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

Colleen M. Norris, PhD, MSc, BScN, RN; Cindy Y. Y. Yip, PhD, MASc, PMP; Kara A. Nerenberg, MD, MSc; Marie-Annick Clavel, DVM, PhD; Christine Pacheco, MD, MSc; Heather J. A. Foulds, PhD, MSc, CEP; Marsha Hardy, MSW, RSW; Christine A. Gonsalves, PhD; Shahin Jaffer, MD, MHSc; Monica Parry, MEd, MSc, PhD, NP-Adult, CCN(C); Tracey J. F. Colella, RN, PhD; Abida Dhuikai, NP, PhD Candidate; Jasmine Grewal, MD; Jennifer A. D. Price, PhD, RN, CCN(C); Anna L. E. Levinsson, PhD; Donna Hart, BA, RSW; Paula J. Harvey, BMBS, PhD; Harriette G. C. Van Spall, MD, MPH; Hope Sariﬁ; Tara L. Sediak, MD; Sofia B. Ahmed, MD, MMSc; Carolyn Baer, MD; Thais Coutinho, MD; Jodi D. Edwards, PhD; Courtney R. Green, PhD, MSc; Amy A. Kirkham, PhD; Kajenny Srivaratharajah, MD, MSc; Sandra Dumanski, MD; Lisa Keeping-Burke, RN, PhD; Nadia Lappa, BEng; Robert D. Reid, PhD, MBA; Helen Robert, BComm; Graeme Smith, MD, PhD; Michelle Martin-Rhee, PhD; Sharon L. Mulvagh, MD, FRCPC, FACC, FASE, FAHA

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...
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 Practice6 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.
Sex- and Gender-Specific Differences in CVD Comorbidity

Certain comorbid conditions affect women differently than men (Table 4). 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. Canadian women, and especially those who are younger, are more likely than men to die within 1 year after an acute MI.

| 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                     | 5          | 5   | 10                      |
| Nova Scotia                  | 460              | 175     | 270    | 70            | 55               | 85 | 40                     | 15         | 15  | 10                      |
| New Brunswick                | 305              | 140     | 170    | 90            | 35               | 40 | 20                     | 20         | 15  | 10                      |
| 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  | 10                      |
| 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             | 1800    | 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.

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. The sex-specific impacts of selected traditional CVD risk factors are shown in Table 5.

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.
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 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.

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 cardiotoxicity.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 men24,25 • 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 diagnosis29,30; 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.

DOI: 10.1161/JAHA.119.015634
## 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 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. 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. 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.

Knowledge of CVD mortality and risks is greater among urban women compared with nonurban women. 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; 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.

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.

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. 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.

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, potentially explaining the lower prevalence of obstructive atherosclerotic IHD and plaque rupture in premenopausal women. 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.

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 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. 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.

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.
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%). 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. 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.

HF With Reduced Ejection Fraction
Approximately 40% of patients having HF with reduced ejection fraction, defined by left ventricular ejection fraction ≤40%, are women. 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. 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).

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 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. 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.

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.

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. Risk factors for developing peripartum cardiomyopathy include multiparity, twin pregnancies, black ethnicity, and advanced maternal age.

Although myocarditis is more common in men, there are sex differences. 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.

Women are more likely to present with rheumatic mitral VHD than men. 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. Posterior leaflet prolapse, which results in more successful surgical repair, occurs less frequently in women. Mortality after mitral valve surgery is similar in men and women, 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.96,99 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. Normal stress echocardiography results are associated with a low risk of cardiac events in women, whereas abnormal test results are predictive of CVD.

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.

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.

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

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 and can evaluate subendocardial perfusion qualitatively, which is of particular interest in women with angina and no obstructive CAD.

**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.

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. 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.

**Acute coronary syndrome**

Women do not receive recommended pharmacologic treatment during an ACS as often as men, and they have worse clinical outcomes. In the short-term setting, there appear to be sex-specific differences in the efficacy of standard treatments for various presentations of ACS. For ST/MI, 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.

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. 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%. However, women are 10% to 15% less likely to be treated acutely or discharged from hospital on evidence-based therapy for ACS.

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.

**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, β blockers, 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).

**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...
PCI. Women who undergo PCI in this setting experience a lower risk of major bleeding, including intracranial bleeding, and lower mortality, compared with fibrinolytic therapy. 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. Protocolized diagnosis of STEMI may help reduce this gap and improve prompt referral to the cardiac catheterization laboratory for PCI in women.

