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Review

Canadian Women's Heart Health Alliance

The Canadian Women's Heart Health Alliance Atlas on the Epidemiology, Diagnosis, and Management of Cardiovascular Disease in Women — Chapter 6: Sex- and Gender-Specific Diagnosis and Treatment

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ABSTRACT

This chapter summarizes the sex- and gender-specific diagnosis and treatment of acute/unstable presentations and nacute/stable presentations of cardiovascular disease in women. Guidelines, scientific statements, systematic reviews/meta-analyses, and primary research studies related to diagnosis and treatment of coronary artery disease, cerebrovascular disease (stroke), valvular heart disease, and heart failure in women were reviewed. The evidence is summarized as a narrative, and when available, sex- and gender-specific practice and research recommendations are provided. Acute coronary syndrome

RÉSUMÉ

Ce chapitre présente un résumé sur le diagnostic et le traitement des tableaux cliniques aigus/instables et non aigus/stables des maladies cardiovasculaires chez les femmes, et les différences propres à chacun des deux sexes. Les lignes directrices, les énoncés scientifiques, les revues systématiques/méta-analyses et les études de recherche originale sur le diagnostic et le traitement des coronaropathies, des maladies vasculaires cérébrales (AVC), des valvulopathies cardiaques et de l'insuffisance cardiaque chez les femmes ont été examinés. Les données probantes sont résumées sous forme narrative et, lorsqu'elles

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See page 601 for disclosure information.

Cardiovascular disease (CVD) presentation and emergency department delays vary between women and men. These differences are attributable to the biology of being a male or female (ie, biological sex) as well as the sociocultural norms ascribed to women in their roles, identities, opportunities/expectations, and interactions with others (gender). Sex and gender differences necessitate sex- and gender-specific

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presentations and emergency department delays are different in women than they are in men. Coronary angiography remains the gold-standard test for diagnosis of obstructive coronary artery disease. Other diagnostic imaging modalities for ischemic heart disease detection (eg, positron emission tomography, echocardiography, single-photon emission computed tomography, cardiovascular magnetic resonance, coronary computed tomography angiography) have been shown to be useful in women, with their selection dependent upon both the goal of the individualized assessment and the testing resources available. Noncontrast computed tomography and computed tomography angiography are used to diagnose stroke in women. Although sex-specific differences appear to exist in the efficacy of standard treatments for diverse presentations of acute coronary syndrome, many cardiovascular drugs and interventions tested in clinical trials were not powered to detect sex-specific differences, and knowledge gaps remain. Similarly, although knowledge is evolving about sex-specific difference in the management of valvular heart disease, and heart failure with both reduced and preserved ejection fraction, current guidelines are lacking in sex-specific recommendations, and more research is needed.

sont disponibles, des recommandations en matière de pratique et de recherche pour chacun des deux sexes sont présentées. Les tableaux cliniques du syndrome coronarien aigu et les délais d'attente à l'urgence sont différents selon qu'une femme ou un homme en est atteint. L'angiographie coronarienne reste l'examen de référence pour le diagnostic des coronaropathies obstructives. D'autres examens d'imagerie diagnostique (p. ex. la tomographie par émission de positons, l'échocardiographie, la tomographie d'émission à photon unique, la résonance magnétique cardiovasculaire, l'angiographie coronarienne par tomodensitométrie) se sont avérés utiles pour la détection des cardiopathies ischémiques chez les femmes. Le recours à ces modalités dépend de l'objectif de l'évaluation personnalisée et des ressources disponibles. La tomodensitométrie sans agent de contraste et l'angiographie par tomodensitométrie sont utilisées pour le diagnostic des AVC chez les femmes. Malgré les différences entre les sexes quant à l'efficacité des traitements de référence des divers tableaux cliniques du syndrome coronarien aigu, bon nombre des médicaments et des interventions cardiovasculaires qui ont fait l'objet d'essais cliniques n'avaient pas la puissance statistique nécessaire pour détecter des différences selon les sexes, de sorte que les connaissances restent fragmentaires sur ce sujet. De même, malgré l'évolution des connaissances sur les différences sexuelles quant à la prise en charge des valvulopathies cardiaques et de l'insuffisance cardiaque avec fraction d'éjection réduite ou préservée, on ne trouve pas de recommandations pour chaque sexe dans les lignes directrices actuelles, d'où la pertinence d'études supplémentaires portant sur cette question.

approaches to the diagnosis and treatment of CVD. This Atlas chapter aims to summarize these differences across ischemic heart disease (inclusive of both coronary artery disease [CAD] involving the epicardial coronary arteries, and small vessel disease, involving the microvasculature), cerebrovascular disease (stroke), valvular heart disease (VHD), and heart failure (HF). A heterogenous approach is used to present the evidence in this chapter, across the various manifestations of CVD in women, based on the depth and breadth of the evidence. Table 1 summarizes the guidelines and scientific statements related to the diagnosis and treatment of CAD, cerebrovascular disease (stroke), VHD, and HF, and notes where sex-specific analysis/recommendations are included. This chapter focuses on the following: (i) acute or unstable presentations—diagnosis and treatment; and (ii) nonacute or stable presentations—diagnosis and treatment of various manifestations of CVD in women. Sex and gender summary statements are provided at the end of each section, and key messages are summarized in Figure 1.

Acute Presentations: Diagnosis and Treatment

Table 1 summarizes the current guidelines and scientific statements related to the diagnosis and management of CAD, stroke, HF, and VHD and indicates whether they provide any sex and/or gender analyses or recommendations. Table 2 presents the key sex and gender considerations in the diagnosis and treatment of acute presentations of CVD reviewed herein.

Diagnosis

Women have a varied pattern and distribution of cardiovascular pain symptoms associated with both CAD and stroke that are distinct from those of men. These have historically been described as "anginal equivalents" or "atypical,"[1] making accurate diagnosis of acute or unstable CAD and stroke challenging.[2-4] The 2021 American Heart Association/American College of Cardiology/American Society of Echocardiography/American College of Chest Physicians/Society for Academic Emergency Medicine/Society of Cardiovascular Computed Tomography/Society for Cardiovascular Magnetic Resonance (AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR) Guideline for the Evaluation and Diagnosis of Chest Pain recommends describing chest pain as "cardiac," "possibly cardiac," or "noncardiac," as these terms more explicitly describe the potential underlying diagnosis.[1]

Acute coronary artery disease. Chest pain is reported to be the most common presenting symptom in 91% of men (1081 of 1185) and 92% of women (698 of 756) diagnosed with acute coronary syndrome (ACS).[5] Women are more likely than men (61.9% vs 54.8%, $P < 0.001$) to report accompanying symptoms, such as nausea, unusual fatigue, indigestion, dizziness, and palpitations.[6,7] The varied pattern of accompanying symptoms makes it difficult for women to interpret their chest pain as being cardiac-specific.[8-10] Women also may minimize their symptoms, consult with family and friends, have caregiving responsibilities, and have concerns for their family[11,12]—as a result, they may delay seeking care for their chest pain.[13] In the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC), the time from symptom onset to emergency department arrival was longer in women (median: 270 minutes [range: 130-776 minutes]) compared with that in men (median: 240 minutes [range: 120-

Table 1. Summary of guidelines and scientific statements related to the diagnosis and treatment of coronary artery disease, cerebrovascular disease (stroke), valvular heart disease, heart failure, and cardiac rehabilitation/secondary prevention in women

