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Society Guidelines

2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure

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ABSTRACT

Since the inception of the Canadian Cardiovascular Society heart failure (HF) guidelines in 2006, much has changed in the care for patients with HF. Over the past decade, the HF Guidelines Committee has published regular updates. However, because of the major changes that have occurred, the Guidelines Committee believes that a comprehensive reassessment of the HF management recommendations

RÉSUMÉ

Depuis la parution des Lignes directrices sur l'insuffisance cardiaque (IC) de la Société canadienne de cardiologie en 2006, les soins aux patients atteints de ce trouble ont connu d'importants changements. Au cours de la dernière décennie, le Comité des lignes directrices sur l'IC a publié des mises à jour périodiques. Toutefois, en raison des changements importants qui sont survenus, le Comité des lignes

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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is presently needed, with a view to producing a full and complete set of updated guidelines. The primary and secondary Canadian Cardiovascular Society HF panel members as well as external experts have reviewed clinically relevant literature to provide guidance for the practicing clinician. The 2017 HF guidelines provide updated guidance on the diagnosis and management (self-care, pharmacologic, non-pharmacologic, device, and referral) that should aid in day-to-day decisions for caring for patients with HF. Among specific issues covered are risk scores, the differences in management for HF with preserved vs reduced ejection fraction, exercise and rehabilitation, implantable devices, revascularization, right ventricular dysfunction, anemia, and iron deficiency, cardiorenal syndrome, sleep apnea, cardiomyopathies, HF in pregnancy, cardio-oncology, and myocarditis. We devoted attention to strategies and treatments to prevent HF, to the organization of HF care, comorbidity management, as well as practical issues around the timing of referral and follow-up care. Recognition and treatment of advanced HF is another important aspect of this update, including how to select advanced therapies as well as end of life considerations. Finally, we acknowledge the remaining gaps in evidence that need to be filled by future research.

directrices a jugé qu'il était nécessaire de procéder à une réévaluation exhaustive des recommandations sur la prise en charge de l'IC afin de produire un ensemble complet de lignes directrices à jour. Les membres des comités primaire et secondaire sur l'IC de la Société canadienne de cardiologie, ainsi que des spécialistes externes, ont passé en revue la littérature pertinente afin d'indiquer aux cliniciens la marche à suivre. Les lignes directrices de 2017 donnent des indications sur le diagnostic et la prise en charge (autosoins, traitements pharmacologiques et non pharmacologiques, dispositifs et orientation des patients) destinées à faciliter la prise de décisions quotidiennes en matière de soins aux patients atteints d'IC. Parmi les questions abordées figurent notamment les cotes de risque, les différences de prise en charge selon qu'il s'agit d'IC à fraction d'éjection préservée ou réduite, l'activité physique et la réadaptation, les dispositifs implantables, la revascularisation, la dysfonction ventriculaire droite, l'anémie et la carence en fer, le syndrome cardiorénal, l'apnée du sommeil, les cardiomyopathies, l'IC pendant la grossesse, la cardio-oncologie et la myocardite. Le comité a apporté une attention particulière aux stratégies et aux traitements visant à prévenir l'IC, à l'organisation des soins aux patients atteints d'IC, à la prise en charge des comorbidités, ainsi qu'à des questions pratiques concernant les délais d'orientation du patient et les soins de suivi. La reconnaissance et le traitement de l'IC au stade avancé, et notamment le choix des thérapies à ce stade et les considérations en matière de fin de vie, représentent un autre aspect important de cette mise à jour. Enfin, le comité reconnaît les lacunes dans les données probantes qui subsistent et devront être comblées par les recherches futures.

1. Introduction

The Canadian Cardiovascular Society (CCS) heart failure (HF) guidelines program provides guidance to clinicians, policy makers, and health systems as to the evidence supporting existing and emerging management of patients with HF. The 2017 update is a comprehensive set of guidelines that incorporates new evidence and identifies areas of uncertainty and challenges facing health care providers in HF management. It integrates and updates the past decade of HF guidelines, along with a large body of new research and data.

The constitution and roles of the primary and secondary panels, systematic review strategy, and methods for formulating the recommendations are available at www.ccs.ca. The recommendations were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) standards.[1,2] The primary panelists were principally responsible for the document, with input from secondary panelists and external content experts where needed.

The sections on atrial fibrillation (AF), cardiac resynchronization therapy (CRT), and cardio-oncology were developed in collaboration with the respective guidelines committees, and are endorsed by those committees from a HF perspective.

Several sections of this document have been made available as Supplementary Material, including a list of abbreviations and acronyms (see the *Abbreviations and Acronyms* section of the Supplementary Material).

2. Definitions of HF

HF is a complex clinical syndrome in which abnormal heart function results in, or increases the subsequent risk of, clinical symptoms and signs of reduced cardiac output and/or pulmonary or systemic congestion at rest or with stress. Although this has traditionally focused on patients with predominant left ventricular (LV) systolic dysfunction (LVSD), there is an increased awareness of the syndrome spanning patients with acute and chronic HF, right-sided HF, and HF across a spectrum of ventricular or valvular function. We have refrained from using other terms, often older descriptive terms (eg, dilated, congestive), unless a specific definition exists. The term "stable" is not considered to be clinically appropriate because of the inherent risk for future clinical events. We have not adopted a staging system[3] or alternative systems[4] for describing HF.

Chronic HF is the preferred term representing the persistent and progressive nature of the disease. Acute HF (AHF) is defined as a gradual or rapid change in HF signs and symptoms resulting in the need for urgent therapy. Advanced HF is the term often used clinically, yet has no widely accepted definition. In the context of the guidelines, we have outlined some of the key considerations for this term in the section *7.1.4. Advanced HF Management Strategies* as it pertains to selecting advanced mechanical devices, transplantation, or palliative therapies.

2.1. Ejection fraction terminology

This guideline uses the following terms:

- HF with preserved ejection fraction (HFpEF): LV ejection fraction (LVEF) $\geq$ 50%;
- HF with a mid-range ejection fraction (HFmEF): LVEF 41%-49%;

- HF with reduced ejection fraction (HFrEF): LVEF $\leq$ 40%.

This recognizes the uncertainty that often occurs in the measurement of LVEF, the evolving landscape of current clinical trials enrolling patients with different LVEF cutoffs, and evolving ways to evaluate cardiac function. Echocardiography is the most accessible method to evaluate LVEF in Canada. Estimates of ejection fraction (EF) might vary because of patient or technical factors, as well as therapy or clinical deterioration. The previously stated EF cut points recognize that there is a large body of evidence related to treatment for patients with HFrEF and emerging evidence for patients with HFpEF and HFmEF. HFmEF might represent many different phenotypes, including patients transitioning to and from HFpEF.

The term "recovered EF" has also been added to the literature,[5] referring to patients who previously had HFrEF and now have an EF > 40%. These patients might eventually be classified in the HFmEF or HFpEF group but deserve recognition because despite their recovered imaging parameters, they might still carry additional risk for adverse clinical events. Uncertainty exists on strategies for management of individuals with HFmEF including surveillance, treatment, and prognosis.

2.2. Symptoms terminology

Symptoms are described using the New York Heart Association (NYHA) functional class I-IV (Table 1).

Table 1. New York Heart Association functional classification and other symptom descriptors

Class	Definition	Other descriptor
I	No symptoms	Asymptomatic
II	Symptoms with ordinary activity	Mild symptoms
III	Symptoms with less than ordinary activity	Moderate symptoms
IV	Symptoms at rest or with any minimal activity	Severe symptoms

Data from the Criteria Committee of the New York Heart Association.[6]

3. Prognosis and Risk Scores

Table 2 shows examples of HF prognostic scores that can be easily accessed and calculated, and the strengths and limitations of the studies used to develop these scores. Clinical acumen remains important to place these risk scores in context, but methodologically sound and externally valid risk scores might help the clinician and patient. Where possible, these risk scores should be incorporated into practice and used to convey risk to patients, and between clinicians to adequately characterize the overall risk of a patient. The risk scores in Table 2 are not exhaustive; others exist and could be considered by clinicians.

4. Prevention of HF and Asymptomatic LV Dysfunction

4.1. Early detection of LVSD and prevention of HF

HF often progresses from asymptomatic LVSD to symptomatic HF.[16] Early detection of LVSD might allow intervention on contributing risk factors and pharmacotherapy to delay or reverse the progression of adverse LV remodelling. Data on medications, including ACEs, ARBs, and β-blockers are summarized online in evidence reviews at www.ccs.ca.

Conventional risk factors for cardiovascular disease (CVD) are often included in clinical assessment but a detailed family history might also uncover genetic causes or susceptibility to the development of LV dysfunction. The use of NPs might be useful to identify individuals who are at higher risk for the development of HF and in whom preventative strategies have been studied. The cut point used in the Saint Vincent **S**creening **to** **P**revent **H**eart **F**ailure (STOP-HF)[17] trial of BNP > 50 pg/mL to undergo echocardiography and collaborative care resulted in a higher rate of use of renin-angiotensin-aldosterone system inhibition therapies, fewer HF events, and significant reduction in hospitalizations for major cardiovascular events over a follow-up on an average of 4.2 years. The NT-proBNP Selected **P**revent**io**n of Cardiac Eve**n**ts in a Popula**t**ion of D**i**abetic Patients Without **a** History of **C**ardiac Disease (PONTIAC) study[18] used a cut point of NT-proBNP > 125 pg/mL to apply further cardiology consultation and individualized β-blockade and renin-angiotensin-aldosterone system uptitration. Patients in the group randomized to intensified therapy had a 65% relative risk reduction (RRR) in the primary combined event rate of hospitalization or death due to cardiac disease at 2 years. Therapies used in these 2 trials are guideline-based, reinforcing the opportunity to enhance neurohormonal therapy in all individuals with cardiovascular risk factors, limited only by the availability of NP measurement to identify patients.

