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Review

The Development of a Chest-Pain Protocol for Women Presenting to the Emergency Department

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in women worldwide, and of premature death in women in Canada. Despite improvements in cardiovascular care over the past 15-20 years, acute coronary syndrome (ACS) and CVD mortality continue to increase among women in Canada. Chest pain is a common symptom leading to emergency department visits for both men and women. However, women with ACS experience worse outcomes. compared with those of

RÉSUMÉ

Les maladies cardiovasculaires (MCV) sont la principale cause de décès chez les femmes dans le monde et de décès prématuré chez les femmes au Canada. Malgré les progrès réalisés dans le domaine des soins cardiovasculaires au cours des 15 à 20 dernières années, les taux de syndrome coronarien aigu (SCA) et de mortalité due aux MCV continuent d'augmenter chez les femmes au Canada. La douleur thoracique est un symptôme fréquent qui pousse les hommes et les

Lay Summary

An easy-to-follow flowchart to address the underrecognition and underdiagnosis of heart and blood vessel disorders in women with chest pain was developed. This flowchart could be posted in emergency departments to increase awareness of symptoms and risk factors specific to women. We anticipate that such posting may improve diagnosis and reduce treatment delays in women. The protocol can be made available on the cwhha.ca Web site and can be shared with the medical community.

Cardiovascular disease (CVD) is the leading cause of mortality for women globally, and of premature death for women in Canada.[1] Nearly 25,000 women die annually, and one woman dies every 20 minutes from heart disease in Canada.[2,3] Over the past 15-20 years, Canadian women have experienced increased mortality rates compared to Canadian men and at a faster rate than the initial decline seen in the early 2000s.[4] This increase has especially affected younger women aged 35-54 years.[5] CVD morbidity also is disproportionately greater in women than in men, as women are 20% more likely than men to die within the year following an acute myocardial infarction (MI) and to experience heart failure or stroke within 5 years after acute MI.[3,6-8] The observation has been made that CVD risk factors, including smoking, hypertension, diabetes, obesity, physical inactivity, depression, and anxiety, are disproportionately more harmful in women than they are in men,[9] and that sex- and gender-specific differences exist in awareness, symptom presentation, diagnosis, prognosis, and treatment of CVD, with women receiving fewer referrals to indicated procedures and therapies.[10]

In the fall of 2021, the first author (S.J.) was invited to present a lecture titled "Cardiovascular Disease in Women in

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men, due to misdiagnosis or lack of diagnosis resulting in delayed care and underuse of guideline-directed medical therapies. CVD mortality rates are highest in Indigenous and racialized women and those with a disproportionately high number of adverse social determinants of health. CVD remains underrecognized, underdiagnosed, undertreated, and underresearched in women. Moreover, a lack of awareness of unique symptoms, clinical presentations, and sex-and-gender specific CVD risk factors, by healthcare professionals, leads to outcome disparities. In response to this knowledge gap, in acute recognition and management of chest-pain syndromes in women, the Canadian Women's Heart Health Alliance performed a needs assessment and review of CVD risk factors and ACS pathophysiology, through a sex and gender lens, and then developed a unique chest-pain assessment protocol utilizing modified dynamic programming algorithmic methodology. The resulting algorithmic protocol is presented. The output is intended as a quick reference algorithm that could be posted in emergency departments and other acute-care settings. Next steps include protocol implementation evaluation and impact assessment on CVD outcomes in women.

femmes à se rendre aux urgences. Toutefois, les femmes atteintes d'un SCA présentent de moins bons résultats cliniques que les hommes, en raison d'erreurs de diagnostic ou d'une absence de diagnostic causant des retards dans les soins prodigués et une sous-utilisation des traitements médicaux préconisés dans les lignes directrices. Les taux de mortalité liée aux MCV sont les plus élevés chez les femmes autochtones et les femmes racialisées ainsi que chez celles qui présentent un nombre particulièrement élevé de déterminants sociaux de la santé défavorables. Les MCV continuent d'être sous-estimées, sous-diagnostiquées et sous-traitées chez les femmes et ne sont pas suffisamment étudiées dans cette population. De plus, la méconnaissance par les professionnels de la santé des symptômes, des tableaux cliniques et des facteurs de risque de MCV selon le sexe et le genre entraînent des disparités dans les résultats cliniques. Pour combler ces lacunes dans les connaissances en matière de reconnaissance et de prise en charge des symptômes de douleur thoracique chez les femmes, l'Alliance canadienne de la santé cardiaque des femmes a réalisé une évaluation des besoins et un examen des facteurs de risque de MCV et de la physiopathologie du SCA en tenant compte des particularités liées au sexe et au genre, et a ensuite élaboré un protocole unique d'évaluation de la douleur thoracique faisant appel à une méthodologie algorithmique par programmation dynamique modifiée. Nous présentons le protocole algorithmique qui en est issu. Ce résultat se veut un algorithme de référence rapide pouvant être diffusé dans les services d'urgences et les autres services de soins de courte durée. Les prochaines étapes de notre travail seront d'évaluer la mise en œuvre du protocole et son incidence sur les issues cardiovasculaires chez les femmes.

the Emergency Department" at the 19th Annual St. Paul's Emergency Medicine Update Conference, in Vancouver, British Columbia (BC), Canada. Subsequently, the Clinical Resource Lead of the BC Emergency Network requested the development of a 3-page point-of-care clinical summary for emergency physicians in BC.[11] The Canadian Women's Heart Health Alliance (CWHHA), a pan-Canadian network of over 150 volunteer cardiovascular health experts, advocates, and women with lived experience, was approached to assist with creating this summary document. The mandate of the CWHHA is to enhance collaborative action, develop, implement, and disseminate evidence-based programs and strategies, transform clinical practice, and impact public policy related to women's cardiovascular health.[12] This publication details the CWHHA Knowledge Translation and Mobilization Working Group's approach to this initiative, and describes the background research, design methods, and results, and introduces the plan for implementation assessment.