Condition	Guideline/scientific statement	Sex-specific analysis / recommendations
Coronary artery disease	• AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain (2021)[1]	Yes
	• ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)[122]	Yes
	• Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the AHA (2018)[23]	Yes
	• ESC Guidelines for the Management of Cardiovascular Diseases During Pregnancy (2018)[54]	Yes
	• Acute Myocardial Infarction in Women: A Scientific Statement From the AHA (2016)[43]	Yes
	• AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the ACC/AHA Task Force on Practice Guidelines (2014)[44]	Yes
	• ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease (2014)[113]	No
	• CCS/CAIC/CSCS Position Statement on Revascularization—Multivessel Coronary Artery Disease (2014)[64]	No
	• CCS Guidelines for the Diagnosis and Management of Stable Ischemic Heart Disease (2014)[97]	Yes
	• Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Ischemic Heart Disease: A Consensus Statement From the AHA (2014)[86]	Yes
	• ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the ACCF/AHA Task Force on Practice Guidelines (2013)[45]	Yes
	• Management of Patients With Refractory Angina: CCS/CPS Joint Guidelines (2012)[123]	No
	• Effectiveness-based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update: A Guideline From the AHA (2011)[51]	Yes
	• ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: Executive Summary (2011)[63]	Yes
	• Percutaneous Coronary Intervention and Adjunctive Pharmacotherapy in Women: A Statement for Healthcare Professionals From the American Heart Association (2005)[49]	Yes
Cerebrovascular disease	• Canadian Stroke Best Practice Recommendations: Rehabilitation, Recovery, and Community Participation Following Stroke. Part One: Rehabilitation and Recovery Following Stroke; 6th Edition Update (2020)[208]	No
Valvular heart disease	• ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the ACC/AHA Joint Committee on Clinical Practice Guidelines (2021)[107]	Yes
	• CCS Position Statement for Transcatheter Aortic Valve Implantation (2019)[196]	No
Heart failure	• ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: Developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the ESC With the Special Contribution of the HFA of the ESC (2021)[26]	Yes
	• CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction (2021)[137]	Yes (digoxin)
	• How to Diagnose Heart Failure With Preserved Ejection Fraction: The HFA-PEFF Diagnostic Algorithm: A Consensus Recommendation From the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) (2019)[102]	Yes
	• Sex Differences in Cardiac Arrhythmia: A Consensus Document of the EHRA, Endorsed by the HRS and APHRS (2018)[168]	Yes
	• Comprehensive Update of the CCS Guidelines for the Management of Heart Failure (2017)[166]	Yes
	• ACCF/AHA/HRS Focused Update Incorporated Into the ACCF/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the ACCF/AHA Task Force on Practice Guidelines and the HRS (2013)[159]	No
	• Society Position Statement: CCS/CAS/CHRS Joint Position Statement on the Perioperative Management of Patients With Implanted Pacemakers, Defibrillators, and Neurostimulating Devices (2012)[147]	No
	• CCS Consensus Conference Guidelines on Heart Failure, Update 2009: Diagnosis and Management of Right-Sided Heart Failure, Myocarditis, Device Therapy and Recent Important Clinical Trials (2009)[160]	No

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; APHRS, Asia Pacific Heart Rhythm Society; ASE, American Society of Echocardiography; CAIC, Canadian Association of Interventional Cardiology; CAS, Canadian Anesthesiologists' Society; CCS, Canadian Cardiovascular Society; CHEST, American College of Chest Physicians; CHFS, Canadian Heart Failure Society; CHRS, Canadian Heart Rhythm Society; CPS, Canadian Pain Society; CSCS, Canadian Society of Cardiac Surgery; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HFA, Heart Failure Association; HRS, Heart Rhythm Society; SAEM, Society for Academic Emergency Medicine; SCCT, Society of Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance.

600 minutes]), which resulted in increased 30-day mortality for women, even after controlling for baseline variables (odds ratio: 1.58; 95% confidence interval [CI], 1.27-1.97).[14]

Treatment for acute presentations of CAD depends on accurate and timely diagnosis, with imaging being critical to the process. The initial tests for women presenting with a possible ACS are an electrocardiogram (ECG) and biomarkers, which, based on the results, may trigger further diagnostic imaging. An initial normal or nondiagnostic ECG should be followed by serial ECGs based on symptoms, serial biomarkers, and further diagnostic imaging.[1] The evidence for using sex-specific biomarker cutoffs (ie, high-sensitivity cardiac troponin [cTn]) for the diagnosis and management of ACS is unclear, with emerging evidence to suggest its clinical value in younger women.[15] In the setting of ACS, the preferred diagnostic/therapeutic imaging is invasive coronary angiography for both women and men. However, evidence suggests that the underappreciation of ACS in women (based on anginal equivalent symptoms/ECGs/biomarkers) leads to sex- and gender-based differences in referral for coronary angiography in the setting of ACS.[3,4,16-18]

Important to note is that up to 15% of those presenting with acute myocardial infarction (MI) have MI with nonobstructive

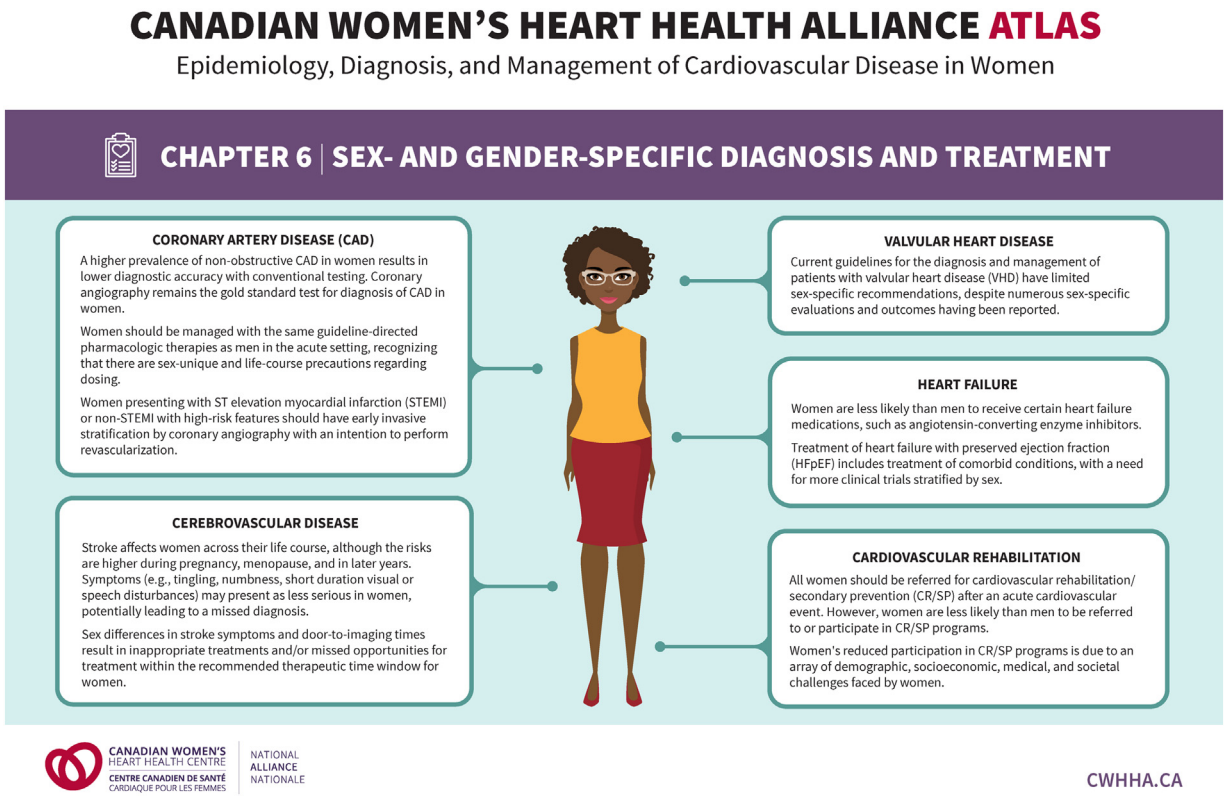

Figure 1. Summary of sex- and gender-specific diagnosis and treatment considerations for coronary artery disease, cerebrovascular disease, valvular heart disease, and heart failure; including appropriate referrals for cardiovascular rehabilitation.

CAD (MINOCA), which disproportionately affects women.[19] The etiology of MINOCA includes stress-induced cardiomyopathy, myocarditis, underappreciated plaque rupture, coronary thrombosis/emboli, coronary spasm, microvascular disease, and spontaneous coronary artery dissection. Based on a meta-analysis of studies using cardiovascular magnetic resonance (CMR) as a diagnostic tool in the setting of suspected MINOCA, a diagnosis can be made in 87% of cases when CMR is done early,[20] with myocarditis being diagnosed in 37% of cases.[21] Echocardiography and CMR also should be performed when considering stress-induced cardiomyopathy or when looking for evidence of an infarct that may have occurred secondary to plaque rupture, coronary emboli, or spasm. Whereas CMR provides a thorough evaluation of the myocardium, intravascular ultrasonography and optical coherence tomography can be used to assess the coronary arteries in further detail when trying to determine alternate mechanisms of MINOCA. A recently published study examining coronary optical coherence tomography and CMR in the workup of MINOCA suggested a cause in 84.5% of patients when one or both imaging modalities were used.[22] An ischemic etiology was identified in 63.8% of women (most commonly plaque disruption, such as plaque rupture), whereas a nonischemic cause was discovered in 20.7 %.[22] Coronary computed tomography angiography (CCTA) also can be considered as a noninvasive test to assess the coronary arteries and the presence of vulnerable plaque in intermediate- and low-risk patients presenting with ACS. The sensitivity and specificity of CCTA for the diagnosis of spontaneous coronary artery dissection (SCAD) have not yet been defined. However, noninvasive follow-up with CCTA may be useful in patients with SCAD in proximal or large-caliber coronary arteries[23]; it is likely less sensitive in identifying discrete dissections in distal small-caliber coronary arteries.[24] Pathophysiologic and diagnostic SCAD details have been published previously in chapter 5 of this Atlas.[25]

