Review
Canadian Women’s Heart Health Alliance

Introducing the Canadian Women’s Heart Health Alliance
ATLAS on the Epidemiology, Diagnosis, and Management of Cardiovascular Diseases in Women

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ABSTRACT
Despite a global understanding that indicators and outcomes of cardiovascular disease (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. The Canadian Women’s Heart Health Alliance (CWHHA) was established as a network of experts and advocates to develop and disseminate evidence-informed strategies to transform clinical practice and augment collaborative action on women’s cardiovascular health in Canada. As an initial project, the CWHHA membership undertook 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. This comprehensive review of the

Cardiovascular disease (CVD) is the leading cause of premature death for women in Canada. 1 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 The Canadian Women’s Heart Health Alliance (CWHHA) was established as a network of experts and advocates to develop and disseminate evidence-informed strategies to transform clinical practice and augment collaborative action on women’s cardiovascular (CV) 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. Supported by the University of Ottawa Heart Institute (UOHI), the coordinating body of the CWHHA, the CWHHA along with the

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evidence focused on the sex- and gender-specific differences in comorbidity, risk factors, disease awareness, presentation, diagnosis, and treatment across the entire spectrum of CVD. In the process of creating the review, it was recognized that the team of CWHHA experts had also assembled an expansive collection of original research articles that were synthesized into detailed chapters reporting on the present state of the evidence unique to each cardiovascular condition in women. This work comprises an “ATLAS” on the epidemiology, diagnosis, and management of CVD in women. The overall goal of the ATLAS is to create a living document that will help clinicians and the public recognize the unique aspects of women’s heart health care and provide policy makers with information they need to ensure equitable care for women with CVD.

A comprehensive review of the evidence regarding sex- and gender-specific differences in comorbidity, risk factors, disease awareness, presentation, diagnosis, and treatment across the entire spectrum of CVD.

The team that generated the review included clinicians, scientists, allied health, program managers, and patient partners with professional or personal experiences in women’s heart health advocacy, education, knowledge translation, and policy. The intent of the review was to synthesize the state of the evidence for CVD in women, with a uniquely Canadian perspective, and identify significant knowledge gaps that hinder the transformation of clinical practice into one that is truly tailored for women—a significant health challenge that has only been recognized in Canada relatively recently.

In the process of creating the comprehensive and concise review on the evidence in women’s heart health, it was recognized that the team of CWHHA experts had also assembled an expansive collection of original research articles that were synthesized into detailed chapters reporting on the present state of the evidence unique to each CV condition in women. This work comprises an ATLAS on the epidemiology, diagnosis, and management of CVD in women. The chapters of the ATLAS will be published serially in CJC Open over the next year, and subsequent updates will be incorporated as additional evidence becomes available. The overall goal of the ATLAS is to create a living document that will help clinicians and the public recognize the unique aspects of women’s heart health care while providing policy makers with information they need to ensure equitable care for women with CVDs.

Specific aims of the ATLAS include the following: (1) report an environmental scan of the status of women’s heart health and disease in Canada; (2) summarize the existing research on CVD in Canadian women; (3) identify importance of sex- and gender-specific differences and approaches to CV care in Canada; (4) identify knowledge gaps to guide future research; and (5) describe a unified approach to CV health promotion, disease management, and research in Canadian women with an ultimate goal of improving CV outcomes.

Methods

The writing groups comprised members of the Knowledge Translation and Mobilization, and Health Systems and Policy Working Groups of the CWHHA, a volunteer pan-Canadian professional organization powered by the Canadian Women’s Heart Health Centre at UOHI, whose vision and mission is to improve women’s CV health across their life span by supporting clinicians, scientists, patients, and decision-makers to work collaboratively to implement evidence to transform clinical practice and impact public policy related to women’s CV health in Canada. In a key collaboration with CWHHA experts, HSFC staff complemented the writing group. The HSFC is dedicated to policy and advocacy, system change, knowledge translation, public awareness and education, and CVD research. In recent years, HSFC has identified women’s heart and brain health as a priority, forming a Women’s Research Network consisting of CV experts from across Canada and launching a women’s awareness campaign in 2018. All writing group members have in-depth expertise on CVD in women. Following 2 national planning teleconferences of the CWHHA Knowledge Translation and Mobilization and Health Systems and Policy Working Groups, a topic outline based on the scope of the problem was developed. Chapter lead authors and writers were selected on the basis of experience and expertise to complete evidence-based summaries of their assigned topic areas. The chapter leads oversaw the compilation of the evidence and the writing of the chapter topic. All writing group members had opportunities to comment on, edit, and approve the chapters, 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 and analyzed by HSFC authors. Components of the demographic material are based on comparative data and information obtained from the Canadian Institute of Health Information for the most recently available years, 2016 to 2017.
Evidence on CVD in women

