes often unmask or exacerbate prepregnancy cardiac and brain conditions (eg, congenital heart disease and VHD) or lead to the development of new cardiac conditions (eg, arrhythmia, pregnancy-associated MI, peripartum cardiomyopathy, aortic dissection, and aneurysm). As a result, CVD is a leading cause of maternal morbidity and mortality during pregnancy and postpartum. Hypertensive disorders of pregnancy, gestational diabetes mellitus, preterm birth, and infertility are independent sex-specific CVD risk factors associated with subsequent premature atherosclerotic CVD, arrhythmia, and HF.[49]

Premature menopause occurs before the age of 40 years and may be spontaneous as a result of primary or secondary ovarian insufficiency or surgical after bilateral oophorectomy. In general, women are at lower risk of CVD than age-matched men during their reproductive years, but this advantage disappears after menopause.[50] There are conflicting data as to whether the type of menopause (spontaneous versus surgical) affects CVD risk. Early (at age 40–45 years) and especially premature menopause are associated with increased CVD morbidity and mortality.[50] The adverse effects of menopause on cardiovascular health are largely attributed to hypoestrogenemia.[50] This includes an atherogenic cardiometabolic profile with impaired glucose tolerance, an increase in total and low-density lipoprotein cholesterol and lipoprotein(a), a decrease in high-density lipoprotein cholesterol, an elevated blood pressure, an increase in central obesity, and a withdrawal of the beneficial effects of estrogen on vasodilation.

Demographic

Demographic risk factors, such as socioeconomic status, race and ethnicity, and disability, disproportionately impact women's risk of CVD. Paired with the challenges of undertaking risk-reducing behaviors, women of lower socioeconomic status are more susceptible to CVD than those with a higher socioeconomic status.[51] Even in the context of the Canadian universal healthcare system, associations between socioeconomic status and CVD outcomes have been identified. Compared with other income groups and men, lower socioeconomic status women in Canada have less access to cardiac catheterization and higher 30-day mortality after acute coronary syndrome (ACS).[52]

CVD risk factors and rates are higher among ethnic minority groups, including South Asian, Afro-Caribbean, Hispanic, and Chinese North Americans, when compared with their Caucasian counterparts, with poorer outcomes in women, especially those of lower socioeconomic status.[53–55] The CVD mortality rate for indigenous women in Canada is 53% higher than in non-indigenous women,[56] and the social, economic, and political inequalities they experience contribute to an increased risk of CVD.[57]

Women with disabilities may have more difficulty distinguishing cardiac symptoms from those related to their

disability; this may influence the time between symptom onset and access to medical care. Adjusted for age, women with physical disabilities have a higher odds ratio for CVD (odds ratio, 6; 95% CI, 5.2–8.4) yet are less likely to receive preventive or urgent care[58] compared with women without disabilities.

Knowledge and Awareness of CVD Risk

Most women in Canada are unaware of CVD symptoms, risk factors, and their own risk status.[59] A recent (2017) national survey of 2000 women in Canada found low rates of CVD risk awareness that varied by age, race and ethnicity, and place of residence.[3] Overall, 28% knew that heart disease and stroke were the leading cause of death in women worldwide; 48% knew that 9 of 10 women have at least one risk factor for CVD. Among women aged 19 to 29 years, 37% believed that heart disease could be different between women and men, compared with 67% of women aged 50 to 69 years.[59]

Knowledge of CVD mortality and risks is greater among urban women compared with nonurban women.[60] Those living in remote and sparsely populated areas have fewer family physician visits, less lipid screening, poorer blood pressure control, and lower use of statins compared with urban residents[61]; and it can be postulated that differences in exposure to CVD-related healthcare services in remote, nonurban areas may contribute to the lower rates of awareness. These findings underscore the unmet opportunities for patient education and intervention for risk and prevention of heart disease.

Presentation (Symptoms)

Clinical presentation and characteristics of IHD between the sexes can differ. Women are more likely to present with non–ST-segment–elevation myocardial infarction (NSTEMI) and with a varied pattern and distribution of symptoms, creating challenges for healthcare providers and women themselves to interpret symptoms as cardiac specific.[62,63]

Compared with men, women are more likely to develop angina as their first CVD manifestation (47% versus 32%) and less likely to present with an acute MI (6% versus 10%). Sex differences in the clinical presentation of IHD are more pronounced in women aged <45 years with acute MI, who are more likely to present with chest pain equivalents and have higher in-hospital 30-day mortality; these sex differences are not as pronounced in women aged >65 years.[64]

Although most women report central chest pain during an ACS, they may describe it as tightness, pressure, or burning, and it is frequently accompanied by nonchest symptoms, such as dyspnea, fatigue, weakness, nausea, and discomfort in the upper back, shoulder, jaw, or arm. Defining chest pain as typical, atypical, and noncardiac, according to its relation to exertion, rest, or emotional stress, is derived from predominantly male cohorts and is less predictive of obstructive coronary artery disease (CAD) in women, especially those aged <65 years.

Pathophysiological Characteristics

IHD: Atherosclerotic/Obstructive

Sex-specific pathophysiologic mechanisms exist in the development of coronary atherosclerosis. Women who present with obstructive atherosclerotic CAD are typically older than men who present with the same condition, and they have multiple comorbid conditions and cardiovascular risk factors. In most women with ACS, the underlying mechanism is similar to men because of the formation of thrombus caused by a rupture of atherosclerotic plaque.[65] However, women, especially younger women, are more likely to present with plaque erosion, where a discontinuation of the endothelium without evidence of fibrous cap plaque rupture is identified.[65]

Sex differences in atherosclerosis formation and plaque instability are not completely understood. Estrogen may prevent atherosclerotic development through decreased inflammatory activation, low-density lipoprotein oxidation and binding, and increased vasodilation,[50] potentially explaining the lower prevalence of obstructive atherosclerotic IHD and plaque rupture in premenopausal women.[35] Conversely, estrogen may aggravate inflammatory activation and thrombosis in postmenopausal women with established atherosclerosis, which may explain the paradoxical effects observed in secondary prevention trials of menopausal hormone therapy.[66]