Exercise as a strategy to prevent ischemic heart disease has supported guideline-recommended minimum physical activity of at least 150 minutes per week of moderate intensity activity (approximately 500 metabolic equivalents of task minutes). A meta-analysis of 12 prospective cohort studies by Pandey et al.[19] reported the risk of HF is reduced by 10%, 19%, and 35% in people who were participating in leisure activity of 500, 1000, and 2000 metabolic equivalents of task minutes per week, respectively, compared with individuals with no physical activity. This article noted an inverse dose-response relationship between physical activity and development of HF.

The importance of prevention of HF is supported by evidence that preventing and treating cardiovascular risk factors and conditions that cause atherosclerotic disease leads to fewer patients developing HF. Many of these risk factors also contribute to the development of HF independently from atherosclerotic disease (Table 3). Previous HF guidelines have reviewed the substantial evidence supporting the screening and management of common risk factors for the development of HF such as hypertension, diabetes, smoking, dyslipidemia, obesity, alcohol use, and sedentary behaviour.[20-27] Patients with established coronary artery disease (CAD) and/or previous acute coronary syndrome (ACS) should have these appropriately treated to prevent future HF events.

Table 2. Risk scores

Score Name	Population	End point	Other considerations	Access	Variables
Seattle Heart Failure Model[7]	HFrEF	Mortality risk at 1, 2, and 5 years with or without intervention; mean life expectancy	Restricted to clinical trial patients with 'severe' HF; laboratory data entry non-SI units; >20 variables to enter	https://depts.washington.edu/shfm	Age, sex, NYHA class, weight, EF, SBP, ischemic etiology, diuretic dose, Na, lymphocyte count, Hgb, cholesterol, uric acid, use of ACEi/ARB/β-blocker/aldosterone blocker/allopurinol/statins, QRS > 120 ms, use of device therapy
MAGGIC risk score[8]	HFrEF and HFpEF	Mortality risk at 1 and 3 years	Cohorts from many sites; missing data in the overall analysis	www.heartfailurerisk.org	Age, sex, NYHA class, diabetes, COPD, timing of diagnosis, EF, smoking, SBP, creatinine, body mass index, use of β-blocker/ACEi/ARB
3C-HF[9]	HFrEF and HFpEF	Mortality risk at 1 year	Patients from centres with experience with HF management; mostly Caucasian patients; laboratory data entry in non-SI units	http://www.3chf.org/site/home.php	Age, NYHA class, atrial fibrillation, valvular heart disease, EF, anemia, diabetes, hypertension, creatinine, use of ACEi/ARB or β-blockers
BCN bio-HF[10]	HFrEF and HFpEF	Mortality risk at 1, 2, and 3 years	Limited to patients with chronic HF treated in HF unit in a tertiary hospital; laboratory data entry in US units; use of biomarkers improves accuracy but is optional	www.BCNBioHFcalculator.cat	Age, sex, NYHA class, Na, estimated glomerular filtration rate, Hgb, EF, diuretic dose, use of statins, β-blockers, or ACEi/ARB. Optional: hs-cTnT, ST2, NT-proBNP
EFFECT[11]	Hospitalized HFrEF and HFpEF	30-day and 1-year mortality	Limited to hospitalized patients; missing current clinically important variables	http://www.ccort.ca/Research/CHFRiskModel.aspx	Age, respiratory rate, SBP, BUN, Na, CVD, dementia, COPD, cirrhosis, cancer, Hgb
EHMRG[12]	HFrEF and HFpEF patients presenting to the ED	7-day mortality	Limited to patients presenting to the ED and only short-term mortality; missing current clinically important variables	https://ehmrg.ices.on.ca	Age, arrival by ambulance, triage SBP, triage HR, triage O_2 saturation, potassium, creatinine, active cancer, metolazone, troponin; optional: BNP
ELAN-HF[13]	Hospitalized HFrEF and HFpEF	180-day mortality	Limited to hospitalized patients		Age, edema, SBP, serum sodium, serum urea, NYHA class at discharge, NT-proBNP at discharge, and change in NT-proBNP
ADHERE[14]	HFrEF and HFpEF	In-hospital mortality	Limited to hospitalized patients		BUN, creatinine, SBP
LACE[15]	Hospitalized patients	30-day mortality or readmission	Limited to hospitalized patients		Length of stay, acute admission, comorbidity index, number of ED visits in past 6 months

ACEi, angiotensin-converting enzyme inhibitor; ADHERE, **A**cute **D**ecompensated **He**art Failure National **Re**gistry; ARB, angiotensin receptor blocker; BCN bio-HF, **Bar**celo**n**a **Bio**-**H**eart **F**ailure Risk Calculator; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; 3C-HF, **C**ardiac and **C**omorbid **C**onditions **H**eart **F**ailure score; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ED, emergency department; EF, ejection fraction; EFFECT, **E**nhanced **F**eedback **f**or **E**ffective **C**ardiac **T**reatment; EHMRG, **E**mergency **H**eart Failure **M**ortality **R**isk **G**rade; ELAN-HF, **E**uropean Co**ll**aboration on **A**cute Decom-pe**n**sated **H**eart **F**ailure; HF, heart failure; HFpEF, HF with preserved EF; HFrEF, HF with reduced EF; Hgb, hemoglobin; HR, heart rate; hs-cTnT, high-sensitivity cardiac troponin T; LACE, **L**ength of Stay, **A**cuity of Admission, **C**omorbidities, **E**mergency Department Visits; MAGGIC, **M**eta-**A**nalysis **G**lobal **G**roup **i**n **C**hronic Heart Failure; NT-proBNP, N-terminal propeptide B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SI units, International System of Units; ST2, suppression of tumorigenicity 2.

RECOMMENDATION

1. We suggest clinical assessment in all patients to identify known or potential risk factors for the development of HF (Weak Recommendation; Moderate-Quality Evidence).
2. We recommend an angiotensin-converting enzyme (ACE) inhibitor (ACEi) be used in all asymptomatic patients with an EF < 35% (Strong Recommendation; Moderate-Quality Evidence).
3. We recommend that an ACEi should be prescribed in established effective doses to reduce the risk of developing HF in patients with evidence of vascular disease or diabetes with end organ damage (Strong Recommendation; High-Quality Evidence).
4. We recommend that in ACE-intolerant patients, an angiotensin receptor blocker (ARB) be considered for reduction of the risk of developing HF in patients with evidence of vascular disease or diabetes with end organ damage (Strong Recommendation; High-Quality Evidence).
5. We recommend that health professionals caring for overweight or obese individuals should educate them about the increased risk of HF (Strong Recommendation; Moderate-Quality Evidence).
6. We recommend physical activity to reduce the risk of developing HF in all individuals (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Natriuretic peptide (NP) screening of individuals at risk for the development of HF can aid decision-making on whom to send for echocardiography. A value of B-type (BNP) > 50 pg/mL or N-terminal propeptide BNP (NT-proBNP) > 125 pg/mL should prompt a request for specialist consultation and imaging, and/or initiation or intensification of neurohormonal blocking agents and lifestyle interventions.

Practical tip. Dyslipidemia should be treated in patients with evidence of vascular disease or diabetes with lipid-lowering drugs, especially statins.

Practical tip. Smoking cessation, improved cardiorespiratory fitness, and weight reduction for overweight or obese individuals are important preventive strategies for HF.

Practical tip. Patients at high risk for developing HF should receive annual influenza vaccine and periodic pneumococcal pneumonia immunizations.

Table 3. Selected risk markers for the development of heart failure

Demographic and lifestyle	Medical history	Markers
Older age	Hypertension*	Abnormal ECG
Male sex	Coronary artery disease	Increased cardiothoracic ratio on CXR
Heavy alcohol use	Diabetes mellitus*	Elevated neurohormonal biomarkers
Smoking*	Hyperlipidemia*	Elevated resting heart rate
Physical inactivity*	Obesity*	Microalbuminuria

CXR, chest x-ray; ECG, electrocardiogram.
*Important public health targets for prevention.

4.2. Preventing HF in patients with hypertension

Hypertension has been well documented as a risk factor for HF and the treatment of hypertension has been shown to reduce the risk of developing HF.[28-30] In addition to the high-quality meta-analyses, more recent evidence from the **S**ystolic Blood **Pr**essure **In**tervention **T**rial (SPRINT) supports a more aggressive approach to hypertension management.[31] This trial of 9361 participants deemed high risk for a cardiovascular event, randomized to intensive (systolic BP < 120 mm Hg) vs standard (systolic BP < 140 mm Hg) BP control showed there was a 25% risk reduction in the primary outcome of myocardial infarction (MI), ACS, stroke, HF, or death from cardiovascular causes after only a median of 3.26 years. There was a 33% reduction of future HF outcomes (patients with a history of symptomatic HF in the past 6 months or with LVEF < 35% were excluded). Readers are directed to Hypertension Canada's 2017 Guidelines (http://www.onlinecjc.ca/article/S0828-282X(17)30110-1/fulltext) for additional information.