Important note about terminology: Although the terms sex and gender are often used interchangeably, we recognize that they have distinct definitions. Sex typically is described as female or male and refers to biological constructs that are associated primarily with physical and physiological features, including genes, hormones, and anatomic and physiological characteristics Gender refers to socially constructed roles, behaviours, identities, and expressions and is described as woman or man.[13] In this document, we attempted to follow these definitions; however, if the source article did not support sex and gender definitions, we applied the term that made the most sense contextually.

Methods

Needs assessment: the scope of the problem

Many women who present to the emergency department (ED) with cardiovascular-related health concerns feel "stopped at the gate"—that is, denied critical assessment and management for acute CVD symptoms and signs.[14] A recent Canada-wide survey also did not identify any formal female-specific protocols for addressing acute coronary syndrome (ACS) in EDs across the country.[15] Moreover, the Heart and Stroke Foundation of Canada report highlighted that early heart attack symptoms were missed in over 50% of women presenting to the ED.[3]

Furthermore, despite the existence medical directives in the ED (eg, standing orders and protocols), cognitive bias and diagnostic errors, such as delays in diagnosis, do occur, resulting in patient harm, including death. The Canadian Medical Protective Association () analyzed 28 closed medico-legal cases (hospital complaints, regulatory authority [ie, College] complaints, and civil legal actions) involving emergency physicians in Canadian EDs between 2016 and 2021.[16,17] Patient sex was female in 14 of 28 (50%) of those in the sample, and the mortality rate was 25% (7 of 28). Peer experts were critical of the physicians' less-than-thorough initial assessments, failure to reassess patients, delays or failures in ordering and interpreting electrocardiograms (ECGs), and delays or failures in ordering cardiac enzymes. As well, clinical decision-making, such as recognizing risk factors, was one of several important factors contributing to harm and medico-legal risk. Given the increased incidence of morbidity and mortality associated with delayed diagnosis of ST-

elevation MI (STEMI), the Canadian Medical Protective Association recommended that EDs implement systems, such as medical directives, to diagnose ACS early.

Thus, to improve diagnosis, reduce treatment delays, and potentially mitigate CVD morbidity and mortality in women presenting to the ED, we sought to develop an intersectional diagnostic algorithmic protocol through a *sex and gender lens* addressing the following: (i) symptoms; (ii) (a) female-specific, (b) traditional, and (c) underrecognized, female predominant, intersectional); (iii) sex-specific thresholds for high-sensitivity cardiac troponin (hs-cTn); and (iv) unique aspects of the pathophysiological spectrum of ACS in women. First, each of these component sections of the diagnostic algorithm was explored through both a detailed literature search and expert consensus, using a sex and gender lens. Electrocardiography plays a pivotal role in the diagnosis of ACS, and as it displays no acute sex or gender differences, it required no modification in the algorithm development.

Symptoms

Recognition of differences in the symptoms during the presentation of ACS in women is vital to improving patient management and outcomes. Chest pain, sometimes also described as a pressure, tightness, or discomfort, is the most common symptom experienced by men and women with ACS.[18] Reports of chest pain in suspected ACS cases have been as high as 92% in women and 91% in men in large prospective trials.[19] Women, more so than men, may additionally experience symptoms such as radiation to the left arm, back, neck, or jaw and are more likely to report nausea, epigastric discomfort, dyspnea, profound fatigue, and palpitations. Women often also present with 3 or more of these associated symptoms in addition to chest pain.[19,20] Current best practice argues against the use of the descriptor term "atypical" for ACS symptoms in women, as they are characteristically "typical" for chest pain syndromes *in women*.[19] A high index of suspicion will avoid significant delays in the triage, diagnosis, and management of women with ACS.[19,21,22]

Cardiovascular risk factors: the triad approach

Early recognition of female patients at risk for ACS is essential. Although traditional CVD risk factors are well recognized by the medical community, these are not always present in women experiencing chest pain. Women's cardiovascular health risks comprise a triad of intersectional factors—they are female-specific, traditional, and underrecognized—and these factors may exist independently or in combination, placing women at a disproportionately greater risk for CVD. Comprehensive assessment of CVD risk using this triad concept is essential to ensure that an appropriate identification of at-risk women occurs (Fig. 1).[23]

Traditional risk factors. Traditional risk factors (hypertension [HTN], diabetes mellitus [DM], obesity, smoking, hyperlipidemia) portend a greater burden of morbidity and mortality in women than in men.[9,24] Women with DM have an increased risk of stroke, heart failure, and earlier occurrence and 3-fold excess risk of fatal MI, compared with men. Hypertension is more prevalent in women aged over 60 years and is less well controlled in women than it is in men. Obesity and cigarette smoking significantly increase the risk of coronary artery disease (CAD) in women, as compared to men. Lipid profiles change over the course of a woman's life, and they become less favourable after menopause, with relative increases in low-density lipoprotein and decreased high-density lipoprotein.[25]

Female-specific risk factors

Cardio-obstetrics. Cardio-obstetrics is a specialized multidisciplinary practice that has developed as a response to recognition that the physiological and hemodynamic changes of pregnancy are a stress test that may predict future CVD risk in women.[26,27] In Canada, cardiac disease affects almost 5 per 100,000 deliveries and is the most common diagnosis associated with maternal mortality in pregnancy and postpartum periods.[28] Adverse pregnancy outcomes (defined as hypertensive disorders of pregnancy, gestational DM, and maternal placental syndrome: preeclampsia, preterm birth, placental abruption, and intrauterine growth restriction) occur in 20% of Canadian pregnancies and are sex-specific risk factors associated with increased future CVD risk.[29]