Acute heart failure. New-onset acute HF diagnostic workup begins with a thorough patient history, assessment of clinical signs and symptoms, and investigations that include an ECG, echocardiography, cTn concentration, and levels of natriuretic peptides (brain natriuretic peptide [BNP], N-terminal pro b-type natriuretic peptide [NT-proBNP], and mid-regional pro atrial natriuretic peptide [MR-proANP]).[26] Up to 93% of individuals with acute HF have increased high-sensitivity cTn concentrations[27]; however, sex-specific reference values are lacking.[28] The NT-proBNP level appears to differ by sex,[28] increase with age,[29] and vary by HF phenotype (ie, is lower in patients with HF with preserved ejection fraction [HFpEF], compared with that in patients with HF with reduced injection fraction [HFrEF]).[30-32] NT-proBNP sex-specific cutoffs are also not recommended.[28] Further details have been published in chapter 5 of this Atlas.[25]

Women, compared with men, hospitalized for acute HF are, on average, 5 years older and more commonly reside in nursing homes.[33] On admission for acute HF, women have a higher prevalence of dementia, hypertension, and gastrointestinal bleeding, and a lower prevalence of MI and peripheral vascular disease. Women report a poorer quality of life than men during hospitalization,[34] and they are less commonly discharged on angiotensin-converting enzyme inhibitors (ACEIs) and

Table 2. Key takeaways regarding sex and gender considerations in the diagnosis and treatment of acute presentations of cardiovascular disease

Evidence
- 80% of CAD, 63% of HF, and no stroke-related guidelines or position statements provided sex-specific analysis or recommendations

Diagnosis
- ACS and stroke presentations are different in women, compared with those in men, which can lead to delayed diagnosis and treatment
- In women, an initial normal or non-diagnostic ECG should be followed by serial ECGs based on symptoms, serial biomarkers, and further diagnostic imaging
- Emerging evidence indicates that using sex-specific high-sensitivity cTn cutoffs in the setting of ACS, especially in younger women, improves detection of ischemic heart disease
- Coronary angiography remains the preferred imaging modality for confirming and/or characterizing the diagnosis of ACS in women as obstructive or nonobstructive CAD

Treatment
- Early invasive stratification by coronary angiography with intention to perform revascularization is recommended for women who present with STEMI as well as NSTEMI with positive troponins
- Technical success rates of PCI are similar in women and men, but differ for CABG surgery
- Women less frequently receive appropriate pharmacologic treatment during an ACS, compared with men
- In the setting of acute HF, NT-proBNP sex-specific cutoffs are not recommended
- Sex-specific evidence is lacking for effects of tissue plasminogen activator and endovascular treatment on stroke outcomes
- Women are much less likely to be referred to and participate in secondary prevention/cardiovascular rehabilitation programs following an acute CVD event/diagnosis due to gender-related barriers, despite experiencing similar or greater benefit, compared with men

ACS, acute coronary syndromes; CABG, coronary artery bypass graft; CAD, coronary artery disease; cTn, cardiac troponin; CVD, cardiovascular disease event; ECG, electrocardiogram; HF, heart failure; MRI, magnetic resonance imaging; NSTEMI, non-ST-elevation myocardial infarction; NT-proBNP, N-terminal pro b-type natriuretic peptide; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

mineralocorticoid receptor antagonists (MRAs).[33] The length of hospital stay for acute HF is similar in men and women.[33,35] The direct cost of inpatient care for acute HF is lower among women than among men,[35] likely due to lower procedural utilization. The risk of in-hospital mortality after adjusting for age and comorbidities is lower in women than in men.[35]

Cerebrovascular disease. Stroke affects women across their life course, although the risks are higher during pregnancy and menopause, and in later years.[36] Evaluation of patients presenting with symptoms possibly consistent with stroke warrants emergent neuroimaging to exclude hemorrhage as a cause, determine the vascular territory responsible for the deficit, and determine which patients will benefit from thrombolytic therapy. Stroke can present with nontraditional symptoms in women that may be interpreted as less significant (eg, tingling, numbness, short-duration visual or speech disturbances), This interpretation can delay stroke recognition and lead to a missed diagnosis.[2,37] However, once stroke is recognized, the approach to diagnostic imaging among women and men is similar, with early non-contrast computed tomography (CT) to exclude hemorrhage.[38] When possible, this imaging should include simultaneous CT perfusion imaging and CT angiography, which together show improved detection of acute infarction, compared with non-contrast CT alone.[39,40] The multimodal CT approach provides additional information relating to the site of vascular occlusion, infarct core, salvageable brain tissue, and extent of collateral circulation.[41,42]

Treatment

Acute coronary artery disease

Pharmacologic. Women less frequently receive appropriate pharmacologic treatment during an episode of ACS and have worse outcomes, compared with men.[43] In the acute setting, there appear to be sex-specific differences in the efficacy of standard treatments for diverse presentations of ACS. For ST-elevation MI (STEMI), women have a more favourable outcome with percutaneous coronary intervention (PCI), compared with thrombolytic therapy, and they seem to benefit more from an early invasive approach in the setting of a non ST-elevation MI (NSTEMI).[43-45] However, as demonstrated in the Canadian **Gend**er and **S**ex Determ**in**ant**s** of Cardiovascular Disease: From Bench to Beyond **Pr**emature **A**cute Coronary **Sy**ndrome (GENESIS-PRAXY) study of patients with ACS aged 18-55 years, women with STEMI are less likely than men to receive reperfusion therapy.[46]

Debate remains as to whether women and men respond differently to pharmacologic therapies during an ACS event. For example, in a large meta-analysis of glycoprotein IIb/IIIa inhibitors and intravenous antiplatelet therapy used at the time of primary PCI, a reduction in the risk of death or recurrent ACS events was seen in men but not in women. However, when the analysis was limited to only those with biomarker-confirmed ACS, the sex-associated effect was no longer observed.[47] Similarly, anticoagulant (unfractionated heparin, low-molecular weight-heparins, bivalrudin) and oral antiplatelet (P2Y12 receptor inhibitors) agents have been shown to reduce adverse outcomes in both women and men with ACS who have undergone PCI.[48] Importantly, the bleeding risk of thrombolytic, anticoagulant, and antiplatelet therapies in ACS is higher in women than in men,[49] and it may be due to sex-related differences in body surface area, drug metabolism, and pharmacokinetics; weight and renal dose corrections must be considered. In premenopausal women who are still menstruating, antiplatelet therapy may substantially increase menstrual bleeding.[50]

The use of aspirin, acutely at the time of ACS, and for secondary prevention, is of clear benefit in both sexes.[51] Indeed, the long-term benefits of aspirin, beta-blockers, ACEIs, and statins after MI are similar in both women and men, with risk reductions for major adverse cardiac events of 20%-30% for both sexes in each of these drug classes.[43] Despite a definite role for these medications in the treatment of ACS, women are 10%-15% less likely than men to be treated acutely and/or prescribed these medications upon discharge from the hospital.[52,53] A point of note is that specific cautions are in place regarding medical therapy for cardiovascular syndromes in pregnant women: ACEIs and angiotensin II receptor blockers (ARBs) are in pregnancy category C (meaning animal studies have demonstrated an adverse effect on the fetus) for the first trimester of pregnancy and are labeled as being in pregnancy category D (meaning human fetal risk has been demonstrated) during the second and third trimesters.[54] Similarly, all statins are in pregnancy category X, indicating that studies in animals or humans have demonstrated

associated fetal abnormalities, so they must be avoided during pregnancy.[55] Of additional consideration in women diagnosed with ACS is the discontinuation of harmful medications or medications that are of no benefit. Other pregnancy-related medication recommendations have been published in Chapter 4 of this Atlas.[56] Menopausal hormone therapy, either estrogen plus progestin or estrogen alone, has been linked to an increased incidence of recurrent infarction and should not be given for the prevention of coronary events. For those women already receiving menopausal hormone therapy at the time of their ACS event, its discontinuation is recommended.[44,45]

Nonpharmacologic: Revascularization—percutaneous coronary intervention. Women undergo PCI at a lower rate than men following diagnosis of ACS.[57] In 23,473 patients undergoing cardiac catheterization for ACS in an Ontario cohort, a significantly lower proportion of women, compared with men, received coronary revascularization during the index hospitalization (51.8% vs 66.0%). In women diagnosed with STEMI, primary PCI was linked to lower numbers of major adverse cardiovascular events, including target revascularization.[43] Women who undergo PCI in this setting, compared with fibrinolytic therapy, have a lower risk of major bleeding, including intracranial bleeding, and lower mortality.[43] Interestingly, variables related to gender including time-to-presentation, time-to-diagnosis, and door-to-device times are longer in women, and they may contribute to excess mortality.[58] Protocolized diagnosis of STEMI may help reduce this observed gap, thereby improving prompt referral to cardiac catheterization for PCI in women.[59]