RECOMMENDATION

7. We recommend that most patients should have their blood pressure (BP) controlled to < 140/90 mm Hg; those with diabetes or at high risk for cardiovascular events should be treated to a systolic BP of < 130 mm Hg to reduce the risk of developing HF (Strong Recommendation; Moderate-Quality Evidence).
8. We recommend that β-blockers should be considered in all asymptomatic patients with an LVEF < 40% (Strong Recommendation; Moderate-Quality Evidence).

4.3. Preventing HF in patients with diabetes

Diabetes mellitus (DM) is an established risk factor for the development of HF.[29,32,33] However, the relationship between glycemic control and the development of HF is inconsistent and complicated further by the long-term effects of diabetes on other organ systems (eg, kidneys) or development of CAD.[34] It is recognized, however, that DM can produce HF independently of CAD by causing a diabetic cardiomyopathy.[29] In several studies, the incidence of HF was two- and fourfold higher in patients with DM than in those without.[32,33,35-38] Approximately 12% of DM patients have HF,[35] and older than the age of 64 years, the prevalence increases to 22%.[37] It is thought that diabetes promotes the development of myocardial fibrosis and diastolic dysfunction, autonomic dysfunction, and worsened renal and endothelial function.

Moreover, there has been uncertainty regarding whether any glucose-lowering strategy, or specific therapeutic agent, is safe from a cardiovascular standpoint or can decrease cardiovascular risk. Older trials on the effects on cardiovascular outcomes of specific glucose-lowering strategies or medications either have been insufficiently powered or have shown no significant cardiovascular benefit or an increased risk of death or HF.

4.3.1. Glycemic control in diabetes to prevent HF

In the past, several diabetes guidelines have advocated for tight glycemic control (lower Hb A1c); however, there is no

evidence that this approach improves cardiovascular outcomes and some studies suggest harm, including increased HF, not to mention increased risk for hypoglycemia. There are no specific studies targeting patients with HF. Data are largely extrapolated from the **D**iabetes **C**ontrol and **C**omplications **T**rial (DCCT) study of patients with type 1 diabetes,[39] the **UK P**rospective **D**iabetes **S**tudy (UKPDS) study,[40] the UKPDS Follow Up study,[41] the **A**ction to **C**ontrol **C**ardi**o**vascular **R**isk in **D**iabetes (ACCORD) study,[42,43] the **A**ction in **D**iabetes and **V**ascular Disease: Preterax and Diamicro**n** MR-**C**ontrolled **E**valuation (ADVANCE) study,[44] and the **V**eterans **A**ffairs **D**iabetes **T**rial (VADT) study.[45] With the available evidence, an intensive glycemic control strategy cannot be recommended for all patients with diabetes. Instead, each individual should be assessed for his or her optimal glycemic target for the prevention of macrovascular events or HF.

RECOMMENDATION

9. We recommend that diabetes should be treated according to the Canadian Diabetes Association's national guidelines to achieve optimal control of blood glucose levels (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. There is no convincing evidence from randomized controlled trials (RCTs) that tighter glycemic control reduces cardiovascular outcomes. Potential risks of tight glycemic control might outweigh its benefits in certain individuals such as those with a long duration of diabetes, frequent episodes of hypoglycemia, those with advanced CVD, advanced age, frailty, or multiple comorbidities.

Practical tip. Each individual patient should be assessed for his or her "optimal" glycemic control hemoglobin (Hb) A1c target. Considerations include an individual's risk of hypoglycemia, the duration of diabetes, the presence or absence of CVD, kidney function, overweight or not, or frailty, among others.

Metformin. Metformin is still considered first-line pharmacological therapy for type 2 diabetes. It is effective, has a known safety profile, and is well tolerated in patients with HF.[46]

RECOMMENDATION

10. We suggest that metformin might be considered a first-line agent for type 2 diabetes treatment (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. Metformin is the current Canadian Diabetes Association first-line treatment for type 2 diabetes.

Practical tip. If the estimated glomerular filtration rate (eGFR) is < 30 mL/min, a temporary discontinuation of metformin and certain other diabetes medications should be considered.

SGLT-2 inhibitors. The **Empa**gliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients -**R**emoving **E**xcess **G**lucose (EMPA-REG OUTCOME) trial,[47] is an RCT to show cardiovascular benefit in the treatment of diabetes. A sodium-glucose co-transporter-2 (SGLT-2) inhibitor empagliflozin was compared with placebo in 7020 patients with type 2 diabetes and established CVD and eGFR ≥ 30 mL/min. The primary composite outcome was death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The primary end point occurred less commonly in the patients treated with empagliflozin (10.5%) than in those who received placebo (hazard ratio [HR], 12.1%; 95% confidence interval [CI], 0.74-0.99). Moreover, empagliflozin had an RRR for cardiovascular mortality of 38%, all-cause mortality of 32%, and HF hospitalization of 35%. SGLT-2 inhibitors have not yet been studied in populations of patients with HF. Of note, only a subgroup of approximately 10% of patients in the EMPA-REG OUTCOME trial had a reported history of HF. There are ongoing trials of SGLT-2 inhibitors, and those might affect future recommendations, namely for patients with established HF.

RECOMMENDATION

11. We suggest that the use of empagliflozin, an SGLT-2 inhibitor, be considered for patients with type 2 diabetes and established CVD for the prevention of HF-related outcomes (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places weight on the fact that empagliflozin is the first diabetes-related medication to show a reduction in HF hospitalization. Empagliflozin was well tolerated and associated with an acceptable side effect profile within the clinical trial establishing its efficacy and safety. There are ongoing trials of this class of medications that might change this recommendation.

DPP-4 inhibitors. The **S**axagliptin **A**ssessment of **V**ascular **O**utcomes **R**ecorded in Patients With Diabetes Mellitus—**T**hrombolysis **i**n **M**yocardial **I**nfarction 53 (SAVOR-TIMI 53) trial[48] randomized 16,492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events to receive the dipeptidyl peptidase-4 (DPP-4) inhibitor saxagliptin or placebo and followed them for a median of 2.1 years. The primary end point was a composite of cardiovascular death, MI, or ischemic stroke. At a median follow-up of 2.1 years, rates of composite cardiovascular events were similar with saxagliptin and placebo, but hospitalization for HF was higher with saxagliptin (3.5% vs 2.8%; HR, 1.27; $P = 0.007$).

In contrast, the **T**rial **E**valuating **C**ardiovascular **O**utcomes With **S**itagliptin (TECOS) study,[49] an RCT of 14,671 patients comparing another DPP-4 inhibitor, sitagliptin, with placebo showed no increase in HF hospitalization (HR, 1.00; 95% CI, 0.83-1.20; $P = 0.98$). Studies involving other DPP-4 inhibitors alogliptin[50] and linagliptin[51] have not shown additional increases in the risk of HF events.

RECOMMENDATION

12. We do not recommend the use of the DPP-4 inhibitor saxagliptin in patients with or at risk for

HF (Strong Recommendation; Moderate-Quality Evidence).

13. We suggest that if a DPP-4 inhibitor is to be used, linagliptin or sitagliptin should be considered for patients with diabetes and with, or at risk for HF (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. The **S**axagliptin **A**ssessment of **V**ascular **O**utcomes **R**ecorded in Patients With Diabetes Mellitus (SAVOR) trial showed an increase in HF hospitalizations with use of saxagliptin. Other DPP-4 inhibitors (eg, sitagliptin, alogliptin, linagliptin) did not have the same adverse effect as saxagliptin of HF hospitalization; there are ongoing trials of other DPP-4 inhibitors.

Glucagon-like peptide. Human glucagon-like peptide (GLP-1) agonists have been tested in patients with diabetes for the outcomes of cardiovascular events. One such agent, liraglutide, was tested in the **L**iraglutide **E**ffect and **A**ction in **D**iabetes: **E**valuation of Cardiovascular Outcome **R**esults (LEADER) trial, and 14% of the patients had a clinical history of HF. Overall, liraglutide was shown to be noninferior to placebo, and had fewer cardiovascular events overall. There was no statistically significant decrease or increase in the number of HF events. There are ongoing trials with other GLP-1 agonists that will inform a recommendation on this class of agents for the prevention of HF.[52]

Thiazolidinediones. Two such drugs (pioglitazone and rosiglitazone) have each been shown to increase the risk of HF events.

Prospective Pioglit**a**zone **C**linical **T**rial **i**n Macro **V**ascular **E**vents (PROactive)[53] was a randomized study of 5238 type 2 diabetic patients, comparing pioglitazone with placebo. More pioglitazone (5.7%) than placebo patients (4.1%) had a serious HF event during the study ($P = 0.007$). Of patients in the placebo group, 108 needed hospital admission for HF (153 admissions) compared with 149 (209 admissions) in the pioglitazone group (HR, 1.41; 95% CI, 1.10-1.80; $P = 0.007$).

Rosiglitazone **E**valuated for **C**ardiac **O**utcomes and **R**egulation of Glycaemia in **D**iabetes (RECORD)[54] was an RCT of 4447 people with type 2 diabetes randomized to add-on rosiglitazone (n = 2220) or to a combination of metformin and sulfonylurea (n = 2227). Patients with any HF were excluded. Rosiglitazone-treated patients had a greater risk for at least 1 admission to hospital for HF compared with the placebo group (HR, 2.6; 95% CI, 1.1-4.1; $P = 0.001$). A meta-analysis of 42 trials of rosiglitazone[55] showed a 43% increase in MI and a 64% increase in death from cardiovascular causes with use of rosiglitazone.

RECOMMENDATION

14. We recommend that thiazolidinediones should not be used in patients with HF (Strong Recommendation; High-Quality Evidence).