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). 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. 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.

**Coronary artery bypass grafting**

The Canadian Cardiovascular Society position statement 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 study.

### 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. | 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) |
| ARBs | Maximum serum concentrations (given the same dosage) of losartan and telmisartan are 2 times higher in women than in men. |  |
| | No sex-specific restrictions for ARBs, except for pregnant and lactating women (see box below on pregnancy). |  |
| Aspirin | Platelet inhibition effect of aspirin varies in women and men; the underlying reasons are unclear. | Daily low-dose aspirin use in pregnancy is recommended for women at high risk of preeclampsia. |
| |  | 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, women are less likely to receive treatment with β blockers than men. | β Blockers are among list of first-line antihypertensive monotherapies for use during pregnancy. |
| Statins | In primary and secondary prevention trials, women and men achieve equal benefit from statins in reducing recurrent CVD events. | Statin therapy during pregnancy for LDL-C reduction is reported to be safe for mother and fetus. |

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

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

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

MI indicates myocardial infarction.
randomized controlled trials. Female sex is a known risk factor for early in-hospital and late mortality 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. 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.

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.

**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, 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, 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{130} There is a clear underrepresentation of women in clinical trials of ICD therapy (8\%–32\%)\textsuperscript{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).\textsuperscript{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\%).\textsuperscript{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.\textsuperscript{135} However, sex-specific, stricter QRS duration criteria recommendations (QRS duration $\geq$140 ms for men and $\geq$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.\textsuperscript{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.\textsuperscript{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 $\geq$1200 Angstrom Unit (AU) in women and $\geq$2000 AU in men.\textsuperscript{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;\textsuperscript{139}
2. Women are more prone to prosthesis/patient mismatch, which is less prevalent after TAVR;\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{143} and, once they are referred, are 36\% less likely to participate than men.\textsuperscript{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.\textsuperscript{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 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, under-diagnosed, 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.

Acknowledgments
We thank Dr Louise Pilote, Dr Karin Humphries, Dr Patrice Lindsay, and Dr Martha Gulati for their scientific reviews. The authors gratefully acknowledge Sabrina Pillay, Julie-Anne Lamarche, Lisa Comber, and Dr Kerri-Anne Mullen for their coordination of this effort. We thank Dr Leigh Botly, Cindy Chiu, and Gail Williams for reference management and technical writing. The authors also gratefully acknowledge the Heart and Stroke Foundation of Canada for its contributions to this work. This article has been submitted on behalf of the Canadian Women’s Heart Health Alliance (CWHHA), a pan-Canadian network of ∼60 clinicians, scientists, allied health professionals, program administrators, and patient partners, whose aim is to develop and disseminate evidence-informed strategies to transform clinical practice and enhance collaborative action on women’s cardiovascular health in Canada. The CWHHA is powered by the Canadian Women’s Heart Health Centre at the University of Ottawa Heart Institute. Administrative data were obtained from the Canadian Institute for Health Information (CIHI) and analyzed by Heart and Stroke Foundation of Canada authors. Components of the demographic material are based on comparative data and information obtained from CIHI for the most recently available years, 2016 to 2017. However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors and not those of CIHI.

Disclosures
Dr. Kara A. Nerenberg has received grants from Heart and Stroke Canada, Heart and Stroke Foundation of Alberta, and Canadian Institutes of Health Research. Dr, Christine A. Gonsalves has received postdoctoral fellowship funding from government of Canada. Dr. Marie-Annick Clavel has received grants from Edwards Lifesciences and Medtronic. Dr. Anna L.E. Levinsson has received grants from Astra Zeneca. The remaining authors have no disclosures to report. Sharon L. Mulvagh has received research grant from GE Healthcare, a member of Novo Nordisk steering committee and a consultant of Lantheus Medical Imaging.

References
1. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Lond Engl. 2017;390:1151–1210.
2. Norris CM, Tannenbaum C, Pilote L, Wong G, Cantor WJ, McMurtry MS. Systematic incorporation of sex-specific information into clinical practice guidelines for the management of ST-segment-elevation myocardial infarction: feasibility and outcomes. J Am Heart Assoc. 2019;8:e011597. DOI: 10.1161/JAHA.118.011597.
3. Heart and Stroke Foundation of Canada. 2018 Heart report: Ms. understood. 2018. https://www.heartandstroke.ca/-/media/pdf/canda/2018-heart-month/fs_2018-heart-report_en.pdf. Accessed August 17, 2019.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotoons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Lachmann M-L, Løløgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Die I, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37:2315–2381.
5. Government of Canada, Statistics Canada. Leading causes of death, total population, by age group. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039401. Accessed November 5, 2019.
6. Garcia M, Miller VM, Gulati M, Hayes SN, Manson JE, Wenger NK, Bailey Merz CD, Bankad R, Pollak AW, Mieres J, King J, Mulvagh SL. Focused cardiovascular care for women: the need and role in clinical practice. Mayo Clin Proc. 2016;91:226–240.

7. Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology. 2013;52:2136–2148.

8. Carmina E. Metabolic syndrome in polycystic ovary syndrome. Minerva Ginecol. 2006;58:109–114.

9. Ehrmann DA, Liljenquist DR, Kasza K, Aziz R, Legro RS, Ghazzi MN. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;91:48–53.

10. Wild RA, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease in patients with chronic kidney disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer. JAMA. 2019;322:116–126.

11. Wild RA, Bartholomew MJ. The influence of body weight on lipoprotein lipids in patients with polycystic ovary syndrome. Am J Obstet Gynecol. 1988;159:423–427.

12. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2010;16:347–363.

13. Vgontzas AN, Legro RS, Bieler EG, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. J Clin Endocrinol Metab. 2001;86:517–520.

14. Tassai E, Van Cauter E, Ehrmann DA. Relationships between sleep disordered breathing and glucose metabolism in polycystic ovary syndrome. J Clin Endocrinol Metab. 2001;86:391–396.

15. Fairweather D, Frisano-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. Am J Pathol. 2008;173:600–609.

16. Mason JC, Libby P. Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions. Eur Heart J. 2015;36:482–489c.

17. Mavrogenis S, Dimitroulis T, Bucciarelli-Ducci C, Ardois S, Stifakis P, Kolovou G, Kitas G. Rheumatoid arthritis: an autoimmune disease with female preference and cardiovascular risk equivalent to diabetes mellitus: role of cardiovascular magnetic resonance. Inflamm Allergy Drug Targets. 2014;13:81–93.

18. Gernaat S, M Ho PJ, Rijnberg N, Emaus MJ, Baak LM, Hartman M, Grobbee DE, Verkooijen HM. Risk of death from cardiovascular disease following breast cancer in women: a retrospective cohort study. Breast Cancer Res Treat. 2017;164:537–555.

19. Patnak JL, Byers T, DiGiuseppe C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res BCN. 2011;13:R64.

20. Kirkham AA, Beaudry RI, Paterson DI, Mackey JR, Haykowsky MJ. Curing breast cancer and killing the heart: a novel model to explain elevated cardiovascular disease and mortality risk among women with early stage breast cancer. Prog Cardiovasc Dis. 2019;62:116–126.

21. Nitche D, Grams M, Sang Y, Black C, Cirillo M, DJurdjev O, Iseki K, Jassal SK, Kimm H, Kronenberg F, Oien CM, Levey AS, Levin A, Woodward M, Hemmеляar BR. Chronic Kidney Disease Prognosis Consortium. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. BMJ. 2013;346:f324.

22. Dehmer EW, Phadnis MA, Gunderson EP, Lewis CE, Bibbins-Domingo K, Engel J, Merz CD, Bankad R, Pollak AW, Mieres J, King J, Mulvagh SL. Focused cardiovascular care for women: the need and role in clinical practice. Mayo Clin Proc. 2016;91:226–240.

23. Carrero JJ, de Dager DJ, Verdulín M, Ravaní P, De Meester J, Hafg JF, Finne P, Holsma AJ, Pascual J, Jarraya F, Reisaeter AV, Collart F, Dekker FW, Jager KJ. Cardiovascular and noncardiovascular mortality among men and women starting dialysis. Clin J Am Soc Nephrol. 2011;6:1722–1730.

24. Albert PR. Why is depression more prevalent in women? J Psychiatry Neurosci. 2015;40:219–221.

25. Finks SW, Spencer A, Hume A. Cardiovascular disease in women. In Richardson M, Chant C, Cheng JWM, Chessman KH, Hume AL, Hutchison LC, et al., eds. Pharmacother Self-Assess Program. Vol 1. 7th ed.Lexnexa KS: Pharmacother Self-Assess Program Book; 2006:179–199.

26. Hare DL, Toukhsati SR, Johannson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. Eur Heart J. 2014;35:1365–1372.