For the purpose of the chapters included in the ATLAS, CVD refers to diseases, disorders, syndromes, and conditions that affect the heart and blood vessels. Vital Canadian statistics and hospitalization administrative data were extracted using International Classification of Diseases, 10th Revision, and codes (Supplemental Table S1). When available, studies with Canadian data were prioritized for inclusion to provide a Canadian perspective. When unavailable, studies with data from outside of Canada were included. Because of the lack of evidence covering the full scope of topics included in the ATLAS, it was not possible to perform a systematic literature review unique to CVDs in women. On the basis of the specific areas and the level of evidence, various search strategies were used to review the chapter topics. Please see the Supplemental Table S2 for listing of keywords used for literature searches to identify articles selected for inclusion in each chapter.

One of the first steps in moving past a one-size-fits-all approach to CVD treatment and management involves ensuring that studies systematically account for each patient’s biologic sex, as well as other intersecting factors over and above sex that are associated with outcomes such as gender, age, race, and socioeconomic status. New policies implemented at research funding agencies along with the implementation of editorial guidelines at peer-review journals include sex and gender analysis as one benchmark among many when evaluating grants or publications. The overarching goal is to increase transparency, promote inclusion, and ensure the research community carefully considers sex and gender, where appropriate. The terms “sex” and “gender” are often incorrectly used interchangeably despite clear and distinct definitions. Sex refers to biological constructs that are primarily associated with physical and physiological features, including hormones, genes, anatomy, and physiology typically categorized as female or male. Gender refers to socially constructed roles, behaviors, expressions, and identities, and typically categorized as woman/girl or man/boy. Although Tannenbaum et al. report that CV medicine is arguably the most advanced specialty in its understanding of clinically significant biological differences between the sexes, prevention to treatment, the lag time between discovery and implementation of sex-specific considerations accounts for disparities in CV morbidity and mortality.

Sex differences unique to women with CVD

It has been long recognized that age reduces many estrogen-related vascular responses. The increasing evidence indicates that as women’s vessels spend considerable time under widely fluctuating hormonal influence, including puberty, pregnancy, peripartum, and menopause, women’s vessels may be preset for more severe functional alterations compared with men. The structural findings in the vasculopathy of women with ischemic heart disease demonstrate that both macro and micro vessels are smaller in size, have increased stiffness including fibrosis and remodeling, and have more diffuse disease whereby erosion is greater than plaque rupture. Sex hormones are known to exert effects on the vascular reactivity via the endothelium and directly on smooth muscles. Very recently reported is the intriguing finding from longitudinal sex-specific analyses of blood pressure that women, compared with men, exhibit a steeper increase in blood pressure beginning as early as in the third decade and continuing through the life course, which suggests sex-unique biological characteristics of the vasculature, even independent of hormonal influence. Women in the Women’s Ischemia Syndrome Evaluation (WISE) study had coronary endothelial dysfunction that independently predicted adverse outcomes. Bugiardini and Merz reported that in the large arteries of women presenting with chest discomfort, endothelial dysfunction is an indication of early atherosclerosis before structural changes to the vessel wall are seen on angiography. Furthermore, endothelial dysfunction of the microvasculature has significant potential to limit myocardial perfusion.