Table 4. Clinical presentations of heart failure

Common	Uncommon
Dyspnea	Cognitive impairment*
Orthopnea	Altered mentation or delirium*
Paroxysmal nocturnal dyspnea	Nausea
Fatigue	Abdominal discomfort
Weakness	Oliguria
Exercise intolerance	Anorexia
Dependent edema	Cyanosis
Cough	
Weight gain	
Abdominal distension	
Nocturia	
Cool extremities	

*Might be a more common presentation in elderly patients.

5. Diagnosis of HF

5.1. General considerations

HF is a complex clinical syndrome in which abnormal heart function results in, or increases the subsequent risk of, clinical symptoms and signs of reduced cardiac output and/or pulmonary or systemic congestion at rest or with stress. The cardinal triad of edema, fatigue, and dyspnea is not a sensitive or a specific manifestation of HF, and atypical presentations should be recognized, particularly when evaluating women, obese patients, and elderly patients (Table 4). A thorough clinical history and physical examination should be performed in all patients, and initial investigations should be targeted to confirm or exclude HF as the diagnosis as well as to identify systemic disorders (eg, thyroid dysfunction) that might affect its development or progression (Fig. 1, Table 5). Measurement of plasma NPs is helpful because low concentrations are very useful in excluding HF and high concentrations can confirm HF in patients who present with dyspnea when the clinical diagnosis remains uncertain.[57]

Two-dimensional and Doppler transthoracic echocardiography are the initial imaging modalities of choice in patients suspected to have HF because they are used to assess systolic and diastolic ventricular function, wall thickness, chamber sizes, valvular function, and pericardial disease. Contrast echocardiography or radionuclide angiography might be useful in patients in whom echocardiographic images are poor. Cardiac catheterization with hemodynamic measurements and contrast ventriculography, computed tomography (CT), and CMR imaging can be used when other noninvasive tests are inconclusive and might be required for specific cardiomyopathies (see the section *7.5.1. Cardiomyopathies* and Figs. 1 and 2).

RECOMMENDATION

15. We recommend the choice of investigations should first be guided by careful history and physical examination and when clinical evidence suggests a possible cause and the planned test(s) result(s) would be reasonably expected to lead to a change in clinical care (Strong Recommendation; Low-Quality Evidence).
16. We recommend that a 12-lead electrocardiogram (ECG) be performed to determine heart rhythm, heart rate, QRS duration, and morphology, and to

detect possible etiologies (Strong Recommendation; Low-Quality Evidence).
17. We recommend that echocardiography be performed in all patients with suspected HF to assess cardiac structure and function, to quantify systolic function for planning and monitoring of treatment, and for prognostic stratification (Strong Recommendation; Moderate-Quality Evidence).
18. We recommend that cardiac magnetic resonance (CMR) imaging might be used when echocardiographic imaging (including contrast echocardiography) is nondiagnostic, or help to elucidate the etiologies (eg, myocarditis) (Strong Recommendation; Low-Quality Evidence).
19. We recommend that in a patient suspected to have a cardiomyopathy, an inquiry should be made regarding family history, concomitant illnesses, previous malignancy requiring radiation or chemotherapy, symptoms of hypo- or hyperthyroidism, pheochromocytoma, acromegaly, previous travel, occupational exposure to chemicals or heavy metals, nutritional status, alternative medicine or naturopathic agents, illicit drug use, and exposure to HIV (Tables 6-8) (Strong Recommendation; Low-Quality Evidence).
20. We recommend that tachycardia-induced cardiomyopathy should be suspected when LVSD, with or without typical HF signs or symptoms, occurs with a persistent inappropriate tachycardia or tachyarrhythmia without another identified cause for the heart dysfunction (Strong Recommendation; Low-Quality Evidence).

Practical tip. Patients might have HF even without a history or current evidence of volume overload.

Practical tip. An imaging-based assessment (typically with echocardiography) of valvular abnormalities should be done early in the diagnosis of HF.

6. Biomarkers/NPs

Biomarkers, for the context of this guideline, refer to substances measured in the blood other than commonly used laboratory tests and imaging studies. Several general criteria have been proposed for what constitutes a relevant biomarker in cardiovascular medicine.[58]

Over the past decade, the NPs became the gold standard for biomarkers in HF and have been extensively investigated in various clinical settings. NPs might be elevated in relation with other cardiovascular conditions leading to increased LV filling pressures, such as valvular heart disease, ischemia, or uncontrolled hypertension.[59] Noncardiac conditions, such as increasing age, renal dysfunction, anemia, pulmonary diseases, and sepsis have also been associated with increased NP levels.[59,60] Obesity has been associated with lower NP levels.[61] The prognostic utility of NPs has been shown in HF.[62-65] The availability of NPs in Canada remains challenging because of the associated costs and/or the perceived variable effect on clinical decisions.[66] The use of NPs does not eliminate the need for cardiac imaging in most cases. Hence, NPs provide additional evidence in favour of HF but need to be placed within the clinical context (Fig. 1).

6.1. NPs and optimization of medical therapy

One of the reasons for the so-called "mismatch" between risk and treatment is the lack of reliable markers to guide the titration of effective treatments. Persistently elevated or increasing NP levels are associated with an increased risk of hospitalization and mortality. In otherwise clinically stable patients with HF, a change in NP levels $\geq$ 30% between visits indicates a change greater than would be expected from daily variation[67] and is likely clinically relevant and should therefore call for more intensive follow-up and/or intensified medical treatments.

Data suggest that serial monitoring of NP levels can provide powerful information about response to therapy and residual risk.[68-70] Initial studies on NP-guided therapy[71-73] have targeted a large reduction or a very low NP level in the intervention group; and generally compared this intervention with contemporary guideline-directed medical therapy (GDMT). Targeting a specific reduction in NP levels (or "NP-guided therapy") has shown an improvement in clinical outcomes, although these studies were smaller and ongoing studies will provide further guidance.[74,75]

NP concentrations have been shown to decrease in response to commonly used therapies for either acute or chronic HF. This includes loop diuretics, ACE inhibitors (ACEis), ARBs, mineralocorticoid receptor antagonists (MRAs), and CRT.[73,76,77] With β-blockers, an initial increase in NP levels might be seen during the first 8-12 weeks followed by a decrease.[78] The interaction between NP levels and neprilysin inhibitors is more complex but evidence suggests that NT-proBNP might more reliably reflect the patient status at least in the first 8 months of treatment with sacubitril/valsartan (Fig. 3).[79]

6.1.1. HFpEF and NPs

Although elevated NP levels have been proposed as an additional diagnostic criterion for HFpEF,[80] older age and comorbidities common in this population might also influence NP levels.[81] Among patients with HFpEF, the presence of an elevated NP level is an established marker of risk and discriminates prognosis comparable with that of HFrEF.[82] In the subset of 375 patients randomized in the **P**erindopril in **E**lderly **P**eople with **C**hronic **H**eart **F**ailure Trial (PEP-CHF) with available measurements of NT-proBNP at baseline, those in the highest quartile (> 1035 pg/mL) had more than a fourfold risk of all-cause mortality or HF-related hospitalization over those in the lowest quartile (< 176 pg/mL), and this relationship was independent of therapy.[83] Similarly, in the larger cohort of 3480 patients with measured NT-proBNP levels in the **I**rbesartan in Patients With Heart Failure and **Preserve**d Ejection fraction (I-PRESERVE) trial, values above the median of 339 pg/mL at baseline were independently associated with a twofold increase in risk of all-cause mortality.[84] In the **T**reatment **o**f **P**reserved **Ca**rdiac Function Heart Failure With an Aldos**t**erone Antagonist (TOPCAT) trial, patients randomized in the trial on the basis of elevated NPs derived outcome benefits from spironolactone, whereas those randomized on the basis of a previous hospitalization for HF did not.[31] These findings might have been influenced by significant regional variations in the trial[85] but nevertheless, they show the utility of NPs in selecting patients who might respond to a specific treatment.[86]