In women presenting with NSTEMI with high-risk features, such as a positive troponin test, early invasive stratification by coronary angiography with intention to perform revascularization is recommended (class I recommendation).[44] However, compared with men in a population-based cohort in Canada, women who had coronary revascularization following an NSTEMI had higher risk for recurrent cardiovascular events. Sex-based differences in outcomes following coronary angiography for NSTEMI-ACS persisted despite revascularization.[60] Additionally, evidence suggests that invasive angiography and PCI are associated with a higher risk of bleeding, vascular complications, and renal insufficiency in women.[43,44] Low-risk women with a negative troponin test are at higher risk of periprocedural complications, and an early-invasive approach is not recommended (class III).[44]

Technical success rates of PCI are reported to be similar in women and men.[61] Newer-generation drug-eluting stents (DESs) are associated with a reduction in death and recurrent MI, compared with bare-metal stents and older-generation stents. More recently, in a pooled analysis of 2 all-comers randomized controlled trials (RCTs; n = 4605), Bjerking et al.[62] reported that DESs are associated with enhanced safety in terms of cardiac death and nonfatal MI, compared with bare-metal stents in women. Specifically, they report that a DES is safe and more effective and should be considered as the stent of choice for large coronary arteries in women.[62]

Nonpharmacologic: Revascularization—coronary artery bypass graft surgery. Coronary artery bypass graft (CABG) surgery is considered the gold standard for surgical revascularization in CAD that is not amenable to PCI.[63] The Canadian Cardiovascular Society's position statement on revascularization for multivessel CAD recommends CABG in patients who are acceptable surgical candidates and have multivessel CAD and diabetes, as well as those with complex multivessel CAD (strong recommendation, high-quality evidence).[64] In part, the recommendation is based on a meta-analysis of 10 RCTs comparing CABG to PCI.[65] Although the subgroup analysis by sex was nonsignificant, the signal suggests that differences between men and women, and female data, may have been statistically attenuated due to the low proportion of women in the RCTs.[66] Female sex is a known risk factor for early in-hospital[67,68] and late[67,69] mortality after CABG surgery. In comparison to men, women present for CABG surgery with a higher preoperative risk profile that may include the following: older age at diagnosis, and significant comorbidities (hypertension, diabetes, respiratory disease, HF); more urgent/emergent surgery; less-extensive disease, needing less revascularization; and shorter cross-clamp times.[70-72] Smaller body size and smaller coronary vessels in women also have been associated with higher risk.[68] Filardo et al. reinforced the association of female sex and higher short-term mortality risk in isolated CABG using propensity-adjusted analysis (n = 13,327), which equated to a reported 392 "excess" female deaths in the US each year.[73] More recently, Hara and colleagues revealed that female patients had a greater 10-year mortality rate, compared with that of male patients (32.8% vs 24.7%; log-rank $P = 0.002$), but female sex was not an independent predictor of mortality (adjusted hazard ratio [HR]: 1.02; 95% confidence interval [CI], 0.76 to 1.36).[74] Mortality at 10 years was lower after CABG, compared with PCI, with a similar treatment effect for female vs male patients (adjusted HR for female patients: 0.90 [95% CI, 0.54 to 1.51]; adjusted HR for male patients: 0.76 [95% CI, 0.56 to 1.02]; P for interaction = 0.952).[74]

The survival benefits of using bilateral internal thoracic (mammary) artery (ITA) grafts is well established in predominantly male populations.[75] Attia et al. reported that single ITA grafting was associated with better survival in both women and men.[76] However, although bilateral ITA grafting demonstrated improved medium-term and late survival in both sexes, woman were less likely to receive this procedure, and when they did, it was less effective.[77-79] Finally, the evidence indicates that following CABG surgery, women experience added postoperative complications, such as renal failure, neurologic complications, and postoperative MI. Evidence also indicates that women have more difficulty recovering following CABG surgery, with less improvement in physical functioning and more depressive symptomatology.[68] Significant risk factors for readmission post-CABG surgery include female sex, hospital length of stay, in-hospital complications, and acute MI.[76]

Acute heart failure. The etiology and treatment of acute HF vary based on the signs of congestion and/or peripheral hypoperfusion—acute decompensated HF, acute pulmonary edema, isolated right ventricular failure, and cardiogenic shock.[26] Decompensated HF is responsible for 50%-70% of acute HF presentations and is most commonly treated with loop diuretics, and inotropic agents and vasopressors for peripheral hypoperfusion and/or hypotension.[26]

Cerebrovascular disease. Sex differences in stroke symptoms and door-to-imaging times can result in inappropriate

treatments and/or missed opportunities for treatment within the recommended therapeutic window for women.[80]

Pharmacologic. Tissue plasminogen activator is less frequently used in women than in men, resulting in a lack of evidence on sex-specific effects of tissue plasminogen activator on stroke outcomes.[80,81]

Nonpharmacologic. Endovascular treatment of acute ischemic stroke has significant benefit for men with internal carotid or proximal middle cerebral artery occlusion.[82] Evidence suggests that women have a higher prevalence of anterior and intracranial large-artery occlusion, and this may be related to a higher prevalence of atrial fibrillation in women, compared with men.[83] Data related to sex differences in access and outcomes related to endovascular treatment are scarce, and more research is needed.

Nonacute Presentations: Diagnosis and Treatment

Table 3 presents a summary of the key sex and gender considerations in the diagnosis and treatment of nonacute or chronic presentations of CVD reviewed herein.

Diagnosis

Clinical presentation, traditional and nontraditional risks, and the life course of CVD are different for women, compared with men. This difference makes the accurate diagnosis of nonacute or stable presentations of CAD in women challenging.[84,85] A higher prevalence of nonobstructive CAD in women results in lower diagnostic accuracy, compared with obstructive CAD with conventional testing in women.[86] Various noninvasive imaging modalities are now available to assist in diagnosing CAD in women and are reviewed here. In addition, many sex-specific evaluations and outcomes have been reported in VHD and HF, important CVD diagnoses in women.

Coronary artery disease. Exercise treadmill testing can be obtained rapidly, is inexpensive, and is the most common noninvasive evaluation for suspected ischemia. However, its diagnostic value is limited in women by its lower sensitivity and specificity, which range between 31% and 71%, and 66% and 86%, respectively.[87] Diagnostic and prognostic evaluation of CAD in women via exercise treadmill testing can be improved by integrating multiple parameters (eg, exercise time, changes in the ST-segment, presence of angina). Additional risk correlates include heart rate and blood pressure response and recovery. Women with intermediate risk should be referred for additional imaging studies for risk stratification.[86] Despite its false positives and lower accuracy in women, exercise treadmill testing demonstrates similar negative predictive value in both women and men, and it is recommended as a first-line diagnostic test in ruling out CAD in women who are at low risk and can exercise adequately ($>$ 5 metabolic equivalents). In women with an intermediate risk, and the ability to exercise adequately ($>$ 5 metabolic equivalents), functional assessment using stress echocardiography, stress single-photon emission computed tomography (SPECT) or positron emission tomography (PET) myocardial perfusion imaging, or stress cardiac magnetic resonance imaging may be considered.[88]

Imaging (echocardiographic or nuclear) stress tests are recommended if the resting electrocardiogram is abnormal, if there is a history of known ischemic heart disease, or in the event of limited exercise capacity; imaging is an essential component of pharmacologic stress testing. In addition to evaluating the presence of myocardial ischemia, stress echocardiography provides additional information with regard to systolic and/or diastolic dysfunction, pulmonary hypertension, and VHD. Sensitivity (79%) and specificity (83%) have been reported for the detection of obstructive CAD in women.[86] Dobutamine stress echocardiography is recommended for women who are unable to perform exercise, with sensitivity and specificity ranges of 75%-93% and 79%-92%, respectively.[86] Normal stress echocardiography results are associated with a low risk of cardiac events in women.[86] Observational data suggest that stress echocardiography may be more cost-effective than exercise treadmill testing in that it can appropriately diagnose and avoids unnecessary angiography, especially in younger women. However, stress

Table 3. Key takeaways regarding sex and gender considerations in the diagnosis and treatment of nonacute/chronic presentations of cardiovascular disease

Evidence
- There are no current sex-specific guidelines for valvular heart disease, revascularization in women with stable angina, or device therapies for women with HF

Diagnosis
- Diagnostic and prognostic evaluation of CAD in women via exercise treadmill testing can be improved by integrating multiple parameters (eg, exercise time, changes in the ST-segment, presence of angina)
- In symptomatic women with intermediate CVD risk and the ability to exercise adequately ($>$ 5 METS), either functional assessment that includes stress echocardiography, SPECT or PET myocardial perfusion imaging, or stress cardiac MRI, or alternatively, anatomic assessment with coronary CT angiography, are reasonable diagnostic strategies depending upon local resources.
- Evidence suggests rates of referral to surgery for MR are lower in women, and outcomes worse in women with severe MR, compared with men