IHD: Nonatherosclerotic/Nonobstructive

Plaque erosion, coronary microvascular dysfunction, coronary vasospasm, SCAD, and microthromboembolism represent potential causes of ischemia with no atherosclerotic obstruction (ie, <50% stenosis) of the coronary arteries[67] or, in the presence of an ACS, MI with no obstructive coronary arteries, which is at least twice as prevalent in women compared with men.[68] Recent updates to the fourth universal definition of MI include MI with no obstructive coronary arteries as a new category of type 2 MI. More than half of women with ischemia with no atherosclerotic obstruction (ie, <50% stenosis) of the coronary arteries have coronary microvascular dysfunction, which is associated with traditional risk factors, including diabetes mellitus, hypertension, dyslipidemia, and smoking, as well as sex-related risk factors, including autoimmune disease and breast cancer therapies.[67,68]

Epicardial coronary vasospasm, more often seen in women, is thought to be caused by vascular smooth muscle hyperreactivity, endothelial dysfunction, and autonomic nervous system dysfunction.[69]

SCAD is an increasingly observed cause of ACS (estimated at 1%–4% of all MIs in women) that primarily affects younger women, most of whom have few or no traditional risk factors. SCAD is caused by the spontaneous separation of the coronary arterial wall, creating an intramural hematoma that narrows and/or occludes the coronary lumen and requires angiography for diagnosis. SCAD accounts for up to 35% of MIs in women aged ≤50 years, and it is the most common cause of pregnancy-associated MI (43%).[70] In a multicenter, prospective, observational study of patients with nonatherosclerotic SCAD presenting acutely from 22 centers in North America (with most in Canada), 88.5% were women (55% postmenopausal) and the mean age was 51.8 years.[71] SCAD associations with female sex, pregnancy, physical and emotional stress, and concurrent systemic arteriopathies, particularly fibromuscular dysplasia, highlight the differences in clinical characteristics of SCAD compared with atherosclerotic disease.[70]

HF With Reduced Ejection Fraction

Approximately 40% of patients having HF with reduced ejection fraction, defined by left ventricular ejection fraction ≤40%, are women.[72] They are older at diagnosis and live longer with the condition, but have more severe symptoms, more physical limitations (reduced 6-minute walk distance), greater prevalence of anxiety and depression, and poorer quality of life than men.[72,73] They are also more often obese and have a higher prevalence of hypertension, VHD, and nonischemic cardiomyopathy than men and are less likely than men to smoke, consume alcohol, or have preexisting CAD, AF, MI, or stroke.[72] Women with HF with reduced ejection fraction have more strokes than men (hazard ratio, 1.31; 95% CI, 1.07–1.59), which may be a consequence of significantly lower anticoagulation rates for the management of AF (26.7% in women versus 32.4% in men) and higher prevalence of hypertension (70.6% in women versus 65.5% in men).[72]

HF With Preserved Ejection Fraction

After adjusting for age and other risk factors, the risk of HF with preserved (left ventricular ejection fraction ≥50%) ejection fraction is fairly similar in men and women, although the risk of HF with preserved ejection fraction increases sharply with age; and associated comorbidities of hypertension, obesity, and CAD[74] become more impactful in women as they generally live longer than men. Women with HF with preserved ejection fraction may present differently from men, showing cognitive impairment, delirium, nausea, abdominal discomfort, oliguria, anorexia, and cyanosis.[75]

Transthoracic echocardiography is an essential imaging modality for HF assessment in women, to determine left ventricular ejection fraction, left ventricular mass, left atrium size, diastolic function, and presence of comorbid valvular disease, with normative sex-based values for echocardiographic measures of chamber volumes to guide diagnoses.[75]

Cardiomyopathies

Stress cardiomyopathy (Takotsubo syndrome) is an ACS mimicker that occurs primarily (90%) in postmenopausal women and is characterized by short-term onset of chest pain, positive cardiac enzymes, and ECG changes in the absence of obstructive CAD, often in response to an emotional or physical trigger. It may be associated with HF symptoms, ranging from dyspnea to cardiogenic shock.[76]

Peripartum cardiomyopathy occurs toward the end of pregnancy or in the postpartum period in women presenting with signs and symptoms of HF (left ventricular ejection fraction <45%), in the absence of other causes of HF.[77] Risk factors for developing peripartum cardiomyopathy include multiparity, twin pregnancies, black ethnicity, and advanced maternal age.[78]

Although myocarditis is more common in men, there are sex differences.[79] Women generally resolve infections and repair damage without high levels of inflammation or long-lasting damage. Women may be more susceptible to certain types of myocarditis, such as autoimmune myocarditis, which may be hormonally mediated.

Valvular Heart Disease

Almost half (48%) of patients with VHD are women. Sex specificities have been observed for aortic and mitral valve disease. Women with severe aortic stenosis have less aortic valve calcification but more fibrosis than men; mechanisms are thought to be mediated through sex hormone effects on calcification of interstitial cells.[80]

Women are more likely to present with rheumatic mitral VHD than men.[81] Again, this is thought to be modulated by differential sex hormone effects. Mitral valve prolapse is diagnosed more frequently in women, who present with generalized myxomatous degenerative leaflet thickening but less often with flail leaflets than men.[82] Posterior leaflet prolapse, which results in more successful surgical repair, occurs less frequently in women.[82] Mortality after mitral valve surgery is similar in men and women[82]; however, women are more likely to present with postoperative HF, which may be attributable to more advanced disease on presentation.

Arrhythmias

Sex differences in cardiac electrophysiological characteristics have been noted for over a century, when researchers first

found that women had a longer length of systole and a longer QT segment than men.[83]

Sex differences in arrhythmias may be related to sex hormones. The normally occurring increase in progesterone and decrease in estrogen levels during the menstrual cycle correspond to increased frequency, symptomatic burden, and duration of supraventricular tachycardia in women. Sick sinus syndrome, supraventricular tachycardia (especially atrioventricular nodal reentry tachycardia), and postural orthostatic tachycardia syndrome are all more common in women. Until the age of 75 years, AF is more common in men, but after the age of 75 years, most AF occurs in women, with concomitant higher mortality rates.