27. Vaccarino V, Badimon L, Corti R, de Wit C, Dorobantu M, Hall A, Koller A, Marzilli M, Pries A, Bugiardini R; Working Group on Coronary Pathophysiology and Microcirculation. Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors? Position paper from the working group on coronary pathophysiology and microcirculation of the European Society of Cardiology. Cardiovasc Res. 2011;90:9–17.

28. Whang W, Kubzansky LD, Kawachi I, Rexrode KM, Kronenke CH, Glynn RJ, Garan H, Albert CM. Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses’ Health Study. J Am Coll Cardiol. 2009;53:950–958.

29. Möller-Leimkuhler AM. Higher comorbidity of depression and cardiovascular disease in women: a biopsychosocial perspective. World J Biol Psychiatry. 2010;11:922–933.

30. Shankmugasaram S, Russell KL, Kovacs AH, Stewart DE, Grace SL. Gender and sex differences in prevalence of major depression in coronary artery disease patients: a meta-analysis. Maturitas. 2012;73:305–311.

31. Malik S, Spertus JA, Reid KJ, Krumholz HM, Rumsfeld JS, Weintraub WS, Agarwal P, Santra M, Bidyasar S, Lichtman JH, Wenger NK, Vaccarino V; PREMIER Registry Investigators. Depressive symptoms after acute myocardial infarction: evidence for highest rates in younger women. Arch Intern Med. 2006;166:876–883.

32. Meijer A, Conradi HI, Bos EH, Thomsa BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. Gen Hosp Psychiatry. 2011;33:203–216.

33. Benjamin EJ, Levy D, Vaziri SM, D’Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. JAMA. 1994;271:840–844.

34. Izadnegahdar M, Singer J, Lee MK, Gao M, Thompson CR, Kopeck J, Humphries K. Are younger women fare worse? Sex differences in acute myocardial infarction hospitalization and early mortality rates over ten years. J Womens Health. 2014;23:10–17.

35. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK; American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation. 2016;133:916–947.

36. Robbaille C, Dai S, Waters C, Loukine L, Bancej C, Quach S, Ellison J, Campbell N, Tu K, Reimer K, Walker R, Smith M, Blais G, Quan H. Diagnosed hypertension in Canada: incidence, prevalence and associated mortality. Can Med Assoc J. 2012;184:E49–E56.

37. Bushnik T, Hennessey DA, McAlister FA, Manuel DG. Factors associated with hypertension control among older Canadians. Health Rep. 2010;29:3–10.

38. Janzon E, Hedblad B, Berglund G, Engstrom G. Tobacco and myocardial infarction in middle-aged women: a study of factors modifying the risk. J Intern Med. 2004;256:111–118.

39. Garcia M, Mulvagh SL, Merz CNB, Buring JE, Manson JE. Cardiovascular disease in women: clinical perspectives. Circ Res. 2016;118:1273–1293.

40. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endor Rev. 2014;5:278–316.

41. Bryan S, Walsh P. Physical activity and obesity in Canadian women. BMC Womens Health. 2004;4:56.

42. Garriguet D, Colley RC. Daily patterns of physical activity among Canadians. Health Rep. 2012;23:27–32.

43. Colley RC, Michaud I, Garriguet D. Realocating time between sleep, sedentary and active behaviours: associations with obesity and health in Canadian adults. Health Rep. 2018;29:3–13.

44. Dessi M, Noce A, Bertucci P, Manca di Villaromosa S, Zenobi R, Castagnola V, Addesso E, Di Daniele N. Atherosclerosis, dyslipidaemia, and inflammation: the significant role of polyunsaturated fatty acids. ISRN Inflamm. 2013.2013:191823.

45. Lundberg U. Stress hormones in health and illness: the roles of work and gender. Neuro Endocrinol Lett. 2001;22:321–326.
49. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, Smith GN, Cole DC, Ray JC, Redberg K, Platz. Cardiovascular disease burden, mortality and morbidity in women with a history of pregnancy complications. Circulation. 2019;139:1069–1079.

50. Barrett-Connor E. Menopause, atherosclerosis and coronary artery disease. Curr Opin Pharmacol. 2013;13:186–191.

51. Kandasamy S, Anand SS. Cardiovascular disease among women from vulnerable populations: a review. Can J Cardiol. 2018;34:450–457.

52. Fabreux GE, Leung AA, Southern DA, Knudtson ML, McWilliams JM, Ayjaniz JZ, Ghali WA. Sex, socioeconomic status, access to cardiac catheterization, and outcomes for acute coronary syndromes in the context of universal healthcare coverage. Circ Cardiovasc Qual Outcomes. 2014;7:540–549.