Polycystic ovarian syndrome (PCOS). PCOS is the most common endocrine disorder in women and girls of reproductive age and is considered a high-risk vascular condition.[30,31] In addition to polycystic ovaries, and symptoms and signs of chronic anovulation and hyperandrogenism, this condition is associated with central adiposity and insulin resistance. The latter results in cardiometabolic abnormalities such as dyslipidemia, hypertension, glucose intolerance, diabetes, and metabolic syndrome, which increase CVD risk.[32] In one large retrospective study, women with PCOS experienced a significant increase in MI (hazard ratio [HR] 1.26), angina (HR 1.38) and revascularization (HR 1.6), and their composite (HR 1.5), compared to matched controls.[33]

Menopausal status and estrogen-based therapies. Substantial evidence exists to support the fact that higher estrogen levels as seen in premenopausal women portend an anti-atherogenic cardioprotective effect resulting in advantageous protection from CVD.[34,35] However, an overlap of multiple factors can cause a significant increase in CVD risk in the postmenopausal phase of a woman's lifespan. These factors include the following: a rise in chronic low-grade inflammation; declining ovarian secretions of estrogen and progesterone; and adverse changes in body fat distribution, lipoproteins, and structural and functional measures of vascular health (eg, increasing blood pressure).[36-38] Women with premature ovarian insufficiency or early menopause, early (ages 40-45 years) and particularly premature menopause (age $<$ 40 years) have higher rates of ischemic stroke, heart disease, and cumulative CVD mortality rates, as compared to those who have a menopause onset at the usual average age of 50 to 51 years.[9,39] Women using combined oral contraception pills are at 1.5-2-fold increased risk of MI or stroke, with the highest risk observed in those taking $>$ 50 mcg of estrogen.[40,41] Menopausal hormone therapy increases the risk of stroke and thromboembolic events.[42]

Autoimmune diseases. Autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, affect 2.5 and 10

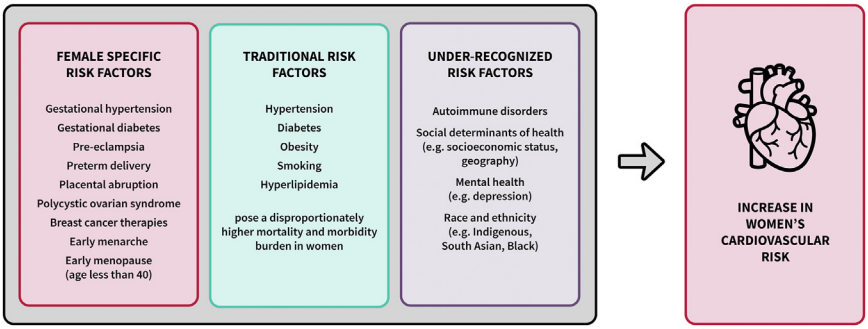

Figure 1. Comprehensive intersectional cardiovascular risk-factor assessment in women.[9,10]

times more women than men.[43] In addition to the increased overall morbidity and mortality incidence associated with these conditions, the systemic inflammation from autoimmune diseases increases the risk of premature CVD, including ischemia and MI, both with and without obstructive coronary arteries, as well as myopericarditis and valvular heart disease in women.[44-48]

Malignancy. Malignancy increases the risk of CVD, including ACS, and it is the most frequent cause of late morbidity and mortality among cancer survivors.[49,50] Women with a history of breast cancer have a greater risk of dying from CVD, compared to women without breast cancer.[51] Breast cancer treatments, including trastuzumab targeted therapy, anthracycline-based chemotherapy, aromatase inhibitors, and radiation therapy (especially for left-sided breast cancer) can cause cancer therapy—related cardiac dysfunction.[52,53]

Underrecognized, female-predominant, and intersectional risk factors. Underrecognized risk factors may exist independently or in combination, placing women at disproportionately greater risk for CVD.

Social determinants of health. The impact of social determinants of health (SDOH), such as socioeconomic status (SES), mental health, geographic location, poverty, social isolation, and violence, on CVD risk and outcomes is well documented.[1,54] Systemic racism, not race, is a primary driver of many adverse SDOH; racism is often experienced by women of colour, and it should be considered when assessing SDOH.[55] Women with lower SES, especially those in racialized communities, are more susceptible to CVD than those with higher SES.[41,56] Low-income women have been shown to have less access to cardiac catheterization, and they had a higher 30-day mortality rate, compared to both higher-income groups and men.[57] Women living in rural, remote, and on-reserve residences experience greater CVD risk factors, morbidity, and mortality.[1] When considering the SDOH as underrecognized risk factors, the failure to recognize the role of intersectionality under-prioritizes the roles our identities can play in CVD development in women. Intersectionality acknowledges the various identities possessed by an individual, and how those identities intersect to generate oppression or privilege.[58,59] Having multiple identities can result in a position of relative power imbalance, and interactions with other SDOH may reinforce and compound privilege, discrimination, and/or inequities known to influence the development of CVD in women.[58]

Recent studies have demonstrated that Indigenous people and South Asians (SAs) in Canada, including women, who were increasingly more socially disadvantaged had the highest probability of CVD, compared to European and Chinese men and women with the same level of social disadvantage.[60,61] Indigenous (First Nations, Metis, and Inuit) women experience significant social, economic, and political inequalities, which contribute to their elevated CVD risk, and in combination with increased traditional CVD risk factors (as described earlier) result in higher rates of atherosclerotic CVD (inclusive of MI, stroke, and peripheral vascular disease).[23,62,63] In 2018, the Heart and Stroke Foundation of Canada reported that Indigenous women in Canada develop CVD at a younger age, are twice as likely to develop CVD, and are 53% more likely to suffer from cardiovascular mortality than non-Indigenous women.[3] Colonial impact, intergenerational trauma, and lack of access to healthcare systems and healthcare professionals also contribute to the increased incidence of cardiovascular morbidity and mortality in Indigenous peoples.[1]