Treatment
- Women with both obstructive and nonobstructive CAD continue to be under-prescribed ASA, beta-blockers, calcium-channel blockers, and ACEIs
- Sex differences in the administration and effects of statins remain under constant debate, although evidence suggests an increased risk of diabetes in women taking statins and a higher risk of statin-induced myotoxicity compared to men
- Women with HF often demonstrate greater symptom burden than men, including more dyspnea and poorer quality of life
- Women with HF are less likely than men to be prescribed ACEIs
- Women are underrepresented in CIED studies; evidence suggests that there are sex-differences in referrals and outcomes for pacemakers, ICDs, and CRTs
- When aortic valve replacement is required, TAVR may be preferred to SAVR in women
- Women are more likely than men to present with postoperative HF following mitral valve repair
- Novel secondary prevention approaches including home-based, online/virtual programs, community programs, and women-only programs may provide alternatives to reduce barriers and enable ongoing support for chronic CVD in women

ACEI, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid; CAD, coronary artery disease; CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; CT, computed tomography; CVD, cardiovascular disease; ECG, electrocardiogram; HF, heart failure; ICD, Implantable cardioverter defibrillator; MET, metabolic equivalent; MR, mitral regurgitation; MRI, magnetic resonance imaging; PET, positron emission tomography; SAVR, surgical aortic valve replacement; SPECT, stress single-photon emission computed tomography; TAVR, transcatheter aortic valve replacement.

echocardiography cannot distinguish between coronary microvascular dysfunction and obstructive CAD.[88]

Gated myocardial perfusion SPECT improves the predictive value in women, with a higher sensitivity range of 80%-91%, and a specificity range of 64%- 91%.[85,86,89-91] Abnormal perfusion on nuclear medicine imaging is predictive of adverse cardiac events in women, and severe abnormalities on pharmacologic stress SPECT testing are predictive of annual cardiovascular mortality in women with diabetes (8.5% per year) and without diabetes (6.1% per year).[92]

Stress myocardial perfusion imaging with PET improves spatial resolution and image quality in women, especially in women with obesity.[86] Meta-analysis data suggest that sensitivity (92%) and specificity (85%) are higher than they are with SPECT, with significant improvement of diagnostic accuracy.[86] Quantification of coronary flow reserve using rubidium is possible and is predictive of prognosis, as PET-measured coronary flow reserve < 2.0 is associated with an increased risk of cardiac death, MI, revascularization, and HF in both men and women and can be diagnostic of coronary microvascular dysfunction in the absence of obstructive CAD.[93] Radiation exposure is present as in SPECT noninvasive testing.[88]

Stress cardiac magnetic resonance imaging (cMRI), most often performed with vasodilator-induced coronary hyperemia (adenosine or regadenoson) allows for assessment of structural abnormalities, stress-induced wall-motion abnormalities, systolic dysfunction, myocardial edema, scarring, and fibrosis.[86] This modality provides higher specificity (91% vs 82%) and similar sensitivity for diagnosing obstructive CAD in women, compared with men.[86] An additional advantage of stress cMRI is the ability to assess subendocardial perfusion qualitatively, which is of specific interest in women with angina and no obstructive CAD.[86,94] Myocardial perfusion reserve index, a quantitative measure of subendocardial perfusion, correlates with and is predictive of coronary microvascular dysfunction on invasive coronary reactivity testing.[94] cMRI is particularly useful in women with obesity, owing to its high spatial and temporal resolution. However, it is relatively contraindicated in end-stage renal disease.[88] Some cardiac centres have determined that combining entities of cMRI and SPECT allows for improved diagnostic and prognostic value of myocardial perfusion.[95]

CCTA provides anatomic coronary artery information and is diagnostically useful in symptomatic intermediate-risk patients. It may be considered as an initial anatomic diagnostic strategy alternative to functional exercise stress testing, or for further evaluation of an abnormal exercise stress test in the context of no known CAD.[1] CCTA is also useful to assess patients with stable angina in the context of known nonobstructive CAD or previous coronary revascularization.[1] Plaque progression and high-risk plaque can be assessed using CCTA. In a secondary analysis of the **I**nternational **S**tudy of **C**omparative **H**ealth **E**ffectiveness With **M**edical and **I**nvasive **A**pproaches (ISCHEMIA) trial, women with evidence of moderate to severe ischemia were less likely than men to have extensive CAD on CCTA (36% women vs 47% men with 3-vessel disease; 32% vs 31% with 2-vessel disease) and more likely to have 1-vessel disease (31% women vs 22% men).[96] Noninvasive fractional flow reserve can also be determined in some centres. Radiation exposure is also a consideration, and patients require beta-blocker therapy pretest to slow heart rate and enhance image quality.[88]

Coronary angiography remains the gold standard test for diagnosis of obstructive CAD. Use of coronary angiography should be considered when noninvasive tests demonstrate high-risk features, or when symptoms persist despite optimal medical therapy (strong recommendation, high-quality evidence).[97]

Chronic heart failure. Typical chronic HF symptoms include dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, reduced exercise tolerance, and ankle swelling. Although the signs and symptoms of HF are similar for women vs men, women often demonstrate greater symptom burden, including more dyspnea and poorer quality of life.[34,98] Women with HF often are underdiagnosed, are undertreated, and experience delays in referral for health services and invasive care.[99] This difference is partly related to sex differences in the etiology of HF; more women than men have HFpEF.[100,101] HFpEF is defined as a normal EF (ie, EF $>$ 50%), a nondilated left ventricle with concentric remodelling, or a hypertrophied left ventricle with left atrial enlargement.[102] Class I recommended diagnostic investigations for chronic HF include measurement of natriuretic peptides (ie, BNP and NT-proBNP),[26] 12-lead ECG, transthoracic echocardiography, chest X ray, and other routine blood tests to assess for comorbidities. Cardiac catheterization is recommended when an intermediate probability of HFpEF is determined to exist after history, physical examination, and other recommended diagnostic evaluations (eg, natriuetic peptide determination, echocardiography) have been performed.[103] In cases in which access to specialized tests is limited, a more simplified pragmatic approach to diagnosing HFpEF is recommended. This includes assessment of the following: (i) signs/symptoms of HF; (ii) a left ventricular ejection fraction (LVEF) $\geq$ 50%; and (iii) objective evidence of cardiac structural and/or functional abnormalities consistent with LV diastolic dysfunction/raised LV filling pressures. With this approach, the greater number of objective noninvasive measures increases the probability of an HFpEF diagnosis.[26] Further details have been published in Chapter 5 of this Atlas.[25]

Valvular heart disease. In aortic stenosis, the concomitance of a low flow rate despite a normal EF (ie, paradoxical low flow or HFpEF associated with aortic stenosis) is reported to be higher in women.[104] The first issue with paradoxical low flow is linked to the assessment of aortic stenosis severity. Indeed, as the gradient and velocity across the stenosed aortic valve are dependent on the flow rate, a decrease in flow rate will lead to a decrease in gradient and velocity, which may underestimate the degree of stenosis severity. On the other hand, a moderately stenosed valve may not open fully, due to a lower flow rate, thus presenting a small valve area, which overestimates the degree of stenosis severity. Therefore, a discordance between gradient/velocity (in the moderate range) and aortic valve area (in the severe range) at rest echocardiography in these patients is not uncommon.[105] The use of multidetector-computed tomography has been validated to assess aortic valve calcification (Agatston method), with sex-

specific thresholds identifying severe aortic stenosis as ≥ 1200 Agatston units (AU) in women and ≥ 2000 AU in men.[106,107] Moreover, the presence of low flow is an independent predictor of adverse outcomes, and these patients should be considered to have at least intermediate risk.[108] Interestingly, low flow, with or without sex-specific thresholds, appears to have a higher impact in women than in men.[109]

Evaluation of patients with mitral regurgitation (MR) requires comprehensive echocardiographic assessment, including evaluation of MR severity and signs of volume overload. Current guidelines suggest absolute measurements of left ventricular (LV) size as surgical cutoff criteria[107]; however, measurements not indexed to body surface area may underestimate LV dilation and disease severity,[110,111] impacting timely diagnosis and intervention in asymptomatic women.

Treatment

Coronary artery disease. In Canada, more women die each year of CAD than of chronic lower respiratory disease, Alzheimer's disease, diabetes, breast cancer, and all female gynecological cancers combined.[112] Pharmacologic and nonpharmacologic treatment strategies reduce morbidity and mortality and improve health-related quality of life (HRQoL).