53. Gasevic D, Ross ES, Lear SA. Ethnic differences in cardiovascular disease risk factors: a systematic review of North American evidence. Can J Cardiol. 2015;31:1169–1179.

54. Rana A, de Souza RJ, Kandasamy S, Lear SA, Anand SS. Cardiovascular risk among South Asians living in Canada: a systematic review and meta-analysis. CMAJ Open. 2014;2:E183–E191.

55. Anand SS, Razak F, Davis AD, Jacobs R, Vuksan V, Teo K, Yusuf S. Social determinants of cardiovascular health and disease: an overview. Int J Epidemiol. 2006;35:1239–1245.

56. Tikshenra M, Wilkins R, Goedhuis N, Pennock J. Cardiovascular disease mortality among South Asians people in Canada, 1991–2001. Chronic Dis Inj Can. 2012;32:200–207.

57. Ziaabakhsh S, Pederson A, Prodan-Bhalha N, Middagh D, Jinkerson-Brass S. Women-centered and culturally responsive heart health promotion among indigenous women in Canada. Health Promot Pract. 2016;17:841–846.

58. Krah GL, Walker DK, Correa-DeAraujo R. Persons with disabilities as an unrecognized health disparity population. J Am Public Health. 2015;105:3193–3206.

59. McDonnell LA, Pipe AL, Westcott C, Perron S, Younger-Lewis D, Elias N, Tu JV, Chu A, Maclagan L, Austin PC, Johnston S, Ko DT, Cheung I, Atzema CL, Booth GL, Bhatia RS, Lee DS, Jackevicius CA, Kapral MK, Tu K, Wijeysundera HD, Desai AS, Dickstein K, Kober L, Mogensen UM, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, McMurray JJV. Differential impact of heart failure with reduced ejection fraction on men and women. J Am Coll Cardiol. 2019;73:29–40.

60. Villablanca AC, Slee C, Lianov L, Tancredi D. Outcomes of a clinic-based educational intervention for cardiovascular disease prevention by race, ethnicity, and urban/rural status. J Womens Health Larchmt. 2016;25:1174–1186.

61. Tu JV, Chu A, Maclagan L, Austin PC, Johnston S, Ko DT, Cheung I, Atzema CL, Booth GL, Bhatia RS, Lee DS, Jackevicius CA, Kapral MK, Tu K, Wijeysundera HD, Desai AS, Dickstein K, Kober L, Mogensen UM, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, McMurray JJV. Contemporary review of heart failure with reduced ejection fraction. Circ Cardiovasc Qual Outcomes. 2017;10:602–611.

62. Stewart GC, Cascino T, Richards B, Khalatabi S, Mann DL, Taddei-Peters WC, Baldwin JS, Jeffries NO, Spiro C, Stevenson LW, Aaronsen KD. Ambulatory advanced heart failure in women: a report from the REVIVAL registry. JACC Heart Fail. 2019;7:E207–E226.

63. Sunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14:591–602.

64. Ezekowitz JA, O’Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshlan SM, Legape S, McKevel RS, Moo GW, Rajda M, Swigum E, Virani SA, Zieroth A, Adeniran A, Cohen-Solal A, D’Autreux M, Des S, Estrella-Holden E, Fuentes S, Green L, Haddad H, Harkness K, Hernandez AF, Kou Z, LeBlanc MH, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 Comprehensive update of the Canadian cardiovascular society guidelines for the management of heart failure. Can J Cardiol. 2017;33:1342–1433.

65. Ghadri JR, Wittstein IS, Prasad A, Sharkey D, Dote K, Akashy Y, Camm VL, Crea F, Galiluto L, Desmet W, Yoshida T, Manfredini R, Etel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Busoncic S, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horovitz JD, Shimokawa H, Lüscher TF, Templin C. International expert consensus document on Takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J. 2018;39:2032–2046.

66. Scott PE, Unger EF, Jenkins MR, Southworth MR, McDowell TW, Geller RJ, Elahi M, Temple RJ, Woodcock J. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. J Am Coll Cardiol. 2018;71:1960–1969.

67. Regitz-Zagrosek V, Hoos-Hesselink JW, Baeursachs J, Blomström-Lundqvist C, Cifkova R, De Bonis M, Lung B, Johnson MR, Kientscher U, Kranke P, Lane IM, Morais J, Peiper FG, Pesipbetro P, Price S, Rosano GCM, Seilander U, Simoncini T, Swan L, Wannes CA, 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018;39:3165–3241.