Another sex difference unique to women relates to adverse pregnancy outcomes (APOs). APOs are disorders caused by placenta dysfunction and maternal vascular abnormalities, including platelet activation, inflammation, and vasospasm. Pregnancy, now commonly referred to as a “women’s first stress test” and related APOs put women at increased risk for future CVD. In a recent comprehensive review on the long-term CV risk associated with APOs, Lane-Cordova et al. report that the vascular abnormalities that are present during an APO (e.g., hypertension, pre-eclampsia, or gestational diabetes) also underlie common, difficult-to-treat forms of CVD in women as they age, including coronary microvascular disease, suggesting shared mechanistic pathways for APOs and CVD. At present, there are no studies addressing the impact of APOs on ischemia and no obstructive coronary artery disease.

Gender differences in women with CVD

Beyond biological sex, gender is increasingly recognized as a pivotal determinant of health and outcomes. However, there is a lack of standardized gender measurement. In a seminal white paper summarizing the findings and recommendations for the development of and integrated approach to identifying and managing patients with ischemia and no obstructive coronary artery disease, it is recognized that the knowledge gaps related to patient phenotypes (including the expressions and influences of sex and gender), mechanistic understanding, and treatment of patients with CVD are numerous. Specifically, there is a need for improved understanding of the biopsychosocial factors that may influence the development and treatment of women with CVD. In a recent editorial, Dr Wenger, a pioneer in women’s heart health, persuasively elucidates that the CV health of women requires more than sex-specific research. Furthermore, she argues that to truly understand the complicated interdependence of sex and gender on outcomes, research going forward must include the domains of women’s beliefs and behaviours as well as the sociocultural (gender) forces that affect women’s lives and ultimately women’s heart health.

Clinical Practice Guidelines for women with CVD

Canada. Guidelines and Position statements for CV care are developed by and available through the Canadian Cardiovascular Society (CCS) in the Guidelines and position statements library on the CCS website (www.ccs.ca). These guidelines, developed through literature review, evidence, and clinical experience, represent the consensus of a multidisciplinary panel of “experts” who are charged with the mandate of formulating
disease-specific recommendations. To date, these guideline recommendations have been assumed to be applicable to both men and women, and have not been reported by sex; when thought to be relevant, a section on “special populations” may include sex-specific statements. A singular sex-specific document addressing ischemic heart disease in women was published in 2000, as a result of a CCS-initiated consensus conference.12 Canadian Clinical Practice Guideline (CPG) developers have yet to endorse a consistent and systematic approach for considering sex-specific CV information in the CPG.

However, an initiative led by the CCS in 2018 was undertaken to determine the feasibility and outcomes of a structured process for considering sex and gender in CPGs, specifically for managing ST-segment elevation myocardial infarction. A sex and gender champion was appointed to the guideline development committee. The feasibility of tailoring the CPG to sex was ascertained by recording (1) the male—female distribution of the study population; (2) the adequacy of sex-specific representation in each study using the participation/prevalence ratio; and (3) whether data were disaggregated by sex. The outcome was to determine whether CPG recommendations based on an assessment of the evidence should differ by sex. It was concluded that implementation of a systematic process for critically appraising sex-specific evidence for CPGs was straightforward and feasible; however, inadequate enrollment and reporting by sex hindered comprehensive sex-specific assessment of the quality of evidence and strength of CPG recommendations on the management of ST-segment elevation myocardial infarction.7 Although gender-specific analyses were deemed not feasible at this time, it was emphasized that going forward it is imperative that results be stratified by sex for clinicians to have the ability to provide sex-specific care. A recognition of the importance of ensuring female participation in CV trials is supported by recently mandated policies of the Canadian Institutes of Health Research1 and the HSFC requiring sex- and gender-based analysis in funded research.1 Moreover, equitable representation in research of high CVD risk groups, such as indigenous and ethnic women, is additionally required.

**United States.** With the support of the American Heart Association, women-specific CV prevention guidelines were first published in 2004,14 updated in 2007,15 and subsequently updated as “effectiveness-based” guidelines in 2011.16 Over the past decade, additional published guidelines, scientific statements, and advisories have increasingly addressed the following aspects of CVD in women: peripheral artery disease (2012),17 trends in awareness of heart disease in women (2013),18 stroke prevention in women (2014),19 role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease (2005) and updated in 2014,20,21 acute myocardial infarction (2016), prevention and experience of ischemic heart disease (2016),22 spontaneous coronary artery dissection (2018),23 and promotion of risk identification and reduction of CVD in women through collaboration with obstetricians and gynecologists (2018).24 All of these documents consistently report that the level of evidence is not available at this time to provide sex-based guidelines for treatment of heart events in women. It is also interesting to note that there are no women-focused statements/guidelines on heart failure, arrhythmias, or valve diseases. Women are considered “special populations” within the few guideline documents that address sex-specific issues on these topics.