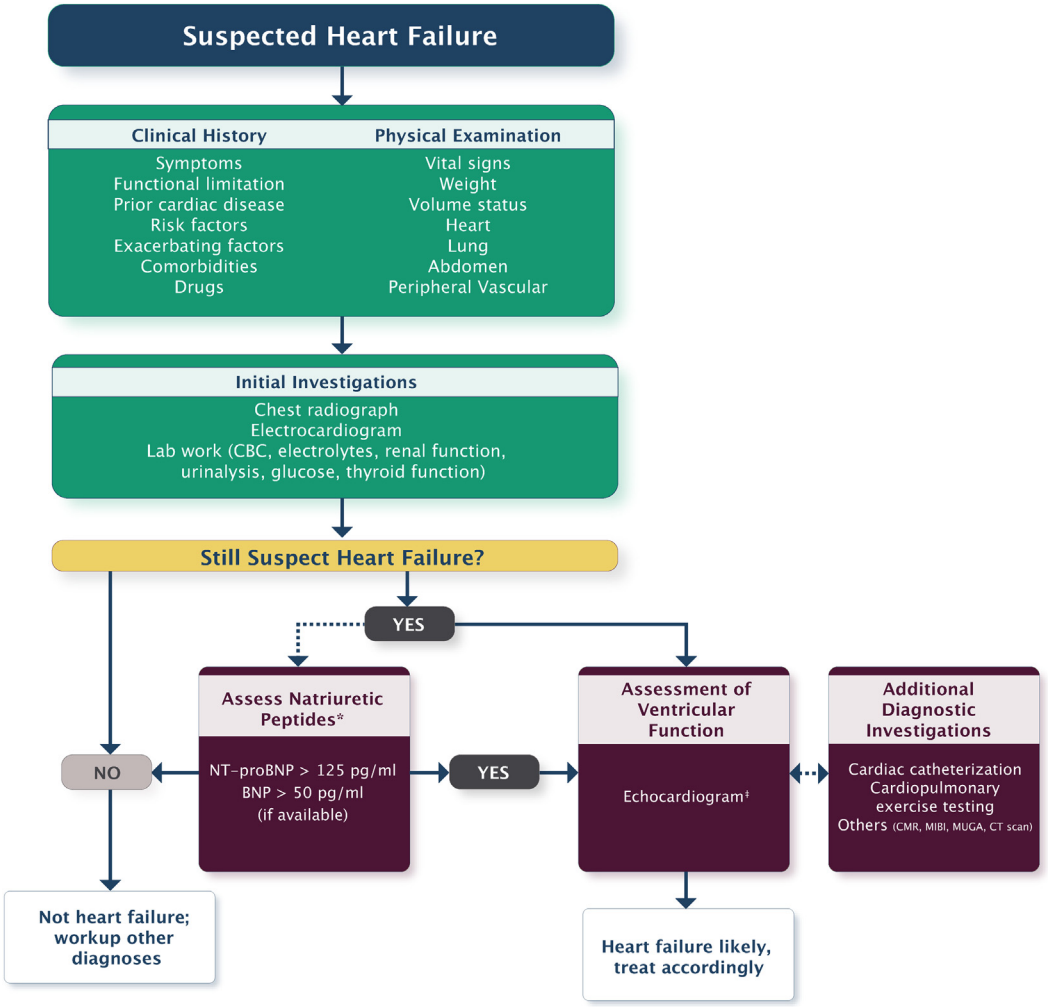

Figure 1. Algorithm for the diagnosis of heart failure in the ambulatory care setting. For patients with heart failure, a history, physical exam, and initial investigations should be supplemented with natriuretic peptides and/or imaging tests. *Natriuretic peptides are not available in all jurisdictions in Canada. ‡Includes systolic as well as diastolic parameters (eg, numeric left ventricular ejection fraction, transmitral and pulmonary venous flow patterns, or mitral annulus velocities); a preserved ejection function on a routine echocardiogram does not rule out the clinical syndrome of heart failure and therefore clinical judgement is required if other indicators point to heart failure as a diagnosis. A lower BNP cutoff for suspecting heart failure in the ambulatory setting facilitates earlier implementation of guideline-directed care. BNP, B-type natriuretic peptide; CBC, complete blood count; CMR, cardiac magnetic resonance; CT, computed tomography; MIBI, myocardial perfusion scan; MUGA, multigated acquisition scan; NT-proBNP, N-terminal propeptide B-type natriuretic peptide.

Table 5. Suggested timing for measurement of LVEF, according to clinical scenario

Clinical scenario	Timing of measurement	Modality of measurement	Comments
New-onset HF	Immediately or within 2 weeks for baseline assessment	ECHO (preferred when available); or CMRI	Report should include numeric EF or small range of EF and diastolic function evaluation
After titration of triple therapy for HFrEF, or consideration of ICD/CRT implantation	3 months after completion of titration	ECHO or CMRI (preferably the same modality and laboratory test as initial test)	LVEF after medical therapy might increase, obviating device therapy
Stable HF	Approximately every 1-3 years, and possibly less frequent if EF is persistently > 40%	ECHO or CMRI	Clinical rationale is to identify improving (better prognosis) or worsening ventricular function (worse prognosis, need for additional therapy such as ICD/CRT)
After significant clinical event (ie, after some HF hospitalizations)	Within 30 days, during hospitalization if possible; not necessary when repeated admissions occur without need to identify a cause	ECHO or CMRI	Frequently helpful information such as EF, degree of valvular dysfunction, and RVSP

Nuclear, computed tomography, or other measures are appropriate and acceptable in certain circumstances taking into account radiation, cost, and information gained.

CMRI, cardiac magnetic resonance imaging; CRT, cardiac resynchronization therapy; ECHO, echocardiogram; EF, ejection fraction; HF, heart failure; HFrEF, heart failure with reduced EF; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular EF; RVSP, right ventricular systolic pressure.

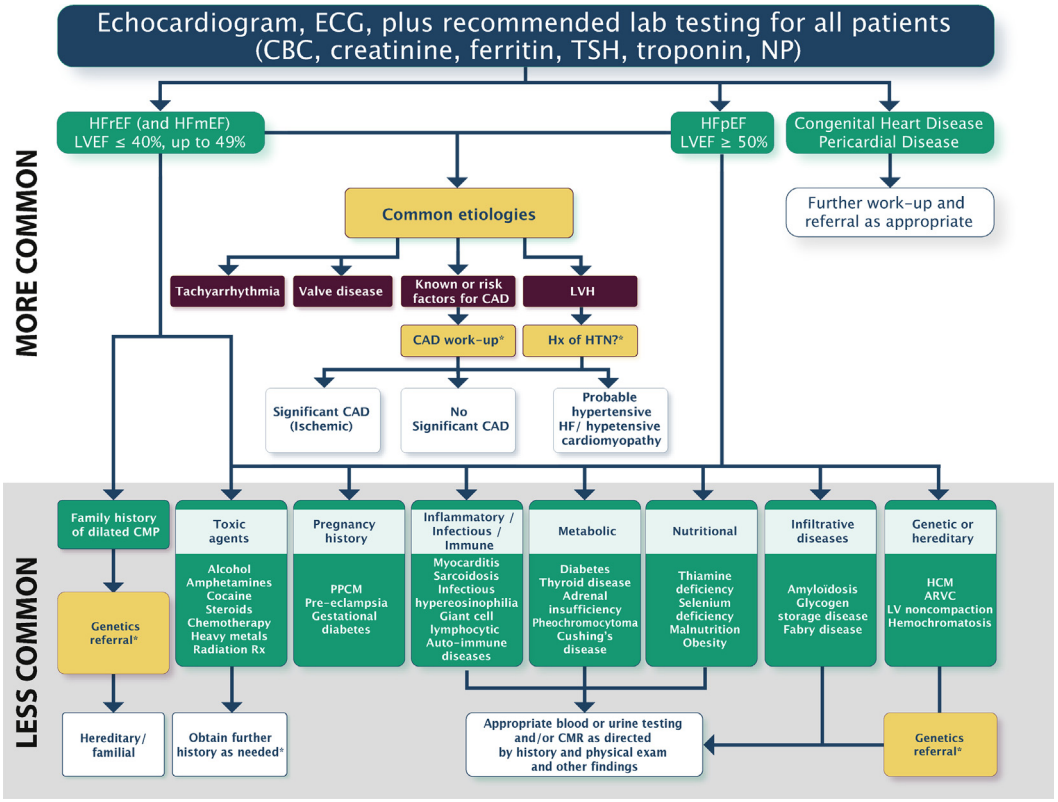

Figure 2. General guidance as to the workup to identify the most probable etiology for a patient's heart failure (HF). At all stages, a thorough clinical history and physical exam should aid in the selection of additional investigations. A detailed family history is invaluable, especially in patients who are younger or do not have an obvious etiology. Testing should be placed in context of the pretest probability, availability, and expertise of the test. More common etiologies (eg, coronary artery disease, hypertension) should be considered first, and further testing should be encouraged if another etiology is suspected in addition to a more common etiology (eg, hemachromatosis in a patient with known coronary artery disease). *Patients might have mixed etiology of HF. A detailed medical and family history might guide investigations and should be completed in all patients (see Recommendation 19 in section *5. Diagnosis of HF*). Direct testing on the basis of pretest probability, availability, and expertise. ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; CBC, complete blood count; CMP, cardiomyopathy; CMR, cardiac magnetic resonance; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; HFmEF, heart failure with a midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; Hx, history; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NP, natriuretic peptide; PPCM, peripartum cardiomyopathy; Rx, prescription; TSH, thyroid-stimulating hormone.

6.1.2. NPs for the diagnosis and management of HF

The levels of NPs for ruling in and ruling out a diagnosis of HF are shown in Table 9. NP levels differ for the diagnosis of patients seen in the acute (eg, emergency department [ED]) vs in the outpatient settings. Several high-quality studies have reported on the utility of NPs for the diagnosis of HF in the outpatient setting where NPs are ideally suited to assist in ruling out HF as a diagnosis, but cannot be used independent of signs, symptoms, and other diagnostic information.

RECOMMENDATION

21. We recommend that BNP/NT-proBNP levels be measured to help confirm or rule out a diagnosis of HF in the acute or ambulatory care setting in patients in whom the cause of dyspnea is in doubt (Strong Recommendation; High-Quality Evidence).

Values and preferences. High-quality RCT evidence in the Canadian setting also shows favourable cost-effectiveness. Elevated NP levels are recommended as an additional diagnostic criterion for HFpEF and are associated with increased risk, although the levels might be lower than in HFrEF. Older age and comorbidities might also influence variations in NP levels.

22. We recommend that measurement of BNP/NT-proBNP levels be considered in patients with an established diagnosis of HFrEF for prognostic stratification, in view of optimizing medical therapy (Strong Recommendation; High-Quality Evidence).