AF in women is typically associated with obesity and VHD, whereas AF in men is more often associated with IHD. Women tend to be more symptomatic with AF and have a higher stroke risk, higher recurrence rate, and more complications than men.[84] However, other than a few studies of supraventricular tachycardia (SVT), most prospective trials and studies continue to rely on data obtained from a minority of female subjects; and although differences in the incidence, characteristics, and treatment outcomes are clear, there is an inadequate understanding as to why these differences exist.[83]

Vascular Disease

Despite the lower likelihood of developing aortopathy, women with thoracic aortic aneurysms have faster aneurysm expansion, are 3 times more likely to dissect (especially at smaller aneurysm sizes), and are 40% more likely to die than men with thoracic aortic aneurysms.[85,86] Similarly, women with abdominal aortic aneurysm experience more rapid aneurysm growth and higher risk of abdominal aortic aneurysm rupture at relatively smaller aneurysm sizes compared with men. Women are less likely than men to be referred for abdominal aortic aneurysm repair, and are more likely to experience surgical complications after repair.[87] A potential explanation for these differences lies in hormonal, molecular, and hemodynamic differences between women and men, but they are not currently understood.

Similar to other atherosclerotic vascular disease, peripheral artery disease (PAD) tends to develop 1 to 2 decades later in women compared with men. Risk factors for PAD are largely similar for both sexes, except that hypertensive disorders of pregnancy increase women's future risk of PAD by 3-fold.[88] Women with PAD are more likely than men to be asymptomatic or have atypical leg symptoms. Conversely, once PAD manifests clinically, women have more complex disease,[89] have greater functional impairment, and, perhaps partially as a result, are more likely to be depressed than men. From a diagnostic perspective, although it has been reported that women have a slightly lower ankle-brachial index than men, this does not appear to affect diagnostic accuracy.[90] The sensitivity and specificity of advanced anatomical imaging techniques does not appear to be different between men and women.[90]

Stroke

Although the overall incidence of stroke is higher in men, stroke incidence in women increases sharply after the age of 75 years, to rates exceeding those observed in men, with higher age-specific mortality, greater stroke severity, increased likelihood of stroke-related disability, reduced quality of life, increased levels of poststroke depression, and higher rates of institutionalization compared with male stroke survivors.[91,92]

Hypertension and AF are more frequent among women with stroke; AF is a major preventable cardiac cause of stroke and the risk is twice as high in women compared with men.[93]

Diagnosis of IHD

Acute Coronary Syndromes: As for men, the initial tests for women presenting with a possible ACS are an ECG and cardiac biomarkers to determine the need for diagnostic imaging. However, women are less likely than men to receive care within benchmark times for electrocardiography (≤10 minutes: 29% versus 38%; P=0.02).[94]

In the clinical setting of an ACS, the preferred diagnostic/therapeutic imaging is cardiac catheterization for both women and men. However, evidence suggests that underdiagnosis of ACS in women leads to sex- and gender-based differences in referral for cardiac catheterization.[95–97] Of those women with ACS undergoing cardiac catheterization, ≈15% to 20% have no evidence of obstructive CAD (ie, have MI with no obstructive coronary arteries).[68]

Chronic Stable IHD: Treadmill testing is the most common noninvasive evaluation for suspected ischemia; however, its diagnostic value is limited in women compared with men by lower ranges of sensitivity (range, 31%–71%) and specificity (range, 66%–86%).[98] Despite lower accuracy in women, exercise treadmill testing demonstrates similar negative predictive value in women and men, and, in the presence of a normal resting ECG, is recommended as a first-line diagnostic test for women and men to rule out IHD.[98,99] In the absence of a normal resting ECG, an inability to exercise adequately (>5 metabolic equivalents), or the presence of known IHD, stress imaging is recommended using echocardiography or nuclear techniques.

Exercise stress echocardiography can provide additional information on systolic and diastolic function, pulmonary hypertension, pericardial effusion, and VHD; sensitivity (81%) and specificity (86%) for detection of IHD have been reported in women.[99] Pharmacologic dobutamine stress echocardiography

is recommended for women who are unable to perform exercise, with similar accuracy.[99] Normal stress echocardiography results are associated with a low risk of cardiac events in women, whereas abnormal test results are predictive of CVD.[99]

Similarly, gated myocardial perfusion single-photon emission computed tomography can be done with exercise or pharmacologic (vasodilator or dobutamine) stress with sensitivity (80%–91%) and specificity (64%–91%) for detection of IHD in women.[99] Abnormal perfusion is predictive of adverse cardiac events in women, and severe abnormalities on pharmacological stress single-photon emission computed tomography testing are predictive of annual cardiovascular mortality in women with (8.5%/year) and without (6.1%/year) diabetes mellitus.[99]

Stress myocardial perfusion imaging with positron emission tomography improves spatial resolution and image quality in women, especially those who are obese.[99] Sensitivity (92%) and specificity (85%) are higher than with single-photon emission computed tomography.[99]

Stress (vasodilator) cardiac magnetic resonance imaging allows for assessment of stress-induced wall-motion abnormalities, structural abnormalities, systolic dysfunction, myocardial scarring, and fibrosis, with higher specificity (91% versus 82%) and similar sensitivity for the detection of obstructive CAD in women compared with men[99] and can evaluate subendocardial perfusion qualitatively, which is of particular interest in women with angina and no obstructive CAD.[99,100]

Treatment

Pharmacological Therapy

Pharmacokinetics and pharmacodynamics

There are multifactorial sex differences in the pharmacokinetics (related to absorption, distribution, metabolism, and excretion) and pharmacodynamics (related to subcutaneous and body fat content, gastric enzymes, transporter proteins, body mass index, plasma volume, and body water) of drugs used to treat CVD.[101]

Recent regulatory changes in Canada have advanced the inclusion of women in clinical trials and now require sex-specific analyses of clinical trial results; however, there is still significant variability in the recruitment of women and in sex-specific reporting in drug treatment studies. Although women are better represented in drug trials submitted to the US Food and Drug Administration for hypertension and AF, their representation in drug trials for HF, IHD, and ACS is below the participation/prevalence ratio deemed appropriate.[77] The low enrollment of women appears to be caused by gender-based issues (eg, familial responsibilities, cultural and socioeconomic barriers, difficulty accessing the study site, and concerns about trial risks) rather than inclusion or exclusion criteria.[77]