68. Fairweather D, Cooper LT, Blauwet LA. Sex and gender differences in myocardiitis and diluted cardiomyopathy. Circ Pump. 2013;38:37–46.

69. Aggarwal SR, Clavel MA, Messika-Zeitoun D, Cuff E, Malouf J, Aryoz PA, Manikad R, Michela H, Vahanian A, Enriquez-Sarano M. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. Circ Cardiovasc Imaging. 2013;6:40–47.

70. Yavkumti S, Jellis C, Mick S, Wu Y, Gillinov AM, Mihaljevic T, Cosgrove DM, Svensson L, Cho L. Sex differences in the etiology of surgical mitral valve replacement. Ann Thorac Surg. 2009;6:419–426.

71. Mohammad SR, Clavel MA, Messika-Zeitoun D, Cuff E, Malouf J, Aryoz PA, Manikad R, Michela H, Vahanian A, Enriquez-Sarano M. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. Circ Cardiovasc Imaging. 2013;6:40–47.
86. Niemier CA, Fattori R, Mehta RH, Bichart BM, Evangelista A, Petzsch M, Cooper JV, Januzzi JL, Ince H, Sechtem U, Bosson E, Fang J, Smith DE, Isselbacher EM, Pape LA, Eagle KA. Gender-related differences in acute aortic dissection. Circulation. 2004;109:3014–3021.

87. Lo RC, Bensley RP, Hamdan AD, Winters M, Adams JE, Schermerhorn ML. Gender differences in abdominal aortic aneurysm presentation, repair, and mortality in the Vascular Study Group of New England. J Vasc Surg. 2013;57:1261–1268.e5.

88. Ray GJ, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPs): population-based retrospective cohort study. Lancet. 2005;366:1797–1803.

89. Ortmann J, Nuesch E, Traupe T, Diehn N, Baumgartner I. Gender is an independent risk factor for distribution pattern and lesion morphology in chronic critical limb ischemia. J Vasc Surg. 2012;55:98–104.

90. Aboyans V, Criqui MH, McClelland RL, Allison MA, McDermott MM, Goff DC, Manolio TA. Intrinsic contribution of gender and ethnicity to normal ankle-brachial index values: the multi-ethnic study of atherosclerosis (MESA). J Vasc Surg. 2007;45:319–327.

91. Bushnell CD, Reeves MJ, Zhao X, Pan W, Prvu-Butter J, Zimmer L, Olson D, Peterson E. Sex differences in quality of life after ischemic stroke. Neurology. 2014;82:922–931.

92. Gall SL, Tran PL, Martin K, Blizzard L, Srikanth V. Sex differences in long-term mortality in women and men who suffer from acute coronary syndromes. J Am Coll Cardiol. 2004;45:319–327.

93. Katula JA, Wijewickreme I, Dornish MD, Schwartz DC, Cooper JV, Januzzi JL, Ince H, Sechtem U, Bosson E, Fang J, Smith DE, Isselbacher EM, Pape LA, Eagle KA. Gender-related differences in acute aortic dissection. Circulation. 2004;109:3014–3021.

94. Pelletier R, Humphries KH, Shimony A, Bacon SL, Lavoie KL, Rabi D, Karp I, Isselbacher EM, Pape LA, Eagle KA. Gender-related differences in acute aortic dissection. Circulation. 2004;109:3014–3021.

95. Cooper JV, Januzzi JL, Ince H, Sechtem U, Bosson E, Fang J, Smith DE, Isselbacher EM, Pape LA, Eagle KA. Gender-related differences in acute aortic dissection. Circulation. 2004;109:3014–3021.

96. Gall SL, Tran PL, Martin K, Blizzard L, Srikanth V. Sex differences in long-term outcomes after stroke: functional outcomes, handicap, and quality of life. Stroke. 2012;43:1982–1987.

97. Emdin CA, Wong CK, Hsiao AJ, Altman DG, Peters A, Woodward M, Oudotuy AA. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. BMJ. 2016;352:h7013.

98. Pelliot R, Humphries KH, Shimony A, Bacon SL, Lavoie KL, Rabi D, Karp I, Isselbacher EM, Pape LA, Eagle KA. Gender-related differences in acute aortic dissection. Circulation. 2004;109:3014–3021.