Practical tip. For patients receiving an angiotensin receptor-neprilysin inhibitor (ARNI) (see section *7.1.1.5. ARNI*), the use of NT-proBNP (rather than BNP) should be preferred to evaluate prognosis during the first year of treatment. BNP

Table 6. Toxins associated with cardiomyopathies

Toxin	Causes	Symptoms and signs	Diagnosis	Treatment
Alcohol	Excessive alcohol use. Heavy drinking: for women more than 1 drink per day and for men more than 2 drinks per day. Binge drinking: for women > 3 drinks and for men > 4 drinks	Symptoms and signs of heart failure and/or chronic liver disease	Detailed history, blood level	Abstaining from alcohol; usual heart failure medications
Illicit drugs and medications	History of drug or chemotherapy use. Might be related to the dose and duration. Includes herbal, nutraceutical, and alternative therapies	Symptoms and signs of heart failure	Careful history-taking of present or previous use of prescribed and over-the-counter medications	Discontinue the drug; supportive measures; usual heart failure medications
Cocaine Methamphetamine, antidepressants, corticosteroids, anabolic steroids, phenothiazines		Cocaine might cause thrombosis, coronary spasm, chest pain, and myocardial infraction. Might also cause myocarditis and aortic dissection	Previous or recent history of cocaine use; urinary metabolites	Calcium channel blockers might be useful in cocaine-induced chest pain or coronary spasm
Chemotherapy,[56] anthracycline (doxorubicin, daunorubicin), bleomycin, adriamycin; cyclophosphamide; cytostatic agents; interferons, interleukin-2, trastuzumab	Cardiotoxic drugs used to treat cancer	Symptoms and signs of heart failure. Symptoms, signs, or history of malignancy	History of malignancies with chemotherapy. Might need myocardial biopsy	Standard heart failure treatment might reverse the abnormalities. Avoid using these agents again
Heavy metals (cobalt, chromium, mercury, phosphorus, iron, gold, silver)	Outbreaks of cardiomyopathy occurred among heavy consumers of cobalt-fortified beer		The 2 main target organs are the skin and the respiratory tract. Cobalt itself might cause allergic dermatitis, rhinitis, and asthma	Avoid exposure. Usual heart failure treatment
Herbal	Chinese herbal mixture, blue cohosh	Symptoms and signs of heart failure	History of herbal product use	Standard heart failure treatment
Radiation	Radiation might cause microcirculatory damage, interstitial fibrosis, accelerated atherosclerosis	Symptoms and signs of diastolic heart failure	History of radiation	Standard heart failure treatment. Avoid further radiation

Table 7. Endocrine disorders associated with cardiomyopathies

Syndrome	Causes	Symptoms and signs	Diagnosis	Treatment
Acromegaly	Growth hormone and insulin-like growth factor 1 excess	Tachycardia and hypertension, diabetes, rhythm disturbances; biventricular hypertrophy and diastolic dysfunction	Nonsuppressibility of serum growth hormone levels after glucose loading	Surgery or pharmacotherapy might improve cardiovascular morbidity
Adrenal insufficiency (Addison disease)	Lack of ACTH	Hypotension, hypokalemia, syncope, bradycardia, prolonged QT, low voltage, and heart failure	Decrease response of the adrenal cortex to ACTH	Replacement of the deficient steroid hydrocortisone
Cushing disease	Excess production of glucocorticoids and androgens	Hypertension, central obesity, proximal muscle weakness, myocardial infarction, stroke, and cardiomyopathy	Lack of appropriate suppression of cortisol secretion by dexamethasone	Treat specific cause
Hypothyroidism (myxedema)	Low production of T3 and T4	Cardiac dilation, bradycardia, weak arterial pulses, angina, hypotension, distant heart sounds, low voltage, and peripheral edema	TSH, free T4	Hormone replacement
Hyperthyroidism	Excess production of T3 and T4	Tachycardia, wide pulse pressure, hyperkinetic cardiac apex, high CO heart failure	TSH, free T4	Treat thyroid disease. Be careful with the use of β-blockers
Pheochromocytoma	Catecholamine-producing tumour	Hypertension 'paroxysmal,' sweating, acute pulmonary edema, tachycardia, LVH, short PR interval, ST abnormalities, heart failure, myocarditis	Metanephrine levels	Phenoxybenzamine hydrochloride, β-blockers, and surgery

ACTH, adrenocorticotropic hormone; LVH, left ventricular hypertrophy; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

Table 8. Nutritional disorders associated with cardiomyopathies

Syndrome	Causes	Symptoms and signs	Diagnosis	Treatment
Carnitine deficiency	Low carnitine intake	Symptoms of heart failure; might see signs of malnutrition	Blood level; endomyocardial biopsy	Exogenous carnitine administration
Hypovitaminosis D and other causes of severe hypophosphatemia	Inadequate endogenous production of vitamin D3; poor diet or malabsorption	Rickets in children, osteomalacia in adults	Good history and physical. Ca, Mg; low 1,25(0H)2D; hypophosphatemia	Treat underlying cause; endocrine consultation; might need supplement
Selenium deficiency	Selenium deficiency is associated with heart failure in geographic areas where dietary selenium is low	Symptoms of heart failure	History and physical	Selenium supplement
Protein intake insufficient (kwashiorkor)	Heart failure is most likely secondary to selenium deficit in infants and young children	Symptoms of heart failure; hypothermia, hypotension, tachycardia, edema, low pulse volume, dermatitis, and others	History and physical	Correction of fluid and electrolytes; management of associated problems
Thiamine deficiency (beriberi)	At least 3 months of diet deficient in thiamine (eg 'polished rice'): alcohol	Edema; high CO heart failure; peripheral neuritis; midsystolic murmur, third heart sound	History and physical; decreased serum thiamine level	Thiamine replacement
Anorexia nervosa	Malnutrition, poor diet	Sinus bradycardia, prolonged QT, arrhythmias, cardiomegaly	History, physical, body mass index, electrolytes, blood urea nitrogen, creatinine, echocardiography, electrocardiogram	Supportive; good nutrition; psychological support; monitor serum electrolytes

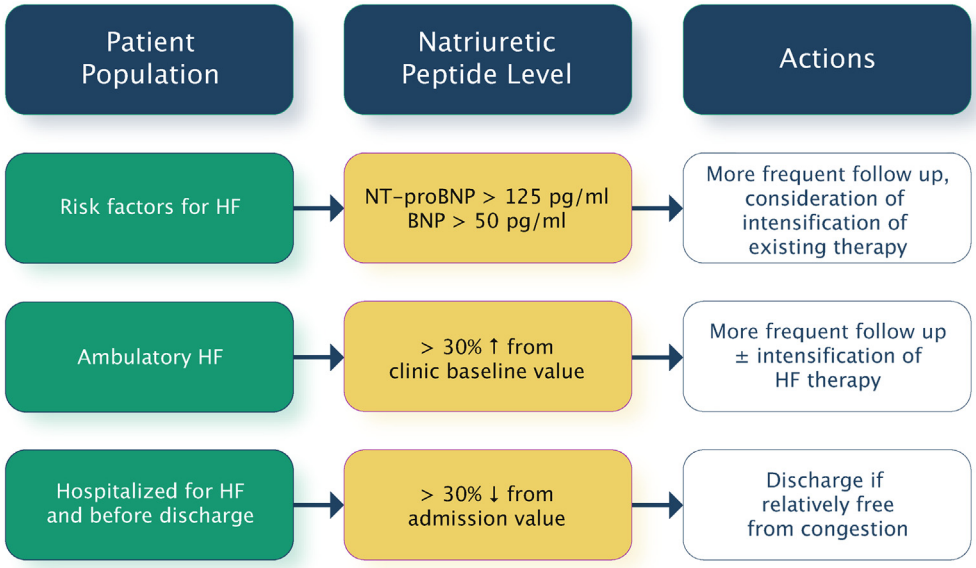

Figure 3. Algorithm for the use of natriuretic peptides in different heart failure (HF)-related clinical scenarios. Clinical evaluation and the risks and benefits of the action suggested should be considered. BNP, B-type natriuretic peptide; NT-proBNP, N-terminal propeptide B-type natriuretic peptide.

levels will be increased as a consequence of the ARNI's mechanisms of action over at least the first 8 months of treatment.

6.1.3. NPs for the management of chronic HFrEF

RECOMMENDATION

23. We suggest, in ambulatory patients with HFrEF, measurement of BNP or NT-proBNP to guide management should be considered to decrease HF-related hospitalizations and potentially reduce mortality. The benefit is uncertain in individuals older than 75 years of age (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. These recommendations are on the basis of multiple small RCTs, most of which showed benefit, and 3 meta-analyses, which universally showed benefit. An ongoing RCT is likely to affect this recommendation.

Practical tip. A change in NP levels by > 30% probably reflects more than daily variation in patients with compensated HF.

Practical tip. The timing of NP measurements in outpatient settings should be dictated according to clinical status; NP measurements should be used when they might aid in clinical decision-making.

6.1.4. NPs for the management of decompensated chronic HFrEF

RECOMMENDATION

24. We suggest that measurement of BNP or NT-proBNP in patients hospitalized for HF should be considered before discharge, because of the prognostic value of these biomarkers in predicting rehospitalization and mortality (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation is on the basis of multiple small RCTs, all of which showed an association with clinical outcomes.

Practical tip. A patient with persistently elevated NP levels might need closer follow-up to reduce the risk of rehospitalization.

Practical tip. For patients who are about to be discharged from the hospital after a HF hospitalization, the NP level should be lower than that on admission. If NP levels remain elevated, clinicians should re-evaluate the patient's condition and consider the possibility of delaying discharge from the hospital to optimize therapy and further reduce the NP level.