Acute coronary syndrome

Women do not receive recommended pharmacologic treatment during an ACS as often as men, and they have worse clinical outcomes.[35] In the short-term setting, there appear to be sex-specific differences in the efficacy of standard treatments for various presentations of ACS. For STEMI, women have more favorable outcomes with percutaneous coronary intervention (PCI) compared with thrombolytic therapy, and similarly benefit more from an early invasive strategy in the setting of an NSTEMI, but only if at high risk.[102,103]

Anticoagulants (unfractionated heparin, low-molecular-weight heparins, and bivalirudin) and oral antiplatelet (P2Y12 receptor inhibitor) agents have been shown to reduce adverse outcomes in women and men with ACS who have undergone PCI, although the bleeding risk of thrombolytic, anticoagulant, and antiplatelet therapy is higher in women.[104] This may be caused by sex-related differences in body surface area, pharmacodynamics, and drug metabolism; weight and renal dose adjustments must be considered. In premenopausal women who are still menstruating, antiplatelet therapy may significantly increase menstrual bleeding.

The long-term benefits of aspirin, β blockers, angiotensin-converting enzyme inhibitors, and statins after an MI are similar in women and men, with risk reductions for major adverse cardiac events in the range of 20% to 30%.[35] However, women are 10% to 15% less likely to be treated acutely or discharged from hospital on evidence-based therapy for ACS.[102,103]

Menopausal hormone therapy is associated with an increased incidence of recurrent infarction and should not be administered for secondary prevention of coronary events. For women receiving menopausal hormone therapy at the time of their ACS, it is recommended that it be discontinued.[102,103]

Chronic stable IHD

The Canadian Cardiovascular Society guidelines for the pharmaceutical management of patients with stable IHD recommend lifestyle interventional therapies for all men and women. When indicated, both women and men should be managed on a combination of evidence-based drugs, including aspirin, statins, βblockers, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, digoxin, diuretics, and antithrombotic drugs. Although CVD drugs have, for the most part, been tested in clinical trials that were underpowered for sex-specific analyses, experience in using these drugs to treat chronic conditions indicates sex differences (Table 6).[78,105–116]

Interventional, Surgical, and Device Therapy

Percutaneous coronary intervention

In women diagnosed with STEMI, primary PCI is associated with lower major adverse cardiovascular events, including target revascularization, than in those who do not undergo

Table 6. Sex Differences for Pharmacologic Therapy for IHD

Treatment	Sex Differences	Pregnancy
ACE inhibitors	• Women are 1.7 times more likely to be ACE inhibitor intolerant.[105]	• ACE inhibitors and ARBs are pregnancy category C (animal studies have shown an adverse effect on the fetus) for the first trimester of pregnancy and are category D (human fetal risk has been shown) during the second and third trimesters[78]
ARBs	• Maximum serum concentrations (given the same dosage) of losartan and telmisartan are 2 times higher in women than in men.[106] • No sex-specific restrictions for ARBs, except for pregnant and lactating women[107] (see box below on pregnancy).	
Aspirin	• Platelet inhibition effect of aspirin varies in women and men; the underlying reasons are unclear.[108]	• Daily low-dose aspirin use in pregnancy is recommended for women at high risk of preeclampsia.[109] • It is considered safe and is associated with a low likelihood of serious maternal or fetal complications or both.
β Blockers	• Despite the beneficial effect of β blockers on cardiac workload and myocardial oxygen demand,[110] women are less likely to receive treatment with β blockers than men.[111,112]	• β Blockers are among list of first-line antihypertensive monotherapies for use during pregnancy.[113]
Statins	• In primary and secondary prevention trials, women and men achieve equal benefit from statins in reducing recurrent CVD events.[114] • Women taking statins may be at a higher risk of diabetesmellitus[115] and statin-induced myotoxicity.[114]	• Statin therapy during pregnancy for LDL-C reduction is reported to be safe for mother and fetus.[116]

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CVD, cardiovascular disease; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol.

PCI.[35] Women who undergo PCI in this setting experience a lower risk of major bleeding, including intracranial bleeding, and lower mortality, compared with fibrinolytic therapy.[35] However, variables related to sex, including time to presentation, time to diagnosis, and door-to-device time, are longer in women, and may contribute to excess mortality compared with men.[117] Protocolized diagnosis of STEMI may help reduce this gap and improve prompt referral to the cardiac catheterization laboratory for PCI in women.[118]

In women presenting with NSTEMI and unstable angina with high-risk features, including positive troponin, early invasive stratification by coronary angiography with intent to perform revascularization is recommended (class I recommendation).[103] However, a population-based cohort study of hospitalized patients with NSTEMI/unstable angina in Canada reported that compared with men, women treated with coronary revascularization had a higher risk for recurrent cardiovascular events, bleeding, and vascular and renal complications.[35,103,119] Drug-eluting stents are safer and more effective than bare metal stents and should be considered as the stent of choice when stenting large coronary arteries in women.[120]

Coronary artery bypass grafting

The Canadian Cardiovascular Society position statement[121] on revascularization for multivessel IHD recommends coronary artery bypass grafting (CABG) for all patients who are acceptable surgical candidates and who have multivessel IHD and diabetes mellitus, as well as for those with complex multivessel IHD (strong recommendation, high-quality evidence).

However, although subgroup analysis by sex is not significant, there is a trend toward greater mortality in women than men, which may have been statistically attenuated because of the low proportion of women in the

Table 7. Barriers to Participation by Women in Cardiac Rehabilitation/Secondary Prevention Programs

Type of Barrier	Examples
Financial	• Low income • Transportation issues (cost and time) • Medical insurance coverage issues
Social	• Racial/ethnic minority • Family responsibilities and stressors • Low education levels
Lifestyle	• Smoking • Physical inactivity
Comorbidities	• Obesity • Diabetes mellitus • Previous MI • Other health issues or beliefs
Institutional	• Limited physician referrals • Long waiting lists • Hours of operation that conflict with work schedules • Location of service

MI indicates myocardial infarction.