Ischemic heart disease is the leading cause of mortality in the Black population in Canada.[64] Cardiometabolic risk factors such as type 2 DM, smoking, and HTN are more prevalent in Black women, compared to Black men, and compared to the White population.[65] The risk of mortality due to DM was approximately 25% higher for Black male patients, and 48% higher for Black female patients, compared with the risk for their respective White counterparts in the age-adjusted models. These relative increased risks of mortality persisted for most causes of death after adjustment for differences in important SDOH.[64] Moreover, these risk factors demonstrate a significant impact on the earlier development of CVD, compared with other ethnicities.[65,66]

SAs are at increased risk of atherosclerotic CVD, HTN, and stroke, compared to Caucasians, and they have higher hospitalization and mortality rates from atherosclerotic CVD.[61,66] MI and stroke occur 5-10 years earlier in SAs than in other groups, including other ethnic communities.[61,67] SAs have at least a 2-fold higher prevalence of DM, and a higher incidence of new-onset DM, which are significant traditional risk factors for CVD and which contribute to CVD mortality in this group.[68] SA women with gestational diabetes are 3 times more likely to develop DM and have metabolic

abnormalities at a lower body mass index and waist circumference than other groups.[61]

Mental health. In the general population, the prevalence of major depression is 1.7- to 2.0-fold higher in women than in men.[69] The higher prevalence in women is thought to be related to hormonal, biological, and psychosocial factors.[69-71] Increasing evidence has demonstrated an association between depression and CVD development in women, increasing a woman's risk for adverse cardiac events by 50%-70%.[72-74] One hypothesis is that women may be more vulnerable to the adverse effects of psychological stressors through altered neurobiological physiology, and that younger women may be disproportionally susceptible to the adverse effects of stress in terms of the risk of CVD.[74] The evidence for anxiety as an independent risk factor for CVD may not be as robust as the evidence for depression. Some studies, however, have demonstrated an association of anxiety with CVD, with increased risk of CAD, stroke, heart failure, and cardiovascular death.[75]

Sex-specific threshold for high-sensitivity cardiac troponin

Along with clinical (history and physical examination) and ECG findings, serologic assessment of cardiac troponins is a key component in the diagnosis of acute MI, as it is detectable in blood within hours after myocardial injury; elevation above the 99th percentile upper reference limit is an indicator of acute myocardial injury.[76] Recently, hs-cTn assays have been developed for use as a criterion in the diagnosis of ACS.

A diagnostic hs-cTn test result is considered to be one that is greater than the 99th percentile upper reference limit (as defined by the manufacturer of the assay used), or a 20% or greater increment on serial testing.[76] Serial hs-cTn testing is performed if the initial result is less than the diagnostic threshold or the onset of chest pain occurs less than 3 hours prior to presentation. Levels of hs-cTn vary with sex (they are higher in men) and age, and comorbid conditions such as HTN and renal disease. The superiority of hs-cTn as a biomarker for detection of sex-specific cardiac troponin differences has improved the sensitivity in diagnosing MI in women.[19,77] In one study, the implementation of sex-specific hs-cTn diagnostic thresholds resulted in a 2-fold increase in the diagnosis of MI in women and improved the identification of women at risk for future cardiac events.[78] The ongoing hs-**c**Tn—**O**ptimizing the **D**iagnosis of Acute Myocardial Infarction/Injury in Wom**e**n (CODE-MI) clinical trial (NCT03819894) is evaluating the effectiveness of the use of sex-specific hs-cTn thresholds in the diagnosis of MI in EDs across 24 sites in 8 provinces in Canada; the enrollment phase has recently concluded, and the study is in a 2-year follow-up phase.[79]

Pathophysiologic spectrum of acute chest-pain syndromes in women

When ACS is suspected based upon the history (symptoms), ECG, and cardiac biomarker (hs-cTn) findings, the differential diagnosis in a woman includes a spectrum of clinical disorders, including those with a specific pathophysiology distinct from that of a man, as detailed below.

Acute coronary syndromes. The classification of ACS according to the 4th Universal Definition of MI 81 classifies ACS as ST-elevation myocardial infarction (STEMI), or non-ST-elevation ACS (NSTEACS), which includes non-STEMI and unstable angina (UA). ACS requires rapid identification in the acute care setting and must be identified early in patients presenting with chest pain or angina equivalents, with a goal of both having an ECG performed and interpreted within 10 minutes of presentation, and having blood for hs-cTn assessment drawn immediately. The diagnosis of UA is defined by a history of ischemic chest pain at rest or minimal exertion without acute myocardial necrosis (ie, normal hs-cTn).[76,80] Further classification systems use pathologic mechanisms to risk-stratify based on coronary angiographic diagnosis.[81,82]

The role of the ED in the acute assessment of chest pain is to determine whether an ACS is occurring, and if emergency (or urgent) cardiac catheterization is required, with appropriate testing and subsequent triage according to institutional protocols (ie, STEMI activation, emergency cardiology consultation, observation, or dismissal and outpatient evaluation and/or follow-up). In the setting of an ACS, a long-recognized difference, from observations in large study populations, is that women are less likely to present with STEMI, compared to men (27%-28% vs 35%-37%), and they are more likely than men to have UA.[82,83] Sex-unique higher risk of initial and recurrent STEMI has been observed in female patients with a history of prior pregnancy complications including preeclampsia.[84]

Cardiac catheterization is performed emergently in patients with STEMI, and urgently in patients with NSTEACS. Findings at cardiac catheterization may reveal obstructive CAD, nonobstructive CAD, or normal coronary arteries. Coronary angiographic results in women more commonly demonstrate nonobstructive CAD or normal coronary arteries, compared to men; indeed, in up to 10% of all patients presenting with ACS, and in up to one third of female patients, no culprit coronary lesion is identified angiographically.[85]

STEMI. If clinical findings and ECG support the diagnosis of STEMI or STEMI equivalents,[86] the local STEMI pathway is activated. For a primary percutaneous coronary intervention centre (PPCI), the recommended "door-to-needle" time is $\leq$ 90 minutes; for non-PPCI centres, it is $<$ 120 minutes. Fibrinolysis (within 12 hours of chest pain) can be considered if a delay to PPCI of $>$ 120 minutes occurs and no contraindications are present.[87] If the travel time from a non-PPCI to PPCI centre is $\leq$ 120 minutes, the recommended course of action is that the patient be transferred without prior fibrinolysis. [88]

NSTEACS. Dynamic ECG changes of ST depression, transient ST elevation, or T-wave inversion are noted in NSTEACS; however, the ECG may be normal 30% of the time, and the diagnosis is made based on abnormal hs-cTn levels. Imperative steps are to initiate recommended early pharmacologic therapy as per current guidelines,[89] consult cardiology, and follow the local NSTEACS protocol.