99. Golberg CL, Pietras GD, Konstam MA, Sklerov J, Shabtai S, Wolkonsky W. The chronic phase of aortic dissection: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e362–e425.

100. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jhund P, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mulkerjea D, Peterson ED, Sabatine MS, Smalling RW, Sjostrom JI. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2014;64:e139–e228.

101. Lansky AJ, Hochman JS, Ward PA, Mintz GS, Fabunmi R, Berger PB, New G, Gersh BJ, Pietras GD, Kereiakes D, Leon MB, Mehra R, White C, Mieres JH, Moses JW, Stone GW, Jacobs AK, American College of Cardiology Foundation, American Heart Association. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. Circulation. 2005;110:940–953.

102. Mahmoodpour SH, Baranova EV, Souvaine PC, Asselbergs FW, de Boer A, Maitland-van der Zee AHH; PREDICTION-ADR consortium. Determinants of angiotensin-converting enzyme inhibitor (ACEI) intolerance and angioedema in the UK Clinical Practice Research Datalink. Br J Clin Pharmacol. 2016;82:1647–1659.

103. Issa ZH. Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. J Hum Hypertens. 2000;14(suppl 1):S73–S86.

104. Cadeddu F, Franconi F, Cassisa L, Campesi I, Pepe A, Cugusi L, Maffei S, Gallina S, Sciomer S, Mercuro G; Working Group of Gender Medicine of Italian Society of Cardiology. Arterial hypertension in the female world: pathophysiology and therapy. J Cardiovasc Med. 2016;17:229–236.

105. Wurtz M. Aspirin in coronary artery disease: an appraisal of functions and limitations. Dan Med J. 2007;54:52–51.

106. Henderson J, Witlock E, Rowland M. Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. preventive services task force. Ann Intern Med. 2014;160:695–703.

107. Ongroviczy M, Detllaff K, Jelinska A. Beta-blockers: current state of knowledge and perspectives. Mini Rev Med Chem. 2016;16:40–54.

108. Butalia S. Hypertension Canada’s 2018 guidelines for the management of hypertension in pregnancy. Can J Cardiol. 2018;34:526–531.

109. Angiolillo DJ, et al. Guidelines for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e426–e543.
Cardiology/Canadian Society of Cardiac Surgery position statement on resvascularization—multivessel coronary artery disease. Can J Cardiol. 2014;30:1482–1491.

122. Jabagi H, Tran DT, Hessian R, Gineur D, Rubens FD. Impact of gender on arterial revascularization strategies for coronary artery bypass grafting. Ann Thorac Surg. 2018;105:62–68.

123. Vaccarino V, Abramson JL, Veledar E, Weintraub WS. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. Circulation. 2002;105:1176–1181.

124. Hassan A, Chiasson M, Buch K, Hirsch GM. Women have worse long-term outcomes after coronary artery bypass grafting than men. Can J Cardiol. 2005;21:757–762.

125. Tam DY, Fang J, Tran A, Tu JV, Ko DT, Deb S, Femes SE. A clinical risk scoring tool to predict readmission after cardiac surgery: an Ontario administrative and clinical population database study. Can J Cardiol. 2018;34:1655–1664.

126. Nowak B, Misselwitz B; on behalf of the expert committee "Pacemaker." Institute of Quality Assurance Hessen, Erdogan A, Funck R, Imrich W, Israel C, Linde C, Bongiorni MG, Birgersdotter-Green U, Curtis AB, Deisenhofer I, Curtis LH, Al-Khatib SM, Shea AM, Hammill BG, Hernandez AF, Schulman KA. Do gender differences exist in pacemaker implantation? Results of an obligatory external quality control program. Europace. 2010;12:210–215.

127. Hernandez AF, Fonarow GC, Liang L, Al-Khatib SM, Curtis LH, LaBresh KA, Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, D’Onorio A, Rapacciuolo A, Savarese G, Pierantozzi A, Marenna B, Ruffa F, Campari M, Malacrida M, Stabile G. Strict criteria for left bundle branch block diagnosis do not improve response to CRT. Pacing Clin Electrophysiol. 2017;40:850–856.

128. Hachicha Z, Dumensnil JG, Bogaty P, Pibarot P. Paradoxical low flow, low gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation. 2007;115:2856–2864.

129. Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal S, Malouf J, Araoz P, Michelele H, Cuffe C, Larose E, Capoulade R, Vahanian A, Enriquez-Sarano M. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler-echocardiographic and computed tomographic study. J Am Coll Cardiol. 2013;62:2329–2338.