Table 8. Recommended Actions to Address Knowledge and Care Gaps for Women and CVD

Gaps	Recommended Actions
Under-aware	• Healthcare institutions, nonprofit organizations, and patient partners should create positive environments and encourage open dialogue with women and men to help them become familiar with their risks, similarities, and differences. • Research funders, including nonprofit and government funding agencies, and researchers should play an active role in knowledge translation and ensuring new research findings are made accessible beyond the research community.
Under-diagnosed and under-treated	• Universities and healthcare institutions should train researchers and healthcare providers at all career stages (undergraduate, graduate, and postgraduate) on sex- and gender-based differences in cardiovascular health and disease as well as analysis and reporting. • Healthcare systems should identify strategies to accelerate the implementation of sex- and gender-specific diagnosis and treatment as new evidence becomes available. • Research institutes, funders, healthcare systems, academic institutions, professional societies and organizations, and nonprofit organizations should focus on translating knowledge into clinical practice, to make emerging sex- and gender-specific therapies and interventions accessible to women. • Governments should develop systems of accountability to ensure sex and gender equity is applied to cardiovascular care and practices.
Under-supported	• Research institutes, funders, healthcare systems, academic institutions, professional societies and organizations, and nonprofit organizations should work with patient partners to better understand barriers to women's ability to adhere to recovery support programs, such as cardiac rehabilitation. • Healthcare institutions, nonprofit organizations, and patient-led support groups should work together to boost knowledge and awareness of risk factors and CVD management that meet the needs of women at all stages of life.
Under-researched	Funders of CVD research should: • Invest in sex- and gender-based analysis and research training, and in building capacity in basic biomedical, clinical, health systems, and population health, to properly design and conduct sex- and gender-based analysis research. • Adopt policies that require researchers to collect, analyze, and report data by sex and gender. • Encourage and support research into understanding sex- and gender-based differences in cardiovascular physiological and pathophysiological characteristics through focused and directed requests in grant application. • Develop strategies to understand women's hesitancy to participate in research and clinical trials and to break down barriers to adopting sex- and gender-based analyses.

CVD indicates cardiovascular disease.

randomized controlled trials.[122] Female sex is a known risk factor for early in-hospital[123] and late mortality[124] after CABG. Compared with men, women undergoing CABG have worse preoperative risk profiles, including older age, more comorbid conditions (eg, diabetes mellitus, respiratory disease, HF, and hypertension), more urgent or emergent surgery, less extensive disease requiring less revascularization, and shorter cross-clamp times. In a recent study from Ontario in Canada, women experienced higher rates of mortality than men after CABG and combined coronary artery bypass/mitral valve surgery, and mortality risk factors differed by sex. Smaller body size and coronary vessels in women have also been attributed to higher risk.[123] The survival benefits from using bilateral internal mammary artery grafts are well established, but predominantly in men, whereas single internal mammary artery grafting is associated with better survival in women and men. Bilateral grafting shows improved late survival in both sexes, but women are less likely to receive this procedure.

Women experience more postoperative complications after CABG, such as kidney failure, neurological complications, and postoperative MI. They also have a more difficult recovery with less improvement in physical functioning and more depressive symptoms.[123]

Significant risk factors for post-CABG readmission to short-term care include female sex, prolonged length of stay, in-hospital complications, and short-term presentation of MI.[125]

Cardiac implantable electronic devices

Evidence on cardiac implantable electronic devices is predominantly available in retrospective, observational, and registry studies in which women are mostly underrepresented.

Sick sinus syndrome and AF with bradyarrhythmias are the main indications for permanent pacemaker implantation in women,[126] whereas in men it is atrioventricular block. There are conflicting reports on the influence of sex on the selection of cardiac pacemakers and the impact on quality of life and functional status. Complications, such as pneumothorax and pocket hematoma, are more prevalent in women and may be related to smaller body size, vessel diameter, and thinner right ventricle wall,[127] whereas hospitalizations for device-related infections are more common in men. Sex may impact long-term outcomes after device insertion; a 30-year follow-up

study found women survived longer than men despite a higher mean age at the time of procedure.[128]

Implantable cardioverters-defibrillators (ICDs) are the recommended treatment for primary prevention (patients at risk for ventricular tachyarrhythmias) and secondary prevention (patients who have survived a life-threatening arrhythmia or prior sudden cardiac arrest) in women and men.[129] Women and men experience similar clinical benefits from ICDs for secondary prevention, especially at an older age. However, the findings for primary prevention are less clear; a meta-analysis of 6 randomized controlled trials, including DANISH (Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality), showed that women did not obtain significant survival benefit from primary preventive ICDs compared with men.[130] There is a clear underrepresentation of women in clinical trials of ICD therapy (8%–32%)[131,132] and registries. To date, studies have not been powered to detect sex-specific differences and reported interactions by sex have been in subgroup analyses.

Cardiac resynchronization therapy (CRT) is the standard of care for refractory HF (class I recommendation).[129] CRT may confer greater benefits on women than men in the setting of nonischemic cardiomyopathy and left bundle branch block: subgroup analysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) identified women as extraordinary responders to CRT, with a 72% reduction in all-cause mortality and greater reduction in left atrial and ventricular volumes at the cost of significantly higher device-related adverse events compared with men (10.5% versus 7.9%).[133,134] Women have a shorter baseline QRS duration than men, with relatively more dyssynchrony for any prolonged QRS duration, which may contribute to a better outcome with CRT.[135] However, sex-specific, stricter QRS duration criteria recommendations (QRS duration ≥140 ms for men and ≥130 ms for women) have been evaluated, with no significant difference in echocardiographic response to CRT between men and women at 12-month follow-up.[136]

Aortic valve repair and replacement

Guidelines to manage patients with stenotic VHD provide no sex-specific recommendations, although sex-specific evaluations and outcomes have been reported. Low flow rate in aortic stenosis, despite a normal ejection fraction (ie, paradoxical low flow), is reportedly higher in women.[137] The impact of low flow reduces aortic valve velocity and gradient despite severe aortic stenosis, thus underestimating aortic stenosis severity and creating a dilemma in clinical management, for which sex-specific multimodality imaging approach is recommended. The use of multidetector-computed tomography has been validated to measure aortic valve calcification (Agatston method), with sex-specific thresholds identifying severe aortic stenosis as ≥1200 Angstorm Unit (AU) in women and ≥2000 AU in men.[138] When aortic valve replacement is required, transcatheter aortic valve replacement (TAVR) may be preferred to surgical aortic valve replacement in women, given that:

1. TAVR may be better for low flow patients, with evidence of lower operative mortality[139];
2. Women are more prone to prothesis/patient mismatch, which is less prevalent after TAVR[140]; and
3. Women at intermediate and high risk enrolled in the WIN-TAVI (Women's International Transcatheter Aortic Valve Implantation) all-female registry had a lower incidence of early mortality and stroke.[141]

Finally, in a multicenter randomized controlled trial of high-risk patients with aortic stenosis, sex was the only subgroup in which there was significant interaction with treatment, with a trend toward superiority of TAVR over surgical aortic valve replacement in women.[142] To date, randomized controlled trials comparing TAVR with surgical aortic valve replacement have not stratified randomization by sex.

Cardiac Rehabilitation, Peer Support, Long-Term Management, and Lifestyle

Cardiac rehabilitation/secondary prevention is a multifaceted risk reduction program (class IA recommendation) for patients with CVD. In Canada, although referral is the sole requirement for enrollment in CP/SP, women are less likely to be referred[143] and, once they are referred, are 36% less likely to participate than men.[143,144] Women may prefer gender-tailored or women-only cardiac rehabilitation programs; some trials show greater adherence and improved mental health outcomes compared with traditional coed programs.[145,146]

Traditional cardiac rehabilitation/secondary prevention programs may not meet the recovery needs of all women. Barriers to women's cardiac rehabilitation/secondary prevention participation occur across referral, enrollment, completion, and adherence[144,147] (Table 7).

Self-management programs have been developed to allow women to take an active role in managing CVD. Online health tools that address cardiac pain, weight management, and physical activity, as well as peer support and social media, may motivate healthy behaviors, reduce symptoms, and improve quality of life, but definitive research is lacking.

Future Directions

It will take a comprehensive multilevel commitment and widespread action to achieve sex and gender equity for women's cardiovascular health to correct the glaring "unders" of CVD in women: under-aware, under-diagnosed, under-treated, under-supported, and under-researched.

Action is needed on multiple fronts, including ongoing and expanded targeted research to generate sex- and gender-specific evidence, translation of evidence into clinical guidelines, continuous training of healthcare providers to implement guidelines, consistent public health policies, and effective use of conventional and social media messaging to boost overall awareness. Recommendations for action are summarized in Table 8.

Conclusions

CVD continues to be one of the greatest noncommunicable health threats facing women today. This collaborative comprehensive review from the CWHHA and HSFC: presents evidence on the status of CVD in women; explores the extent to which CVD in women is under-researched, under-recognized, underdiagnosed, under-treated, and under-supported; and outlines recommendations to improve cardiovascular outcomes in women. The issues described in this review are contributing to the continued ranking of CVD as a leading cause of death for women in Canada and are increasing the burden on already overloaded healthcare systems. Further compounding the matter are knowledge and awareness gaps among the public and healthcare providers. Strategies to intensify and support sex- and gender-based analysis in research, and to translate analysis into widespread knowledge exchange, are vital, especially as new evidence and discoveries emerge.

The sex-specific pathophysiological characteristics of CVD remain unexplained, and the underrepresentation of women in CVD research is a barrier to generating knowledge and developing clinical practice guidelines. Women-specific efficacy and adverse events have not been defined, and, although CVD diagnostic tests increasingly recognize sex-specific differences, explanations for these differences are lacking. Meaningful thresholds are not validated, and sex-specific variations in procedural and pharmacologic treatments for CVD are not fully understood. Finally, there are socioeconomic, demographic, cultural, racial, and ethnicity factors that disadvantage women, reducing their adherence to therapies and limiting their participation in research and clinical trials.

The authors' intent is that this comprehensive review will serve as a foundation and blueprint to make the necessary concerted and sustained actions to transform women's cardiovascular health in Canada. We must wisely use our finite resources to address these urgent CVD issues that impact more than half of our nation's population.

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Key Words: cardiovascular disease • women • risk factors • treatment • sex • gender

Supplemental Material

Data S1

CVD refers to diseases, disorders, syndromes and conditions that affect the heart and blood vessels. Vital statistics data from Statistics Canada data were extracted using the International Classification of Diseases, 10th revision codes (Supplemental Table 1). These data were then used to calculate the number of CVD deaths and the proportion of women in Canada with CVD deaths between 2000 and 2016.

Administrative hospitalization data from April 1 2016 to March 31 2017 were obtained from the Canadian Institute for Health Information Discharge Abstract Database and National Ambulatory Care Reporting System. Hospitalizations for all individuals 0 to 105 years of age were included in this retrospective population-level cohort study. The type of hospitalization was identified using the International Classification of Diseases, 10th revision (ICD-10-CA) diagnostic coding standards (Supplemental Table 2) for the “most responsible diagnosis”.

Population data for the year 2016 were obtained from Statistics Canada, Census of Population, 1851 to 2016. Statistics Canada, Population Projections for Canada (2013 to 2063). These data were used in Supplemental Table 4 for comparison of prevalence of CVD by provinces and territories.

Supplemental Tables

Table S1. International Classification of Diseases, 10th Revision, (ICD-10-CA): Codes used to extract mortality data from Statistics Canada vital statistics.