Type 1 MI defines myocardial necrosis confirmed when coronary vessel occlusion by atherosclerotic plaque rupture or erosion is identified on conventional angiography.[83,9189]

Type 2 MI defines myocardial necrosis due to oxygen supply and demand mismatch and may require further invasive testing if conventional angiography is negative for coronary occlusion.[82,89] The differential diagnosis can include **female-predominant conditions,** including MI or ischemia with nonobstructive coronary artery disease ([M])INOCA, due to coronary artery vasospasm or coronary microvascular dysfunction (CMD), spontaneous coronary artery dissection (SCAD), or thromboembolism. Stress-induced cardiomyopathy (Takotsubo cardiomyopathy), another female-predominant condition, is considered an MI-mimicker. These conditions are summarized below and are further detailed in the CWHHA ATLAS on the Epidemiology, Diagnosis, and Management of Cardiovascular Disease in Women, Chapter 5: Sex-and Gender-Unique Manifestations of Cardiovascular Disease.[10]

Nonobstructive CAD. MINOCA represents 5%-15% of all presentations for ACS, and it can be caused by atherosclerotic or nonatherosclerotic etiologies (SCAD, vasospasm, coronary microvascular disease, thromboembolic disease). Nonobstructive CAD is defined as epicardial coronary artery occlusion of < 50% on conventional angiography. MINOCA is 5 times more prevalent in women than in men, and the typical patient is younger than 55 years. People of Black, Hispanic, and Asian race are also at higher risk.[90,91]

Patients with nonobstructive CAD, so-called "normal" or negative coronary angiograms, are often dismissed as having noncardiac chest pain, thereby missing the opportunities for recommended treatment.[6] The **W**omen's **I**schemia **S**yndrome **E**valuation WISE study[92] demonstrated a significant 31% CVD mortality in women with INOCA in 10-year follow-up. Similarly, the **V**ariation **i**n **R**ecovery: Role of **G**ender on **O**utcomes of Young AMI Patients (VIRGO) study[20] demonstrated that 1-year mortality rates were similar for obstructive ACS and nonobstructive ACS.

SCAD. SCAD is a nonatherosclerotic separation of the coronary arterial wall resulting in compromised coronary artery blood flow and MI[93]; it is estimated to occur in approximately 4% of ACS presentations overall and is more common in younger women. Over 90% of cases occur in women, and chest pain is the most common presenting symptom.[94] Traditional CVD risk factors and genetic risk for atherosclerosis are not associated with SCAD.[95]

Vasospasm and coronary microvascular dysfunction. Coronary vasospasm is more common (> 90%) in women than in men, and angina usually occurs at rest. Diagnosis is confirmed when intracoronary acetylcholine is administered during angiography and the vasoconstrictive response is accompanied by ST-segment elevation changes that appear simultaneously on ECG and resolve with nitroglycerin.[90] A rare subset of vasospastic angina is allergic-mediated ACS, or Kounis syndrome,[96] but it is reportedly not more common in women; an elevated tryptase level may be useful in confirming the diagnosis.[97] Coronary microvascular dysfunction is a structural and functional abnormality of the coronary microvasculature, which is approximately 5 times more common in women than in men, often presenting with angina or dyspnea with exertion, and diagnosis is assessed during coronary angiography with physiologic reactivity testing.[90,98]

Stress-induced cardiomyopathy. Stress-induced cardiomyopathy, also known as Takotsubo syndrome, most commonly (> 90%) presents in postmenopausal women[99] and is considered a "mimicker" of ACS, occurring in approximately 1%-2% of patients[100] in whom cardiac catheterization reveals normal coronary arteries, but severe, most often reversible, left ventricular dysfunction in a characteristic distribution not relating to coronary artery perfusion.[99] Typical symptoms of ACS, such as chest pain and dyspnea are present, often with a precursor of intense emotional or physical stress; the hs-cTn level may be only minimally elevated. ECG changes can show a pattern similar to that of myocarditis with ST elevation followed by normalization, then inversion of T-waves. The ECG also may show QT-prolongation, or left bundle branch block, or may be completely normal.[101]

Other cardiopulmonary and noncardiac causes of chest pain. Other noncoronary cardiopulmonary causes of acute chest pain in women include aortic dissection, perimyocarditis, pulmonary embolism, heart failure, arrhythmias, valvular disease, and hypertensive emergencies.[19] Although acute aortic syndromes, including aortic dissection, aortic rupture, penetrating aortic ulcer, and intramural hematoma, affect men more frequently than women, the prognosis is worse in women.[102] Female patients have a 40% higher risk of mortality and a 3-fold increased risk of aortic dissection or rupture as compared to the risk in male patients.[103] Poorer outcomes in women are thought to be due to the vascular changes secondary to menopausal transition, but they remain incompletely understood.[104,105] The prevalence and risk factors of acute aortic syndromes in women rapidly rise with age, leading to increased age of presentation.[105] In women, times from symptom onset to presentation, and from presentation to diagnosis, are delayed.[104] Moreover, female patients with type A dissection are more commonly treated conservatively than are their male counterparts. A bedside or focused echocardiogram can be helpful in rapid initial assessment, but chest CT (computerized tomography) is an essential investigation to establish or exclude such diagnoses.[103]

Noncardiac causes of acute chest pain in women may also include hypoxia and hypovolemia due to supply-demand mismatch, from conditions such as severe gastrointestinal bleeding (anemia), sepsis, or stimulant and other toxin abuse causing cardiovascular compromise, tachydysrhythmias, and cardiogenic shock, all of which may also cause elevations in cardiac troponin levels.[19] These conditions must be differentiated appropriately and managed by critical care intensivists.