6.1.5. Myocardial injury, myocyte death, and troponins

In the **Val**sartan in **He**art **F**ailure **T**rial (Val-HeFT), 10.4% of subjects had detectable cardiac troponin T (cTnT) with a fourth-generation clinical assay (detection limit 0.01 ng/mL) and this proportion increased to 92% when an hs assay (hs-cTnT; detection limit 0.001 ng/mL) was used.[87] Although

Table 9. Natriuretic peptide cut points for the diagnosis of HF

	Age, years	HF is unlikely	HF is possible but other diagnoses need to be considered	HF is very likely
Acute setting				
BNP	All	< 100 pg/mL	100-400 pg/mL	> 400 pg/mL
NT-proBNP	< 50	< 300 pg/mL	300-450 pg/mL	> 450 pg/mL
	50-75	< 300 pg/mL	450-900 pg/mL	> 900 pg/mL
	> 75	< 300 pg/mL	900-1800 pg/mL	> 1800 pg/mL
Ambulatory care setting				
BNP	All	< 50 pg/mL		
NT-proBNP	All	< 125 pg/mL		

BNP, B-type natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal propeptide BNP.

the pathophysiology of cardiac troponin release in HF remains uncertain, several factors including subendocardial ischemia and myocyte necrosis, cardiomyocyte damage from inflammatory cytokines, or oxidative stress, apoptosis, and leakage of troponin from the cytosolic pool due to increased membrane permeability have been invoked (Table 10).[88] The degree of troponin elevation is a powerful predictor of mortality and cardiovascular events in ambulatory as well as acutely decompensated patients with chronic HFrEF, even after adjustment for traditional risk predictors including NPs.[87,89,90] Limited data are available regarding the prognostic significance of cTnT elevations in the ambulatory population with HFpEF, although levels do appear to be elevated to an extent comparable with that seen in HFrEF.[91] In an analysis of the **A**cute **D**ecompensated **He**art Failure National **R**egistry (ADHERE) of 84,872 patients hospitalized with acutely decompensated congestive HF, patients with positive cardiac troponins had a higher in-hospital mortality independent of other predictive variables in patients with HF.[92] Latini et al tested the prognostic value of the hs-cTnT assay in 4053 patients with chronic HF and showed that cTnT was detectable in 10.4% with the currently available assay compared with 92% using the hs-cTnT assay. Patients with hs-cTnT levels above the median had more severe HF and worse outcomes.[87]

RECOMMENDATION

25. We recommend that high-sensitivity (hs) troponins be measured on admission for AHF, to rule out ACS and for prognostic stratification (Strong Recommendation; High-Quality Evidence).

Values and preferences. The degree of hs troponin elevation is a powerful predictor of mortality and cardiovascular events in ambulatory as well as acutely decompensated patients with chronic HFrEF, even after adjustment for traditional risk predictors including NPs. However, it is yet unclear how the use of serial hs troponin measurements in addition to NPs for HFrEF management would provide additional and cost-effective benefits in terms of improving outcomes. Also, limited data are available regarding the prognostic significance of hs troponin elevations in ambulatory patients with HFpEF.

7. Treatment

7.1. Chronic HF

Pharmacotherapy has been shown to change the natural history of HFrEF. HFpEF however, has been identified as major public health issue and to date, the etiology, diagnosis, characterization, and treatment has remained challenging. Goals of HF therapy include improving survival and reducing morbidity such as hospitalizations and symptoms, while improving functional capacity and quality of life. Figure 4 shows a therapeutic approach to patients with HFrEF that is considered optimal medical therapy and defined as GDMT throughout this section. The evidence-based medications and doses of GDMT are shown in Table 11.

7.1.1. HFrEF pharmacological treatment

Contemporary treatment for most patients with HFrEF encompasses triple therapy, which includes the combination of: (1) an ACEi (or ARB if ACEi-intolerant); (2) a β-blocker; and (3) an MRA. Working on various pathways of the neurohormonal system, the combination of these agents has been shown to improve survival in patients with HFrEF. There are many landmark trials and meta-analyses that support the use of ACEis[93-99] and β-blockers[100-104] in all patients across the spectrum of HFrEF. ARBs have been shown to be superior to placebo in those intolerant to ACEis and are considered a good second-line agent.[105-108] Likewise, there are 2 key clinical trials and 1 meta-analysis[109-111] that support the additional use of an MRA with this combination with an improvement in survival across the spectrum of symptomatic patients with HFrEF. Most recently, the **E**plerenone in **M**ild **P**atients **H**ospitalization **a**nd **S**urv**i**val **S**tudy in **H**eart **F**ailure (EMPHASIS-HF) expanded the use of aldosterone receptor antagonists in HFrEF patients with mild symptoms.[110] In EMPHASIS-HF the effects of eplerenone on clinical outcomes were examined in patients 55 years of age or older, with NYHA II symptoms, LVEF < 30% (if > 30%-35%, a QRS duration of > 130 ms), treated with an ACEi and/or ARB, and β-blockers. A total of 2737 patients with a median follow-up of 21 months were enrolled. There was a 37% reduction in the primary composite outcome of death from cardiovascular causes or first hospitalization for HF with eplerenone.

7.1.1.1. Pharmacologic therapy

In addition to initiating, titrating, and monitoring pharmacologic therapy, there are circumstances in which

Table 10. Selected biomarkers with potential for future clinical use in the management of HF

Biomarker*	Pathophysiological pathways/comorbid conditions with prognostic implications	HF populations targeted	Advantages	Potential benefits	Challenges before implementation
Cardiac high-sensitivity troponins	Myocyte death	Acute and chronic HF	Very sensitive marker predicting higher risk of CV events regardless of etiology	Optimization of therapy in patients with elevated hs-cTn should be more aggressive	Prognostication improves only for mortality and use to modify therapy has not been tested
sST2	Fibrosis/inflammation/ immunity	Acute and chronic HFrEF, HFpEF, and previously low EF recovered	Additional prognostic value beyond NPs suspected low week-to-week variations	Could provide additional value for short- and long-term prognostication, regardless of LVEF	Unclear if using sST2 in acute or chronic HF to modify therapies improves clinical outcomes
Procalcitonin	Bacterial infection	Acute HF	Early detection of bacterial infection	Guiding antibiotic therapy in acute HF and suspected respiratory infection	Levels are increased in HF without ongoing bacterial infection. No clear cutoff has been identified in the HF population
Galectin-3	Cardiac and vascular fibrosis	Incident HF, HFrEF, and HFpEF	Early detection of risk and long-term prognostication in HF	Preventive measures and therapy optimization on the basis of levels could improve outcomes	ST2 might be superior to galectin-3 in a multivariable risk prediction model
Cystatin C	Renal function	Acute and chronic HF	More sensitive detection of changes in renal function	Same as above	Unclear if using cystatin C, over using eGFR, to modify clinical management provides further clinical benefit
NGAL	Renal function	Acute HF	Early detection of renal function deterioration	Adjusting therapy to improve prognosis by avoiding acute renal failure progression	Unclear if using NGAL in acute HF to modify therapies improves clinical outcomes

CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; hs-cTn, high-sensitivity cardiac troponin; LVEF, left ventricular ejection fraction; NGAL, neutrophil gelatinase-associated lipocalin; NPs, natriuretic peptides; sST2, soluble toll-like receptor-2; ST2, suppression of tumorigenicity 2.

*This list is not exhaustive; multiple biomarkers have been and are being studied.

some therapies may be withdrawn (Table 12). There are additionally some common effects of GDMT requiring active surveillance and management. A suggested approach to hyperkalemia is presented in Table 13.

RECOMMENDATION

26. We recommend that most patients with HFrEF be treated with triple therapy including an ACEi (or an ARB in those who are ACEi-intolerant), a β-blocker and an MRA unless specific contraindications exist (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. Preference is given to the use of pharmacotherapy in most patients with HFrEF across the spectrum of symptoms. There are limited clinical trial data to inform decision-making surrounding the use of MRAs as part of GDMT in those without symptoms of HF or high-risk features.

27. We recommend preferentially using the specific drugs at target doses that have been proven to be beneficial in clinical trials as optimal medical therapy. If these doses cannot be achieved, the maximally tolerated dose is acceptable (Table 11) (Strong Recommendation; High-Quality Evidence).

Practical tip (general). If a drug with proven mortality or morbidity benefits does not appear to be tolerated by the patient (eg, low BP, low heart rate, or renal dysfunction), other concomitant drugs, including diuretics, with less proven benefit should be carefully re-evaluated to determine whether their dose can be reduced or the drug discontinued.

Practical tip (general). HFrEF GDMT should be continued at the usual dose during acute intercurrent illness (eg, pneumonia, exacerbation of chronic obstructive pulmonary disease, other systemic infection, etc), unless they are not tolerated (eg, if significant reactive airway disease is present). GDMT should be restarted before discharge if temporarily withheld.