Pharmacologic. Patients with stable CAD are maintained on a combination of evidenced-based drugs, including acetylsalicylic acid (ASA; aspirin), statins, beta-blockers, ACEIs, ARBs, digoxin, diuretics, and anti-thrombotic drugs.[97,113] However, the possibility that the "one size fits all" sex-agnostic approach is not appropriate is becoming apparent. A point now recognized is that cardiovascular (CV) medications have been tested predominantly in clinical trials that were not powered for sex-specific analyses. Nonetheless, experiences in the use of these drugs in chronic conditions indicate the presence of sex differences. Further details are described below.

The maintenance care of stable CAD generally focuses on blood pressure and blood lipid levels. The renin-angiotensin system is one mechanism that regulates blood pressure. Methods of inhibiting the renin-angiotensin system include used of 2 drug classes that operate on different stages in the system. ACEIs act by inhibiting the conversion of angiotensin I to angiotensin II. ARBs function by binding to the angiotensin receptor, thus blocking the angiotensin II access to the binding site. Studies have shown that women are more likely to be ACEI intolerant (odds ratio [OR] 1.70; 95% CI, 1.65-1.75).[114] However, pharmacokinetic differences have been identified with the use of ARBs, such as the finding that women's maximum serum concentrations (given the same dosage) of losartan and telmisartan were twice that in men.[115] Despite such findings, the only sex-specific restriction regarding ARBs is directed to pregnant and lactating women.[116]

Beta-blockers are used in men and women with CAD to decrease the harmful effects of excessive adrenergic stimulation to the heart (ie, angina symptoms in men and women with stable CAD).[117,118] The Canadian Cardiovascular Society 2014 guidelines for the diagnosis and management of stable ischemic heart disease recommend beta-blockers as first-line therapy for chronic stable angina post-MI, and beta-blockers or long-acting calcium channel blockers for uncomplicated chronic stable angina.[97] Registry studies show that women are less likely than men to receive treatment with beta-blockers.[119,120] In Canada, use of beta-blockers in obstructive and nonobstructive CAD did not differ by sex 3 months post-angiography. However, only 67.5% of women with obstructive CAD, and 41.9% of women with nonobstructive CAD, were prescribed beta-blockers.[121] Alternative anti-anginal medications include non-dihydropyridine calcium-channel blockers (CCBs), which lower heart rate and myocardial inotropism.[122] Women with obstructive and nonobstructive CAD are more commonly prescribed CCBs ($P < 0.001$), although only 38.3% of women with obstructive CAD, and 31% of women with nonobstructive CAD, are prescribed CCBs 3 months post-coronary angiography.[121]

Second-line agents for symptom relief include long-acting nitrates, which reduce pre-load and contribute to coronary vasodilation.[122] In cases of refractory angina or intolerance to first-line agents, alternate second-line therapies are recommended.[123] Results from the Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery disease (CLARIFY) international registry across 45 countries suggest that, in addition to calcium-channel blockers, women are more frequently prescribed long-acting nitrates for stable CAD, compared with men ($P < 0.001$).[124]

Although the mechanism of action is not completely understood, ranolazine (recently approved for use in Canada) does not affect heart rate or blood pressure, and it acts on late inward sodium current in myocardial cells, possibly reducing oxygen demand by inhibiting intracellular calcium overload.[122] Effects on potassium currents may cause QT prolongation, and monitoring is warranted when initiating ranolazine. Ranolazine is metabolized by cytochrome P450 family 3 subfamily A member 4 (CYP3A4), and care must be taken to avoid drug-drug interactions with other drugs metabolized or inhibiting CYP3A4, and those causing QT prolongation.[125] Use of ranolazine has been associated with a reduction in angina frequency, nitroglycerin consumption, and total exercise duration in patients with stable CAD,[126,127] with evidence of improved outcomes (ie, less angina, improved function, and better HRQoL) in women with myocardial ischemia and nonobstructive CAD.[128] However, more research powered for sex-based analyses is needed. Nicorandil, a systemic and coronary vasodilator,[122] available through special access programs requiring approval by Health Canada, also has been used for patients with refractory symptoms or vasospastic angina, on a case-by-case basis, but robust trials are lacking.[123]

One of the most commonly used drugs worldwide, ASA, is routinely given to at-risk patients to prevent and treat coronary heart disease.[129] However, the platelet inhibition effect of ASA varies among patients, and the underlying reasons for this are not clear. In the Physician's Health Study, a 44% reduction in risk of MI in men occurred (relative risk [RR], 0.56, 95% CI , 0.45-0.70, $P < 0.00001$) in the aspirin group, compared with the placebo group, with inconclusive benefit for stroke and cardiovascular deaths.[130] The risk reduction in MI was evident in men aged > 50 years ($P = 0.02$). Aspirin appears to have greatest benefit in women of reducing risk of mortality from cardiovascular disease (CAD and stroke; RR,

0.62, 95% CI, 0.55-0.71), with this effect most pronounced within the first 5 years of use and in older women ($P < 0.001$).[131]

Statins are a group of drugs used to lower blood cholesterol in both men and women. The inconclusive results from studies of sex differences in the administration and effects of statins are under constant debate. The **J**ustification for the **U**se of Statins in **P**revention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER) trial showed an increased risk of diabetes in women taking statins, compared with that in men.[132] Women are also at higher risk of statin-induced myotoxicity.[133]

A Dutch cohort study examined adherence to guidelines-based medications after STEMI/NSTEMI by following 52,672 individuals for 12 months after discharge.[134] Findings revealed that use of indicated drugs (ASA, P2Y12-inhibitor, statin, beta-blocker, ACE-/AT2-inhibitor) was higher in male patients, compared with that in female patients, regardless of MI subtype (STEMI male 61% vs female 57%, $P \leq 0.001$; NSTEMI male 43% vs female 37%, $P \leq 0.001$).

Nonpharmacologic. Revascularization can be performed during angiography for obstructive lesions when indicated.[88] Currently, no sex-specific guidelines have been developed regarding revascularization in patients with stable angina.

Chronic heart failure. Women are underrepresented relative to disease prevalence as participants in clinical trials of HF; drug dosing protocols, as well as estimates of treatment efficacy and adverse events, are derived from trials with primarily men as trial participants.[135,136] Trials often are inadequately powered for sex-specific analysis, and subgroup analyses, when reported, often do not include testing for sex-treatment interactions.[135,136] The underrepresentation of women relative to sex distribution of disease has persisted over time, with no change in trends over the past 20 years.[136] Sex-specific eligibility criteria; trial leadership by male investigators; and drug, device, or surgical interventions are independently associated with underenrollment of women with HF, highlighting areas that can be targeted to increase enrollment of women.[136]

Pharmacologic. The recent Canadian Cardiovascular Society/Canadian Heart Failure Society (CCS/CHFS) guidelines for HFrEF recommend 4 classes of medications, as follows[137]: (i) angiotensin receptor-neprilysin inhibitor (ARNI) as first-line therapy (preferably) or following titration of an ACEI/ARB; (ii) beta-blocker; (iii) MRA; and (iv) sodium glucose transport 2 inhibitor. Other medical therapies may be used based on individual patient characteristics. Women and men are commonly prescribed diuretics, beta-blockers, and MRAs at similar rates, but women are less likely to receive ACEIs.[138] Women are more likely to receive digoxin and an ARB, which have not been demonstrated to provide a mortality benefit in HFrEF.[138] The response and effect of beta-blockers, MRAs, ACEIs, and ARBs appear to be similar between the sexes, although women may require lower doses of ACEI to receive mortality benefit.[135,138-141] A post hoc subgroup analysis of the **D**igitalis **I**nvestigation **G**roup (DIG) trial, which originally showed that digoxin use was associated with an overall decrease in hospitalizations, revealed that female patients prescribed digoxin had a 5.8-fold higher absolute risk of all-cause mortality, compared with male patients (interaction $P = 0.034$), raising concerns about using digoxin therapy in female patients.[135] Most eligible women and men with HFrEF do not receive target doses of medical therapy (including ARNIs, beta-blockers, ACEIs, ARBs, and MRAs) following hospitalization, and only a minority have guideline-directed serial incremental dose adjustments over time.[142]