Description	ICD-10-CA diagnosis codes
Heart failure	I50
Atrioventricular and left-bundle branch block	I44
Other conduction disorders	I45
Cardiac arrest	I46
Paroxysmal tachycardia	I47
Atrial fibrillation	I48
Other cardiac arrhythmias	I49
Angina pectoris	I20
Acute myocardial infarction	I21
Subsequent myocardial infarction	I22
Other acute ischemic heart disease	I24
Chronic ischemic heart disease	I25
Abnormal result of cardiovascular function study, unspecified	R94.30
Abnormal electrocardiogram [ECG] [EKG]	R94.31
Atherosclerosis	I70
Aortic aneurysm and dissections	I71
Other aneurysm	I72
Other peripheral vascular disease	I73
Arterial embolism and thrombosis	I74
Other disorders of arteries and arterioles	I77
Diseases of capillaries	I78
Rheumatic mitral valve disease	I05
Rheumatic aortic valve disease	I06
Rheumatic tricuspid valve disease	I07
Multiple valve disease	I08
Non-rheumatic mitral valve disorders	I34
Non-rheumatic aortic valve disorder	I35
Non-rheumatic tricuspid valve disorders	I36
Pulmonary valve disorders	I37
Congenital malformation of cardiac chambers and connections	Q20
Congenital malformations of cardiac septa	Q21
Congenital malformations of pulmonary and tricuspid valves	Q22
Congenital malformations of aortic and mitral valves	Q23

Other congenital malformations of heart	Q24
Congenital malformations of great arteries	Q25
Congenital malformations of great veins	Q26
Other congenital malformations of peripheral vascular system	Q27
Other congenital malformations of circulatory system	Q28
Marfan's syndrome	Q87.4
Essential hypertension	I10
Hypertensive heart disease without heart failure	I11.9
Hypertensive renal disease	I12
Hypertensive heart and renal disease	I13.1, I13.9
Secondary hypertension	I15
Rheumatic fever with heart involvement	I01
Other rheumatic heart diseases	I09
Hypertension heart disease with heart failure	I11
Hypertensive heart and renal disease with heart failure	I13.0, I13.2
Cardiomyopathy	I42
Complications and ill-defined description of heart disease	I51
Subarachnoid hemorrhage	I60
Intracerebral hemorrhage	I61
Cerebral infarction (ischemic stroke)	I63
Stroke, not specified as hemorrhage or infarction	I64
Central retinal artery occlusions (ischemic stroke)	H34
Transient cerebral ischemic attacks and related syndromes (ischemic stroke	G45.0, G45.1, G45.2, G45.3, G45.9
Transient retinal artery occlusions (ischemic stroke)	H34.2
Cerebral infarction due to cerebral venous thrombosis, nonpyogenic	I63.6
Nonpyogenic thrombosis of intracranial venous system	I67.6
Intracranial phlebitis and thrombophlebitis	G08

Table S2. International Classification of Diseases, 10th Revision: Codes used to extract hospital administrative data from Canadian Institute for Health Information National Ambulatory Care Reporting System, 2016 – 2017 and Discharge Abstract Database 2016 – 2017.

Description	ICD-10-CA diagnosis codes
Heart failure	I50
Arrhythmia	I44.1-3; I45.6, I45.9, I47, I49
Atrial fibrillation	I48
Peripheral artery disease	I73
Coronary artery and vascular disease	I21; I22; I20; I24; I25; I70; I71; I72; I73; I74; I77; I78
Myocardial infarction	I21; I22
Valvular heart disease	I34; I05; I06; I35; I07; I36; I37; I08
Congenital heart disease	Q20; Q21; Q22; Q23; Q24; Q25; Q26; Q27; Q28; Q87.4
Stroke	I60, I61, I63, I64, H34.1, G45 (excl. G45.4), I67.6, G08
Spontaneous coronary artery dissection	I25.4
Transient ischemic attack (TIA) /stroke in women with cardiovascular disease (CVD)	Stroke as MRDX (I60; I61; I62; I63; I64; H34.1; G45 (excl. G45.4); I67.6; G08); Any of the 6 main conditions in any other diagnosis position
Comorbid hypertension	I10; I11; I11.9; I12; I13 (excl. I13.0 and I13.2); I15
Comorbid diabetes mellitus	E10; E11; E12; E13; E14
History/presence of autoimmune disease	M05; M06.0; M06.1; M06.4; M06.8; M06.9; or Z82.61 as diagnosis type 3
History of breast cancer	Z85.3 as diagnosis type 3
Metabolic syndrome	E88.81; Z86.3 as diagnosis type 3
Polycystic ovary syndrome	E28.2
Hypertension/diabetes in pregnancy	O11; O13; O14; O16.0; O24

CVD = cardiovascular disease; TIA = transient ischemic attack

Literature Review Search Strategy

The following key sources were searched:

CINAHL, American Heart Association (Guidelines), Biomed Central, Canadian Cardiovascular Society (Guidelines), Cochrane Database of Systematic Reviews, Elsevier, ERIC, European Guidelines for Cardiovascular Prevention, Google Scholar, Ovid MEDLINE, PubMed, Society of Obstetrics and Gynaecology of Canada (Guidelines), Statistics Canada

Table S3. Key terms and algorithms used.

The following sex- and gender-specific search terms were used:	In combination with the following CVD specific search terms:	In combination with the following section specific terms:
("female" OR "gender "OR "sex" OR "sex bias" OR "sex difference" OR "women") (AND)	("cardiovascular" OR "cardiovascular disease" OR "cardiac" OR "CVD" OR "heart" OR "heart disease" OR "ischemic heart disease") (AND)	*Scope of the problem:* ("access" OR "blood pressure" OR "Canada" OR "morbidity" OR "mortality" OR "province" OR "region" OR "territory" OR "disparities" OR "awareness" OR "knowledge") *Co-morbidity:* ("ankylosing spondylitis" OR "autoimmune" OR "arthritis" OR "chronic kidney disease" OR "depression" OR "diabetes" OR "diabetes mellitus" OR "hypercholesterolemia" OR "hyperlipidemia" OR "hypertension" OR "inflammatory rheumatic disease" OR "mental health" OR "metabolic syndrome" OR "mood" OR "PCOS" OR "polycystic ovarian syndrome" OR "psoriatic arthritis" OR "rheumatoid" OR "syndrome x") *Risk factors:* ("anthracyclines" OR "breast cancer" OR "cardiotoxicity" OR "cholesterol" OR "contraception" OR "culture" OR "depression" OR "diabetes" OR "diagnosis" OR "diet" OR "disability" OR "disabled" OR "disadvantage" OR "disparities" OR "ethnic" OR "ethnicity" OR "First Nations" OR "genes" OR "genetics" OR "health region" OR "healthy food" OR "hormone replacement therapy" OR "hormone therapy" OR "hypertension" OR "income" OR "Indigenous" OR "inflammation" OR "Inuit" OR "kidney" OR "knowledge" OR "lifestyle" OR "lp(a)" OR "maternal health" OR "menarche" OR "menopause" OR "menstruation" OR "Metis" OR "morbidity" OR "northern" OR "obesity" OR "physical activity" OR "physical disability" OR "physical inactivity" OR "physician access" OR "post