Development of the algorithm

After considering the sex- and gender-unique aspects as detailed above, the Chest Pain in Women in the Emergency Department protocol was developed by utilizing a modified dynamic programming algorithm.[106] A generic, high-level, horizontal, and vertical step algorithm (Fig. 2a) was developed and comprises the following elements: (i) Input: developing a problem statement and description, clinical data collection, consequences and outcomes, and relationships between data; (ii) rules and criteria: subproblems development, variables, reassessment, and transition; and (iii) output:

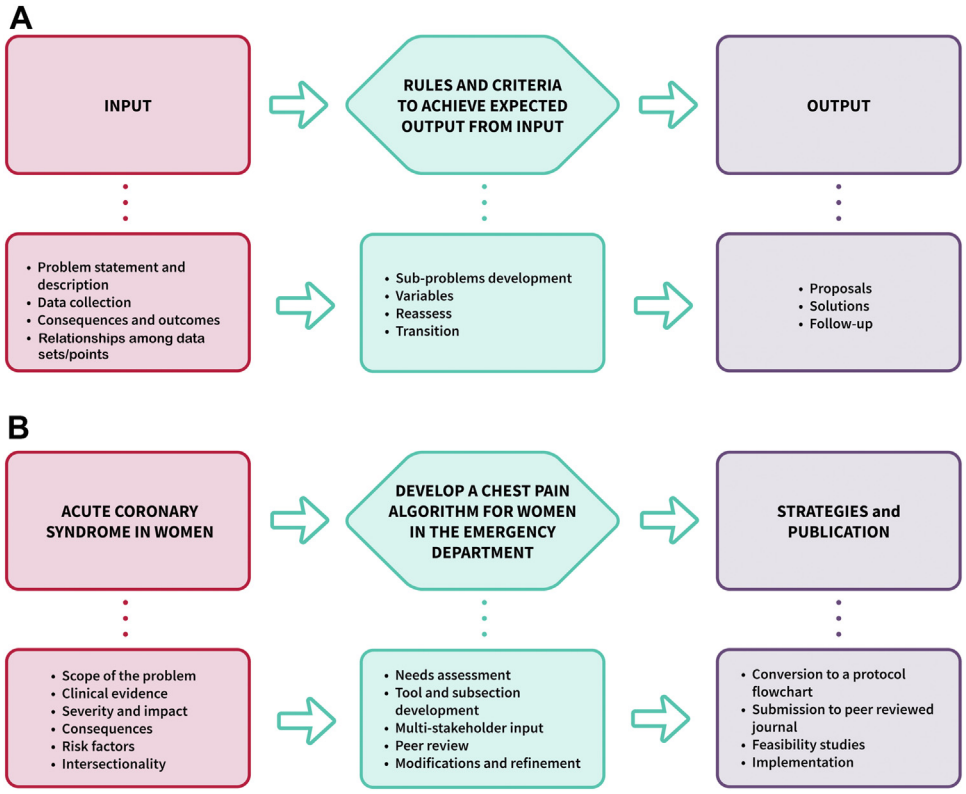

Figure 2. (**A**) Generic modified dynamic programming algorithm. (**B**) Modified dynamic programming algorithm customized to women presenting to the emergency department with chest pain.

proposals, optimal solutions, and follow-up. This algorithm was then reconciled to the clinical scenario of chest pain in women presenting to the ED (Fig. 2b), as follows: (i) input: ACSs in women; scope and gravity of the problem, evidence, impact, outcomes, risk factors and intersectionality, differential diagnosis; (ii) process and methods: needs assessment, tool and subsection development, multi-stakeholder input and expert consensus, peer review, modifications, and refinement; (iii) output: strategies and publication; conversion to a protocol flowchart, journal submission, feasibility studies, and implementation.

Following the posting of the "Chest Pain in Women in the ED: Focus on Acute Coronary Syndrome" point-of-care summary on the British Columbia Emergency Network site in January 2022 (Supplemental Appendix S1), the Knowledge Translation and Mobilization Working Group of the CWHHA formed a committee to further expand the "ACS in Women Checklist."[11] Input from multiple stakeholders, including physicians (cardiologists, internists, emergency physicians), allied health professionals (nurses, nurse practitioners, physician assistants), and women with lived experience, was obtained, and additional adjustments and enhancements to subsections of the document were made, and expert consensus was achieved. The developed draft algorithm was presented at the Canadian Women's Heart Health Summit in Vancouver on April 28, 2023. Feedback and subsequent review by the Executive Committee of the CWHHA resulted in further modifications and refinements, and the final algorithm is presented in this document.