**Global.** Similar to documents in Canada, there are no specific documents dedicated to CV guidelines in women, largely because of a lack of adequate evidence base.25 Within the 2016 European Guidelines for Cardiovascular Prevention, a few recommendations tailored specifically for women are provided and advise against assessing CVD risk in women aged <50 years with no risk factors, although it may be beneficial to assess CVD risk in women before prescribing combined oral contraception; screening of women aged >50 years, or postmenopause, may be considered in the same way that it is for men, that is, for those at increased risk of CVD, for example, family history of CVD or hyperlipidemia, or presenting with major risk factors, including pre-eclampsia. These recommendations are based on an evidence base using 8 risk estimation systems (Framingham,26 SCORE,27 ASSIGN — SCORE,28 QRISK1,29 QRISK2,30 PROCAM31 Pooled Cohort Equations,32 CUORE,33 and Globorisk34) with a percentage of women ranging from 32% to 64% (median 52%, mean 49%) and recommend several sex-specific cutoffs for CVD risk factors, including waist circumference (target value for women is <80 cm and <94 cm for men), high-density lipoprotein cholesterol (>1.2 mmol/L indicates lower risk in women, whereas for men the value is >1.0 mmol/L), and alcohol consumption (limits are 1 glass per day for women and 2 glasses/day for men).

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 underdiagnosis, undertreatment, and current absence of CPGs for women with CVD in Canada. CPGs are developed using national guideline committees made up of groups of experts in the treatment of specific clinical disorders and are a key step in translating evidence into clinical practice. Despite a general understanding that appearances and outcomes of diseases may contrast for male and female patients, the uptake of sex and gender factors into CPG development. Our own research into the lack of sex- and gender-specific guidelines identified the following barriers to the addition of sex and gender considerations in the process of guideline development: (1) an inclination for working groups to develop recommendations for the “general” patient population; (2) a lack of cognizance that attention to sex- and gender-related factors may improve the quality of the guidelines; and (3) the absence of a coordinated process for identifying and systematically evaluating the evidence on sex and gender differences.2

**CWHHA Women’s Cardiovascular ATLAS Project**

The need for a dedicated compilation of articles addressing the state of the science of women’s CV health in Canada is
clear and heretofore unmet. The CWHHA Women’s Cardiovascular ATLAS project aims to fill this void and begins with the present installment that provides a critical appraisal of the currently inadequate evidence base to support female-specific clinical guidelines and recommendations for CVD in Canada. This will be followed by a series of chapters examining in detail the fundamental issues regarding CV health and disease in Canadian women, including an assessment of the burden of CVD on women in Canada, a statement on “the patient’s perspective” written by women with lived experiences of CVD, and examination of the sex- and gender-specific differences in comorbidity, risk factors, and a lack of awareness on the part of women and their healthcare providers. The final chapters will include a discussion of future directions and the action needed on multiple fronts to achieve sex and gender equity for women’s CV health to correct the glaring “unders” of CVD for women in Canada: under-awareness, underdiagnosis, undertreatment, under-researched, and under-supported. Once all of the chapters of the ATLAS have been published in this series, we anticipate that we will have created a living document that can be refreshed annually as the evidence base grows and can provide a ready resource and reference for the development of CPG and synthesis of state-of-the art knowledge in women’s CV health and disease. Most important, it is our intention that the CWHHA Women’s Cardiovascular Atlas will help clinicians and the public recognize the unique aspects of women’s heart health care while at the same time provide policy makers with information they need to ensure equitable care for women with CVDs.

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Supplementary Material
To access the supplementary material accompanying this article, visit CJC Open at https://www.cjcoopen.ca/ and at https://doi.org/10.1016/j.cjco.2020.02.004.