		natal" OR "post partum" OR "poverty" OR "predictors" OR "preeclampsia" OR "pregnancy" OR "pregnancy complications" OR "prevalence" OR "psychosocial" OR "quality of life" OR "race" OR "radiation" OR "recommendation" OR "remote" OR "renal" OR "renovascular disease" OR "risk" OR "risk factors" OR "risk markers" OR "risk prediction" OR "risk profile" OR "risk score" OR "rural" OR "salary" Or "sex hormone" OR "smoking" OR "social cohesion" OR "social determinants" OR "socio-economic" OR "stress" OR "surgical menopause" OR "tobacco" OR "trastuzumab") *Presentation:* ("ACS" OR "acute coronary syndrome" OR "angina" OR "chest pain" OR "coronary artery disease" OR "heart rate" OR "myocardial infarction" OR "non-obstructive coronary artery disease" OR "symptoms") *Pathophysiology*: ("aortic regurgitation" OR "aortic stenosis" OR "arrhythmia" OR "atherosclerosis" OR "atrial fibrillation" OR "cardiomyopathy" OR "cerebral" OR "claudication" OR "cogn*" OR "coronary microvascular dysfunction" OR "coronary vasospasm" OR "critical limb ischemia" OR "dementia" OR "diastolic" OR "electrophysiology" OR "heart failure" OR "inflammation" OR "INOCA" OR "intermittent claudication" OR "ischemia" OR "lower extremity atherosclerotic disease" OR "MINOCA" OR "mitral regurgitation" OR "myocarditis" OR "non-obstructive coronary artery disease" OR "obstructive CAD" OR "outcomes" OR "pathophysiology" OR "peripheral arterial disease" OR "peripheral vascular disease" OR "reduced ejection fraction" OR "SCAD" OR "spontaneous coronary artery dissection" OR "stress cardiomyopathy" OR "stroke" OR "Takotsubo" OR "transient ischemic attack" OR "tricuspid regurgitation" OR "valve" OR "valvular heart disease" OR "vascular" OR "ventricular arrhythmia") *Diagnosis:* ("angiogram" OR "angiography" OR "diagnosis" OR "echocardiography" OR "ECG" OR "computed tomography" OR "magnetic resonance imaging" OR "imaging" OR "cardiac stress testing" OR "treadmill test" OR "SPECT" OR "stress test")

		Treatment: (“adherence” OR “aorto-coronary bypass graft surgery” OR “barriers” OR “cardiac device” OR “cardiac rehabilitation” OR “cardiac resynchronization therapy” OR “cardiac surgery” OR “chronic disease management” OR “clinical outcomes” OR “coronary artery bypass graft surgery” OR “defibrillator” OR “device” OR “drug” OR “end of life care” OR “enrollment” OR “health promotion” OR “intervention” OR “pacemaker” OR “participation” OR “PCI” OR “peer support” OR “percutaneous coronary intervention” OR “pharmacodynamic” OR “pharmacokinetics” OR “pharmacology” OR “prevention” OR “primary prevention” OR “protocols” OR “secondary prevention” OR “self care” OR “self-management” OR “social support” OR “stent” OR “strategies” OR “survival” OR “transplant”)

Table S4. Proportion of women in Canada who died from cardiovascular diseases (CVDs), 2016 – 2017

		% of women in Canada who died from CVDs in 2016 – 2017 (Calculated based on the number of women who died from CVDs in each province or territory divided by the number of women who died from CVDs in Canada)									
Province or Territory	**% of women who died from CVDs**	**IHD (includes MI)**	**MI**	**Stroke**	**Heart failure**	**Vascular disease**	**Afib**	**VHD**	**Arrhythmia**	**PAD**	**Congenital heart disease**
Newfoundland and Labrador	1.85	1.85	1.41	1.82	1.77	2.03	1.65	2.21	0.77	1.20	6.90
Prince Edward Island	0.50	0.58	0.26	0.30	0.35	1.01	0.55	0.63	-	-	-
Nova Scotia	3.45	3.34	3.08	4.10	2.47	3.72	4.68	2.52	2.31	3.61	-
New Brunswick	2.37	2.22	2.46	2.58	3.18	2.36	2.20	1.26	3.08	3.61	-
Quebec	23.30	21.01	28.12	23.07	31.63	17.91	17.91	31.55	56.92	8.43	13.79
Ontario	37.78	40.71	36.56	36.72	28.27	41.89	37.19	34.70	18.46	50.60	41.38
Manitoba	3.88	3.71	3.51	4.17	4.42	3.38	4.41	2.52	2.31	4.82	13.79
Saskatchewan	3.47	3.34	2.46	3.34	5.48	3.04	4.13	2.21	1.54	3.61	-
Alberta	9.28	10.72	7.82	7.74	8.48	11.49	8.54	6.31	3.08	7.23	10.34
British Columbia	14.01	12.40	14.24	15.93	13.78	13.18	18.73	16.09	11.54	16.87	13.79
Yukon	0.05	-	-	0.15	0.18	-	-	-	-	-	-
Northwest Territories	0.05	0.07	0.09	0.08	-	-	-	-	-	-	-
Nunavut	0.02	0.04	-	-	-	-	-	-	-	-	-
Total	100.00	100.0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Afib = atrial fibrillation; CVD = cardiovascular disease; IHD = ischemic heart disease; MI = myocardial infarction; PAD = peripheral artery disease

* Data source: Statistics Canada. 2016. Deaths by province for selected ICD-10-CA codes, custom tabulation. Received May 2019.

† Only sample sizes of five or more are shown. A sample size of fewer than five is indicated by a "-" and does not necessarily mean that no women died from CVD in that province or territory.