No known drug therapies reduce the risk of CV mortality in HFpEF, although a few reduce the risk of HF hospitalization. PARAGON-HF (**P**rospective Comparison of **ARN**I [angiotensin receptor−neprilysin inhibitor] with **A**RB [angiotensin-receptor blockers] **G**lobal **O**utcomes in HF With Preserved Ejectio**n** Fraction), a trial assessing the efficacy of neprilysin inhibition in HFpEF, was associated with lower rates of the composite primary outcome of death or HF hospitalizations, driven by a reduction in HF hospitalizations; a treatment interaction was noted with sex and LVEF such that women derived benefit from sacubitril-valsartan at a higher LVEF than men.[143] The Preserved, **Emp**agliflozin Outcom**e** T**r**ial in Patients With Chr**o**nic Hea**r**t Failure With **Preserved** Ejection Fraction (EMPEROR-Preserved) trial assessed the efficacy of empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, in patients with class II-IV heart failure and an ejection fraction > 40%.[144] Empagliflozin reduced the combined risk of cardiovascular death or HF hospitalization by 21% (HR, 0.79 [95% CI, 0.69-0.90] in both female and male patients, with the effect due largely to reduced HF hospitalizations. Increasing evidence indicates that LVEF should be treated as a continuum, as therapies effective in HFrEF also appear to be effective in HF with mildly reduced EF (HFmrEF) and HFpEF. The management of HFpEF should include the following: (i) identification and treatment of underlying etiologies, such as hypertensive heart disease, with exclusion of mimickers of HFpEF; (ii) identification and treatment of comorbid conditions that account for an increasing proportion of hospitalizations and deaths as LVEF increases; (iii) use of pharmacotherapies to reduce the burden of HF hospitalization; (iv) management of volume overload; and (v) lifestyle modification, including caloric reduction among obese patients, and exercise to improve functional capacity and quality of life.[145] Long-term prognosis after HFpEF onset is poor; however, female patients have better survival, compared with male patients.[146]

Nonpharmacologic: Cardiac implantable electronic devices. An estimated 200,000 Canadians live with a cardiac implantable electronic device (CIED).[147] Indications for CIED use continue to increase. Presently, evidence regarding CIEDs is predominantly only available in retrospective, observational, and registry studies. By and large, women are underrepresented in CIED studies, thereby limiting evidence-based conclusions. Consequently, the available research regarding sex- and gender-specific observations on the outcomes of CIED is presented below.

Nonpharmacologic: Pacemakers. Sick sinus syndrome and atrial fibrillation with bradyarrhythmias have been shown to be the main indications for permanent pacemaker implantation in women, whereas the main indication in men is atrioventricular block.[148] Reports vary on the impact of sex on the selection of cardiac pacemakers; Roeters Van Lennep et al.[149] found no

significant differences in the selection of pacemakers based on sex, whereas others have reported that women are less likely than men to receive dual-chamber pacemakers.[150,151]

Sex may also impact outcomes after device insertion. In a 30-year follow-up study examining the prognostic importance of baseline patient characteristics impacting survival post-permanent pacemaker implantation, women survived longer than men, despite being older at the time of the procedure.[152] The **C**anadian **T**rial **o**f **P**hysiological **P**acing (CTOPP) reported no sex differences in HRQoL in men vs women,[153] whereas the **Mo**de **S**election **T**rial (MOST) revealed lower HRQoL scores and worsening functional status in women.[154] Complications such as pneumothorax and pocket hematoma are more common in women, and hospitalizations for device-related infections are more common in men.[155] Some have suggested that complications in women may be related to smaller body size and vessel diameter, as well as thinner right ventricle wall.[156,157]

Nonpharmacologic: Implantable cardioverter defibrillators. Sudden cardiac arrest can have devastating impacts for individuals and their families.[158] Implantable cardioverter defibrillators (ICDs) are the gold standard of treatment for primary prevention (patients at risk for ventricular tachyarrhythmias) and secondary prevention (patients who have survived a life-threatening ventricular arrhythmia or sudden cardiac arrest) in both women and men.[159,160] Several studies have shown improved survival rates with the use of these devices in high-risk patients with CAD, ventricular dysfunction, and inducible ventricular tachycardia.[159-164] However, a recent meta-analysis of 6 RCTs, including the **D**anish Study to **A**ssess the Efficacy of ICDs in Patients with **N**on-**i**schemic **S**ystolic **H**eart Failure on Mortality (DANISH) trial, revealed that women did not attain significant survival benefit from primary preventive ICDs, but men did.[165] Nevertheless, guidelines make the same recommendations for ICDs in women and men based on overall treatment effect estimates in ICD trials.[166]

Indeed, the underrepresentation of women in clinical trials of ICD therapy (8%-32%) and registries[161-164,167,168] limits assessments for sex-specific differences in treatment effect.[119-122,124,125] According to the Canadian ICD registry of 6021 patients referred for ICD, only 21.4% were women.[169] Female sex may also influence decisions to implant an ICD. Curtis et al. reported that men were 3.2 times more likely than women to receive ICD therapy in a Medicare sample of > 230,000 patients.[167] Subgroup analyses performed on data from the **M**ulticenter **Un**sustained **T**achycardia **T**rial (MUSTT) and the **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial II (MADIT-II) trial indicated that mortality does not differ between men and women[162,163]; however, the **S**udden **C**ardiac **D**eath in **He**art **F**ailure **T**rial (SCD-HeFT) reported a statistically significant improvement in mortality for men only.[161] Further subgroup analyses,[167] meta-analyses,[170] and population-based studies[165,169,171,172] also have shown discrepant effects of sex on ICD benefit in primary and/or secondary prevention populations.

The National Cardiovascular Data Registry (NCDR) ICD registry reported that women had a higher rate of periprocedural complications than men (7.2% vs 4.8%; 95% CI, 1.25-1.53; $P < 0.001$).[160] Women were more likely to have device-related complications at 45 days and 1 year, although mortality did not differ between men and women.

Nonpharmacologic: Cardiac resynchronization therapy. Cardiac resynchronization therapy (CRT) defibrillator (CRT-D) is the current standard of care for refractory HF.[159,160] It is a class I recommendation for patients with HF (New York Heart Association (NYHA)/CCS class II, III, and IV), reduced ejection fraction (EF ≤ 35%) despite maximally tolerated doses of guideline-directed medical therapies, and electrocardiographic evidence of ventricular dysynchrony (left bundle branch block [LBBB] and QRS > 150 ms).[137] In the landmark **Co**mparison of **M**edical Therapy, **P**acing **an**d Defibrillat**ion** in Heart Failure (COMPANION) trial, CRT-D reduced mortality by 36%, compared with medical therapy, with significant reduction in hospitalization and improvement in functional status.[173] CRT implantation should be performed only when the LVEF meets guideline criteria for nonischemic cardiomyopathy (NICM) for patients who have received > 3 months of medical therapy or those with ischemic cardiomyopathy > 40 days post MI.[159,160,174]

In a Swedish registry study,[174] female sex and age were independent predictors of non-referral for CRT. CRT-D may confer greater benefits to women than to men in the setting of NICM and LBBB.[175-178] Subgroup analysis of the **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial With **C**ardiac **R**esynchronization **T**herapy (MADIT-CRT) study identified women as exceptional responders to CRT, with a 72% decrease in all-cause mortality and greater reduction in left atrial and ventricular volumes.[178] Despite men typically being younger at diagnosis, in a retrospective study conducted by Wang et al., women were found to have a lower risk of death, compared with men in LBBB-associated NICM, after controlling for age at diagnosis.[176] Women have a shorter baseline QRS duration (QRSd) and smaller LV volumes than men. Therefore, women have relatively more dysynchrony for any prolonged QRSd, which may contribute to a better outcome with CRT.[175] Sex-specific, stricter QRSd criteria recommendations (QRSd > 140 for men and > 130 for women) have been proposed and evaluated, with no significant difference in echocardiographic response to CRT between men and women at 12-month follow-up.[179,180] Lastly, in the MADIT-CRT trial, women experienced higher device-related adverse events compared with men (10.5% vs 7.9%, respectively, $P = 0.001$).[177] In summary, women appear to be "super-responders" to CRT, but they are under-referred for CRT, relative to men.

Valvular heart disease. When aortic valve replacement is required, transcatheter aortic valve replacement (TAVR) may be preferred to surgical aortic valve replacement (SAVR) in women, given the following: (i) TAVR may be safer for low-flow patients, with evidence of lower operative mortality[181]; (ii) women are more susceptible to prothesis-patient mismatch, which is less prevalent after TAVR[182]; and (iii) women at intermediate/high risk enrolled in the **W**omen's **In**ternational **T**ranscatheter **A**ortic **V**alve **I**mplantation (WIN-TAVI) all-female registry had reduced incidence of early mortality and stroke.[183] Finally, sex was the only subgroup in which a significant interaction with treatment occurred, with a trend toward superiority of TAVR vs SAVR in women.[184] An

unfortunate point to note is that RCTs comparing TAVR to SAVR have not stratified randomization by sex.