130. Hermann HC, Pibarot P, Huerter I, Gertz ZM, Stewart WJ, Kapadia S, Tucuz EM, Babaliaros V, Thorunari V, Szeto WT, Bavaria JE, Kodali S, Hahn RT, Williams M, Miller DC, Douglas PS, Leon MB. Predictors of mortality and outcomes of therapy in low flow severe aortic stenosis: a PARTNER trial analysis. Circulation. 2013;127:2316–2326.

131. Brunner M, Olszewski M, Geibel A, Bode C, Zehender M. Long-term survival after pacemaker implantation: prognostic importance of gender and baseline patient characteristics. Eur Heart J. 2004;25:88–95.

132. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NAM, Freedman RA, Gersh BJ, Gillinov AM, Gregoratos G, Hauer TL, Hayes DL, Hlatky MA, Hsieh HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, Tucuz EM, Babaliaros V, Thorunari V, Szeto WT, Bavaria JE, Kodali S, Hahn RT, Williams M, Miller DC, Douglas PS, Leon MB. Predictors of mortality and outcomes of therapy in low flow severe aortic stenosis: a PARTNER trial analysis. Circulation. 2013;62:2329–2338.

133. Clavel MA, Webb JG, Pibarot P, Altwegg L, Dumont É, Thompson C, De Larochellière R, Doyle D, Masson JB, Bergeron S, Bertrand OF, Rodés-Cabau J. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol. 2009;53:1883–1891.

134. Chieffo A, Petronio AS, Mehilli J, Chandrasekhar J, Sartori S, Lefèvre T, Presbitero P, Capranzano P, Tchetche D, Iadanza A, Sardella G, Van Mieghem NM, Meliga E, Dumonteil N, Fraccaro C, Trabattoni D, Mikhail GW, Sharma S, Ferrer MC, Naber C, Kievet P, Faggioni M, Snyder C, Morice MC, Mehran R. Acute and 30-day outcomes in women after TAVR: results from the WIN-TAVI (Women’s International Transcatheter Aortic Valve Implantation) Real-World Registry. JACC Cardiovasc Interv. 2016;9:1589–1600.

135. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thorunari V, Corso P, Pichard AD, Bavaria JE, Hermann HC, Aki JN, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic valve replacement in high-risk patients. N Engl J Med. 2011;364:2187–2198.

136. Colbert JD, Martin B-J, Haykowsky MJ, Hauer TL, Austford LD, Arena RA, Knudston ML, Meldrum DA, Aggarwal SG, Stone JA. Cardiac rehabilitation referral, attendance and mortality in women. Eur J Prev Cardiol. 2015;22:979–986.

137. Colella TJF, Gravely S, Marzolini S, Grace SL, Francis JA, Oh P, Scott LB. Sex bias in referral of women to outpatient cardiac rehabilitation? A meta-analysis. Eur J Prev Cardiol. 2015;22:423–441.

138. Grace SL, Turk-Adawi K, Santiago de Araujo Pio C, Alter DA. Ensuring cardiac rehabilitation access for the majority of those in need: a call to action for Canada. Can J Cardiol. 2016;32:S358–S364.

139. Beckie TM, Beckstead JW. Predicting cardiac rehabilitation attendance in a gender-tailored randomized clinical trial. J Cardiopulm Rehabil Prev. 2010;30:147–156.

140. Supervia M, Medina-Inojosa JR, Yeung C, Lopez-Jimenez F, Squires RW, Perez-Terzic CM, Brewer LC, Leth SE, Thomas RJ. Cardiac rehabilitation for women: a systematic review of barriers and solutions. Mayo Clin Proc. 2017;Mar 13 pii: 50025-6196(17)30026-5.

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

DOI: 10.1161/JAHA.119.015634

Journal of the American Heart Association

18
Supplemental Material

Data S1 Page 2
Table S1 Page 3
Table S2 Page 5
Literature Review Search Strategy and Table S3 Page 6
Table S4 Page 9
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                       |
| Condition                                                                 | Code  |
|--------------------------------------------------------------------------|-------|
| 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: ("female" OR "gender OR "sex" OR "sex bias" OR "sex difference" OR "women") | In combination with the following CVD specific search terms: ("cardiovascular" OR "cardiovascular disease" OR "cardiac" OR "CVD" OR "heart" OR "heart disease" OR "ischemic heart disease") | In combination with the following section specific terms: 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 "Mets" 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”)

7
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

(Proportion 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                        | 100.00           | 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.