Results

The Chest Pain Protocol for Women in the ED is presented in Figure 3. The flow begins with the overarching presentation of women with symptoms (chest pain or associated symptoms) of acute MI, with or without CVD risk factors (female-specific, traditional, underrecognized) leading to consideration of "possible ACS."[19] This potential diagnosis is then further evaluated by obtaining ECG and hs-cTn assessments. Following the ECG pathway, and depending on the presence or absence of characteristic ST-T changes, women are diagnosed and treated for STEMI or NSTEACS as per standard protocols and guidelines.[87,89] For those with ECG findings of an acute STEMI, a "door-to-balloon" benchmark time of < 120 minutes for PPCI, and if unavailable, fibrinolysis, with "door-to-needle" time of within 90 minutes, is recommended.[87,88.89.107]

In the presence of ECG findings that do not indicate STEMI, the hs-cTn pathway is followed, and depending on whether the troponin levels are diagnostic of ACS (greater than 99th percentile of the upper reference limit), nondiagnostic, or normal, women are evaluated for NSTEACS. Nondiagnostic elevations of hs-cTn level would suggest possible angina (ischemia without myocardial injury), or other cardiopulmonary causes, such as acute aortic dissection, pericarditis, myocarditis, pulmonary embolism, heart failure, valvular heart disease, hypertensive emergency, or arrhythmias. Alternatively, noncardiac causes such as supply-demand mismatch (anemia, toxins, sepsis) must be considered.[19,108]

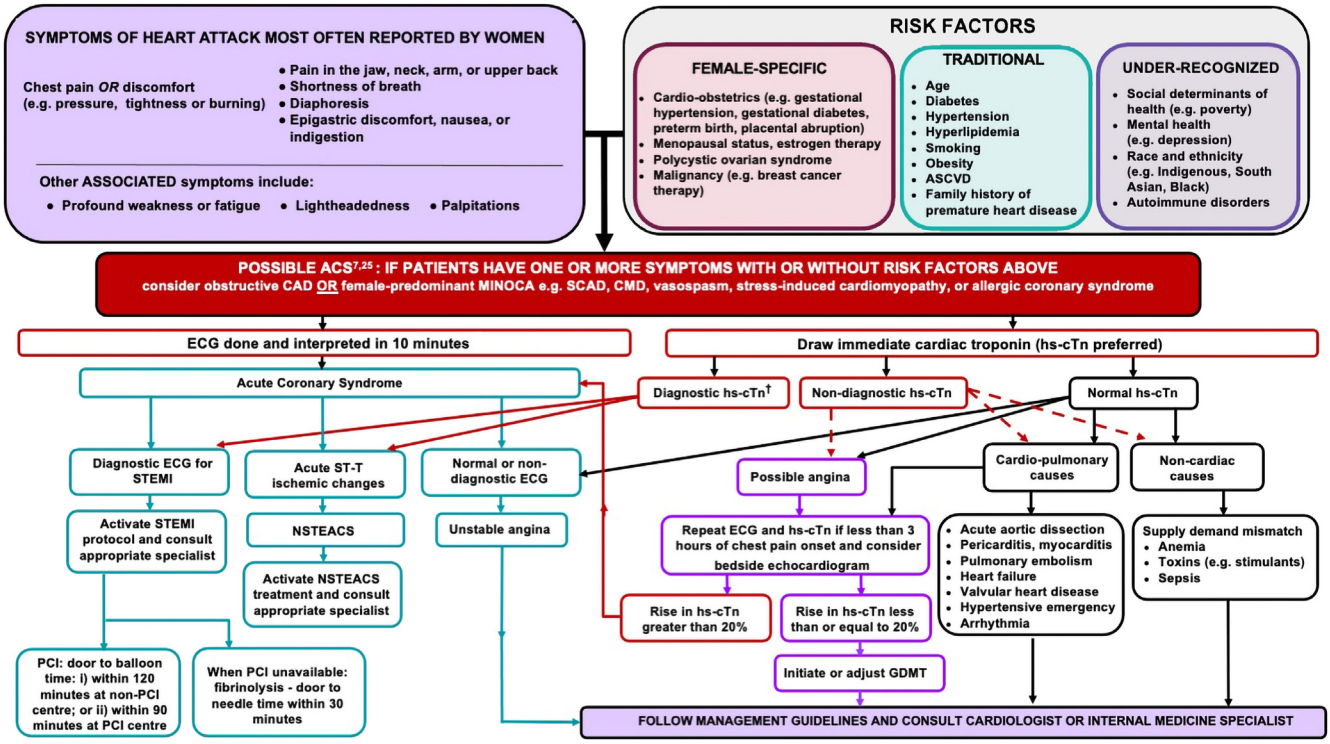

Figure 3. Chest-pain protocol for women in the emergency department. ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CMD, coronary microvascular dysfunction; ECG, electrocardiogram; GDMT, guideline-directed medical therapy; hs-cTn, high sensitivity cardiac troponin; MINOCA, myocardial infarction or ischemia with nonobstructive coronary arteries; NSTEACS, non–ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection; STEMI, ST-elevation myocardial infarction.† Diagnostic troponin: > 99th percentile upper reference limit or a 20% elevation on serial testing.

For the clinical scenario of possible angina, to further identify patients with increased risk of coronary ischemia, a repeat hs-cTn test is ordered if the symptoms have occurred < 3 hours prior to ED presentation. If the troponin rises above 20% from the previous level, the patient is considered to have ACS (NSTEACS) and is treated accordingly. If the repeat (2nd) troponin level is unchanged, or increases ≤ 20%, guideline-directed medical therapy should be initiated or increased, in those with established CAD and those diagnosed with ischemia.[109-111]

Patients with suspected CAD or UA with normal or nondiagnostic ECG findings and a normal troponin level, should have urgent referral to a cardiologist or internal medicine specialist for further management.[112]

Next steps: evaluation and implementation of the algorithm

Tertiary and community hospital EDs, and rural acute care settings across the country will be recruited to assess implementation and impact of the algorithmic protocol as a quality improvement initiative. The multicentre, prospective, observational feasibility assessment of the "Chest Pain Protocol for Women Presenting to the Emergency Department" will be followed by determination of outcomes, with a comparison of historical matched 30-day and longer-term cardiovascular mortality outcomes associated with "usual practice" (prior to utilization of the protocol), to those after implementation of the protocol in the participating sites.