Earlier cohorts of MR patients suggested lower rates of referral to surgery in women, with worse outcomes in women with severe MR, compared with outcomes in men.[111] Mitral valve repair is less often successfully performed in women, attributable to a higher occurrence of rheumatic disease and anterior/bileaflet valve prolapse.[185] Mortality following mitral valve surgery is similar or slightly higher in women, compared with men,[110,111] and women are more likely to present with postoperative HF, which may be due to more-advanced disease on presentation.[111] Transcatheter mitral valve repair with the edge-to-edge approach may have less impact in women, compared with men, as the **C**ardiovascular **O**utcomes **A**ssessment of the MitraClip **P**ercutaneous **T**herapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial demonstrated no superiority of the transcatheter intervention over standard therapy in women and an interaction between sex and treatment with regard to HF rate at 24 months.[186] On the other hand, the study enrolled only 34% of women who may have been at a more advanced stage of LV dilation, as dimensions were not indexed to body surface area. However, as women have a more extensive calcification of the mitral annulus, transcatheter interventions, as well as surgical intervention, may create higher risk in women.[187] Moreover, calcification of the mitral annulus is a contraindication for transcatheter annuloplasty of the mitral valve, and a concern for TAVR.

Surgical intervention for tricuspid regurgitation, as an isolated intervention, is performed more in women than in men, and it is associated with an important risk of mortality. In recent years, several transcatheter devices have been developed to repair or replace the tricuspid valve, and they seem to improve outcomes, compared with conservative management.[188]

Cardiovascular Rehabilitation/Secondary Prevention

Many cardiovascular diseases are chronic in nature, disrupt an individual's life, and create disturbances in various dimensions of HRQoL.

Survivor's quote:

> *"A Woman Survivor's Perspective—With a cardiac diagnosis, there is Loss. Fear. Denial. Anger. There is deep to the core existential uncertainty and angst. One is shaken with the reality of one's mortality. The physical healing and recovery is a task on one level. However, this must be accompanied by the emotional and spiritual re-piecing together of one's 'new life'.*
>
> *The challenge of a cardiac rehab program is to include not just exercise and educational components, but also to provide emotional, psychological and social supports to help heal the fragile and traumatized psyche, in order to give the woman her life—with hope, balance, and perspective—back."*
>
> *—M. Hardy, Woman With Lived Experience, Canadian Women's Heart Health Alliance (personal communication, June 16, 2019)*

A holistic, gender-tailored, and lifelong approach to rehabilitation and secondary prevention is necessary. Self-management programs allow women to take an active role in the management of CVD and are important predictors of successful behaviour change. Comprehensive cardiovascular rehabilitation/secondary prevention (CR/SP) programs offer structured exercise and physical activity promotion, health education, CVD risk factor management, and psychological support to optimize long-term health outcomes for both primary and secondary prevention.[189] CR/SP programs are widely endorsed as a class IA recommendation and as a standard quality-care indicator for patients diagnosed with CAD.[189,190] Participation in CR/SP improves HRQoL and functional status, and reduces morbidity and mortality by 50% in patients with CAD.[191-193] In a recent retrospective cohort study (n = 18,383), exercise-based CR was linked to significantly lower odds of all-cause mortality (0.37; 95% CI, 0.29-0.47) and rehospitalization (0.29; 95% CI, 0.27-0.32) compared with PCI or PCI plus CR.[194] However, results were not stratified by sex.

The "2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure" provides specific recommendations for exercise for HF patients, including in patients with an ICD and/or CRT therapy.[166] A 2019 Cochrane review of 44 RCTs (5783 subjects) of CR/SP in HF (primarily HFrEF) found participation in CR/SP programs to be associated with reductions in all-cause (risk ratio [RR]: 0.70; 95% CI, 0.60 to 0.83) and HF-specific hospitalization (RR: 0.59; 95% CI, 0.42 to 0.84) and improved HRQoL.[195] The role of exercise training in HFpEF patients remains less conclusive; however, available data suggest it does provide benefits, including improved exercise capacity and quality of life.[166]

The "2019 Canadian Cardiovascular Society Position Statement for Transcatheter Aortic Valve Implantation" recommends rehabilitation and physical activity, as appropriate.[196] A 2021 Cochrane review of 6 RCTs in 364 patients who were enrolled in either open or percutaneous heart valve surgery was unable to make conclusions regarding the effect of exercise-based CR on health outcomes in VHD patients.[197] A recent, large cohort study of patients who underwent open valve surgery in the US (n = 41,369; 41% female) found that those who enrolled in CR/SP programs (43.2%) had lower cumulative hospitalization (adjusted HR, 0.66; 95% CI, 0.63-0.69) and mortality (adjusted HR, 0.39; 95% CI, 0.35-0.44) at 1 year, compared with patients who did not participate in a CR/SP program.[198]

In the Canadian healthcare system, referral is the sole requirement for access to and enrollment in CR/SP programs. Ideally, CR referral occurs at hospital discharge through systematic referral, and enrollment should occur within 30 days of acute hospitalization.[199] Unfortunately, women are substantially less likely to be referred to CR/SP programs, and once referred, they are 36% less likely to participate than men.[199-201] Women would benefit from CR participation, as they are more likely to have depression, diabetes, HF, high blood pressure, and reduced HRQoL following a cardiac event, compared with men.[202] There is an inherent need to distinctly enhance the nature and level of CR/SP care provided to women with CVD in Canada.

Strategies such as healthcare provider endorsement, in-hospital discussion with a peer liaison (patient who has completed CR), early follow-up, and telephone interventions can be effective for improving CR/SP program enrollment.

However, many women prefer gender-tailored or women-only CR programs, with a limited number of trials demonstrating greater adherence and improved mental health outcomes, in comparison to traditional co-ed programs.[203,204] Conventional CR/SP programs may not meet the recovery needs of all women; it has been suggested that women's primary "rehabilitative need" may be social support, specifically from women with similar illness experiences. A recent national survey of 1654 Canadian women reinforced the need for social support and revealed perceptions that CR/SP programs are male-centric, lack emotional support and time for social interaction, and reflect a preoccupation with structured exercise that may not be compatible with women's lifestyles.[205] In addition to CR/SP participation barriers for women, consideration of psychological and mental health implications of cardiac diagnoses is encouraged. Programs could benefit from mental health supports incorporated in a seamless, non-stigmatizing manner.[205-207]

Women are also less likely than men to be discharged to inpatient rehabilitation or to participate in rehabilitation following stroke in Canada.[208] The Canadian Stroke Best Practices outline recommendations for rehabilitation and recovery. Following stroke, the recommendation is that inpatient rehabilitation therapy begin as early as possible once patients are medically stable and able to participate. Individuals with ongoing rehabilitation needs after leaving the hospital should continue to have access to interdisciplinary, specialized stroke services, including facility-based outpatient services and/or in-home rehabilitation services.[208]

Women's reduced participation in CR/SP programs is due to a complex and unique mix of demographic, socioeconomic, medical, and societal challenges faced by women.[206] Barriers to women's CR/SP participation occur across referral, enrollment, completion, and adherence.[199,205-207] Common barriers include the following:

(i) financial factors (low income, transportation issues, medical insurance coverage, etc.);
(ii) social factors (racial and ethnic populations, family responsibilities and stressors, low education, etc.);
(iii) lifestyle factors (cigarette smoking, physical inactivity, etc.);
(iv) medical comorbidities (obesity, diabetes, previous MI, etc.); and
(v) institutional factors (limited physician referrals, limited healthcare provider endorsement, etc.).[199,205-207]

Novel approaches, including home-based, online/virtual CR/SP with technology options, and women-only programs, provide alternatives to reduce program barriers.[209,210] A recent online survey of CR availability and delivery in Canada identified 182 CR programs across 10 of 13 provinces/territories. Of the 57 responding programs, 49 (79.0%) offered alternative or home-based CR; 3 (5.5%) had women-only CR programming; and 7 programs (14.6%) in Ontario offered women-only sessions or classes.[211] Other Canadian-based programs include the Heart Wise Exercise (HWE) model (heartwise.ottawaheart.ca), which utilizes existing community-based exercise programs to deliver safe and appropriate exercise classes to stable outpatients with chronic disease. More than 250 HWE facilities and 4400 HWE trained fitness leaders are available in Canada. Approximately 89% of HWE attendees in 2015 were women, with a mean age of 60 years, and in 2016-2017, a total of 77% of HWE attendees were women, with a mean age of 75 years. HWE leaders encourage self-monitoring and daily aerobic exercise, and attendees are satisfied with the HWE model.[212] Mobile health technologies also have been developed to help women manage weight[8] and increase physical activity. Although women in other populations indicate that these technologies are supportive, motivate healthy behaviours, reduce symptoms, and improve HRQoL, more evidence is needed in women with CVD.

Conclusions

Sex- and gender-specific differences are present in the diagnosis and treatment of ischemic heart disease in women. Similarly, although the signs and symptoms of HFrEF are similar between women and men, women often demonstrate greater symptom burden and are less likely to receive guideline-directed medical therapies. Emerging data indicate sex differences in diagnosis and pharmacologic and non-pharmacologic treatments for HFpEF, valvular heart disease, and stroke. Current guidelines are limited in scope and must be further developed and disseminated in order to improve quality of life and outcomes for women with CVDs.

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