Discussion

The main goal of our project was to develop an easy-to-follow algorithm incorporating existing evidence-based guidelines, while recognizing current knowledge gaps for the acute assessment of chest pain in women as addressed through expert consensus of available information. This algorithm could be posted in Eds, to increase provider awareness of female-specific risk factors, female-predominant symptoms, signs, and cardiac conditions that disproportionately affect female patients. We anticipate that this use of the algorithm may reduce diagnosis and treatment delays in women, a population that has been underserved in this context, with resulting poorer outcomes. This tool may help to ensure that timely management occurs, and that treatments and referrals are made to appropriate procedures and specialists, to improve cardiovascular outcomes in women. The protocol can be made available on the https://cwhha.ca/ website, and it can be shared with professional medical associations.

We chose to pursue this project because women at risk for CVD unfortunately remain immersed in a milieu of "under-s"—they are under-informed, under-investigated, under-diagnosed, undertreated, and underrepresented in clinical trials.[36] The diagnosis of ACS in women presenting to the ED has proven to be complex and challenging. Previous studies have found that more than 50% of heart attack symptoms in women are not recognized.[3,21] Moreover, sex- and gender-unique differences exist in chest pain and other associated

symptoms, and women are more likely to present with 3 or more symptoms in addition to chest pain.[18,21] The pathophysiology of CVD may also differ.[10] As detailed above, MINOCA accounts for 6%-15% of all ACS, is 5 times more common in women, can be caused by both atherosclerotic and sex-predominant nonatherosclerotic etiologies, and portends a poor prognosis if not appropriately recognized and treated. Recognizing this, a Canadian Cardiovascular Society Clinical Practice Update addressing MINOCA is currently in press.

The awareness of sex-unique, and sex-predominant CVD risk factors and ACS pathologies is essential to enable rapid diagnosis, and treatment, to improve outcomes. Creation of an easily accessible chest-pain algorithm created through a sex and gender lens may improve awareness of the dissimilarities and disparities between women and men presenting with ACS, which continue to exist in assessment of clinical presentation (comorbidities, risk factors) and to impact access to and delivery of quality medical care, and outcomes.[113] A recent scoping literature review highlighted the gender biases that contribute to these delays in recognition, diagnosis, and treatment of ACS.[114] Women are less likely to undergo coronary angiography and revascularization (odds ratio 0.78), and those who do are more likely to experience periprocedural complications or death (odds ratio 1.51), to have nonobstructive CAD, and to not receive appropriate treatment due to significant referral delays.[115,116] Delays in "symptom-to-door" and "door-to-balloon" times have been shown to result in 30 more minutes of total ischemic time in women than in men. Women also receive less guideline-based ACS therapies, such as dual-antiplatelet therapy, angiotensin-converting enzyme (ACE) inhibitors, statins, and beta-blockers at index admission.[117-119] Unfortunately, these disparities also extend to the recovery phase after an ACS: only 14% of women, as compared to 22% of men, participated in cardiac rehabilitation after an MI,[120] and women had a 36% lower enrollment rate than men in those with an eligible referral diagnosis, influenced by factors such as physician bias and social support (77% with high levels of support, vs 33% with low levels, attended cardiac rehabilitation).

To mitigate these significant gaps, calls-to-action have been made to establish sex- and gender-specific diagnostic protocols and recommendations for women presenting to the ED with symptoms and signs suggestive of ACS.[121] However, to our knowledge, only one study, at a single centre, utilizing a 4-step checklist found that a systems-based approach to STEMI care reduced sex disparities and improved care and outcomes in women,[122] but this study did not address other causes of chest-pain presentations to the ED.

Although we have focused our work on developing a protocol to assess chest-pain symptomatology in women presenting to the ED, we did not explore sex disparities from the perspective of CVD diagnosis in the ED. However, such exploration has been done recently in a report[123] including over 20 million cardiovascular ED encounters (48.7% women; median age was 67 years [interquartile range, 54-78]) in the US. The most common ED encounters were essential hypertension (16.0%), hypertensive heart or kidney disease (14.1%), and atrial fibrillation and/or flutter (10.2%) in women, whereas for men, the most common encounters were hypertensive heart or kidney disease (14.7%), essential hypertension (10.8%), and acute MI (10.7%). Women were more likely to present with essential HTN, hypertensive crisis, atrial fibrillation and/or flutter, supraventricular tachycardia, pulmonary embolism, or ischemic stroke. Women with aortic aneurysm and/or dissection had higher odds of hospitalization and death, whereas men were more likely to die following presentations with hypertensive heart or kidney disease, atrial fibrillation and/or flutter, acute MI, or cardiac arrest.[123] Although no information was provided regarding the approach to initial ED diagnosis as it related to outcomes, this report suggests that we may need to consider developing additional symptom-based algorithmic protocols, through a sex and gender lens, to further address sex disparities in ED presentations.

Our findings are based upon literature review and expert consensus opinion, and we cannot be certain that women from different races, ethnicities, and Indigeneity, as well as other SDOH groups were appropriately represented. We aimed to reduce the risk of potential investigator bias by doing broad literature searches in PubMed and Google Scholar, and reviewing international chest-pain guidelines. The algorithm was reviewed by key stakeholders within the CWHHA representative of different genders, races and ethnicities, including people with lived experience, medical and allied health professionals, and consensus was achieved within this group. However, the appropriateness of extrapolating the results to all populations cannot be ensured.

Conclusions

Significant knowledge and care gaps persist in women's cardiovascular health, and CVD-related morbidity and mortality rates remain high in women. Only a paucity of sex- and gender-specific CVD protocols exist in Canada. We describe the development of an algorithmic protocol for women who present to the ED acutely with chest pain. The protocol addresses the intersectionality of traditional, female-specific, and underrecognized CVD risk factors in the differential diagnosis of ACS as viewed through a sex and gender lens. The chest-pain protocol is unique, comprehensive, and easy-to-follow. This quality-improvement initiative, which is generalizable to all acute and urgent care settings, has the potential to improve cardiovascular care for women and result in better outcomes.

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Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a review article and does not contain unique patient data; therefore, no IRB consent was required.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2023.12.003.