Practical tip (general). In a life-threatening complication, GDMT may be discontinued abruptly, but generally, if there

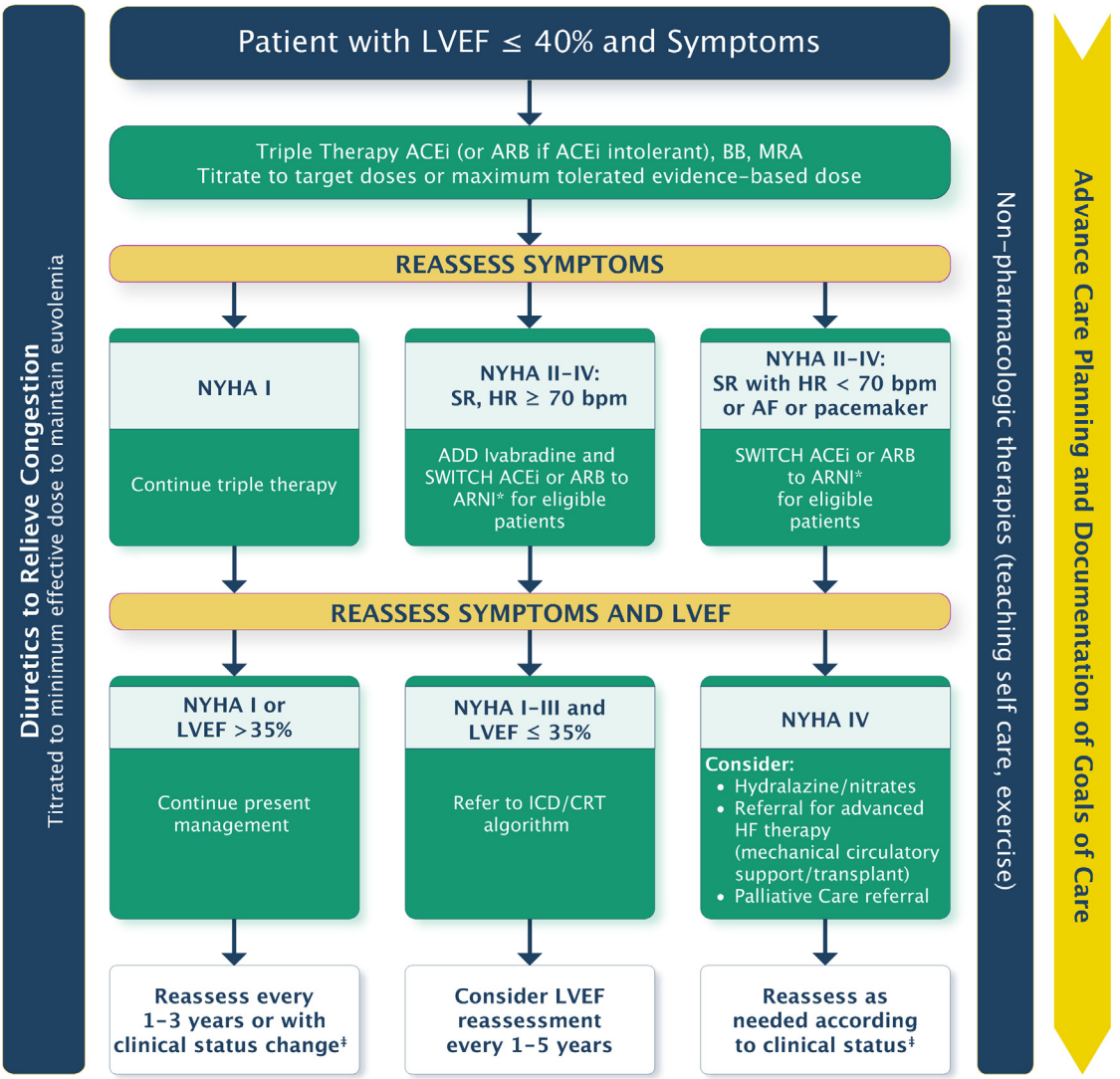

Figure 4. Therapeutic approach to patients with symptoms of heart failure (HF) and a reduced ejection fraction. *Sacubitril or valsartan. ‡Refer to Table 5. ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, β-blocker; bpm, beats per minute; CRT, cardiac resynchronization therapy; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SR, sinus rhythm.

is concern about their use, the dose should be decreased by one-half, and the patient should be reassessed. If the dose is reduced, it should be uptitrated to the previous tolerated dose as soon as safely possible.

Practical tip (general). If symptomatic hypotension persists with GDMT, consider separating the administration of the dose from the timing of other medications that could also lower BP.

Practical tip (ACEi/ARB). ACEi intolerance describes a patient who is unable to tolerate ACEi therapy secondary to a bothersome cough (most commonly, 10%-20%) or those who experience angioedema with ACEi therapy (uncommon; < 1%). ARB therapy is a reasonable alternative in both of these cases, however, caution should be used in patients who develop angioedema while receiving ACEi therapy because there have been case reports of patients who subsequently develop angioedema with ARB therapy. There is no significant difference in rates of hypotension, hyperkalemia, or renal dysfunction between these agents to warrant a substitution between agents.

Practical tip (ACEi/ARB). An increase in serum creatinine or eGFR of up to 30% is not unexpected when an ACEi or ARB is introduced; if the increase stabilizes at ≤ 30%, there is no immediate need to decrease the drug dose but closer long-term monitoring might be required.

Practical tip (ACEi/ARB). BP might lower when an ACEi or ARB is introduced, especially if introduced at a high dose or in combination with diuretic therapy. Check BP with the patient supine and erect to detect whether hypotension is present, requiring slower uptitration.

Table 11. Evidence-based drugs and oral doses as shown in large clinical trials

Drug	Start dose	Target dose
ACEi		
Enalapril	1.25-2.5 mg BID	10 mg BID/20 BID in NYHA class IV
Lisinopril	2.5-5 mg daily	20-35 mg daily
Perindopril	2-4 mg daily	4-8 mg
Ramipril	1.25-2.5 mg BID	5 mg BID
Trandolapril	1-2 mg daily	4 mg daily
ARB		
Candesartan	4-8 mg daily	32 mg daily
Valsartan	40 mg BID	160 mg BID
β-Blockers		
Carvedilol	3.125 mg BID	25 mg BID/50 mg BID (> 85 kg)
Bisoprolol	1.25 mg daily	10 mg daily
Metoprolol CR/XL*	12.5-25 mg daily	200 mg daily
MRA		
Spironolactone	12.5 mg daily	50 mg daily
Eplerenone	25 mg daily	50 mg daily
ARNI		
Sacubitril/valsartan	50-100 mg BID	200 mg BID
I_f inhibitor		
Ivabradine	2.5-5 mg BID	7.5 mg BID
Vasodilators		
Isosorbide dinitrate	20 mg TID	40 mg TID
Hydralazine	37.5 mg TID	75-100 mg TID or QID

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BID, twice per day; HF, heart failure; I_f, inhibiting f-channel; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; QID, 4 times per day; TID, 3 times per day.

*Limited evidence of short-acting metoprolol tartrate in HF. Metoprolol CR/XL is not available in Canada.

Practical tip (ACEi/ARB). Cough occurs in 10%-20% of patients receiving ACEis and does not require discontinuation of the agent unless it is bothersome to the patient.

Practical tip (β-blockers). Objective improvement in cardiac function might not be apparent for 6-12 months after β-blocker initiation.

Practical tip (β-blockers). Patients in NYHA class I or II can be safely initiated and titrated with a β-blocker by nonspecialist physicians.

Practical tip (β-blockers). Patients in NYHA class III or IV should have their β-blocker therapy initiated by a specialist experienced in HF management and titrated in the setting of close follow-up, such as can be provided in a specialized clinic, if available.

Practical tip (β-blockers). The starting dose of β-blockers should be low and increased slowly (eg, double the dose every 2-4 weeks). Transient fluid retention might occur with initiation or uptitration of β-blockers and might require assessment of diuretic dosage (eg, might consider deferring dosage reduction).

Practical tip (β-blockers). If concomitant reactive airways disease is present, consider using more selective β-1 blockade (eg, bisoprolol).

Practical tip (β-blockers). If atrioventricular (AV) block is present, consider decreasing other AV-blocking drugs, such as digoxin or amiodarone (when appropriate). The type and severity of AV block and the patient's history of arrhythmias will help guide the most appropriate treatment modifications.

Practical tip (MRA). MRAs can increase serum potassium, especially during an acute dehydrating illness in which renal dysfunction can worsen, and close monitoring of serum creatinine and potassium is required. High-risk groups include those with diabetes, pre-existing renal dysfunction, and older age.

7.1.1.2. ACEi/ARB

There are extensive data on the use of ACEi and β-blocker treatment for patients with HFrEF to reduce morbidity and mortality and improve quality of life.[112,113] A notable deletion from these guidelines is the recommendation to consider combination ACEi and ARB therapy, previously recommended. The combination of an ACEi with an ARB is no longer recommended. Although some evidence exists to support a reduction in clinically relevant outcomes with the combination, there is also substantial evidence that was published after the previous recommendation, outlining harm in terms of adverse effects (eg, hypotension, hyperkalemia, and renal dysfunction).[108,114,115] More contemporary treatments with MRAs and ARNIs have a stronger evidence base across the spectrum of outcomes (eg, morbidity and mortality) and therefore further limit the role of combination ACEi and ARB therapy.

Table 12. Potential scenarios in which evidence-based medical therapy for heart failure might be withdrawn

Clinical presentation	Conditions to justify stepwise withdrawal of GDMT after 6-12 months of full medical therapy	Comments
Tachycardia-related CM	• Normal EF and LV volumes • NYHA I • Underlying tachycardia controlled	Usually due to atrial fibrillation/flutter with increased HR, might rarely occur because of PVCs. Might need long-term BB for rate control
Alcoholic CM	• Normal EF and LV volumes • NYHA I • Abstinence ETOH	Nutritional deficiency, obesity, and obstructive sleep apnea might coexist and require therapy
Chemotherapy-related CM	• Normal EF and LV volumes • NYHA I • No further drug exposure	Certain types of chemotherapy are more likely to reverse than others (trastuzumab—high rate of LVEF improvement when it is discontinued whereas patients who received anthracyclines should continue LV enhancement therapy) Long-term surveillance strongly recommended
Peripartum CM	• Normal EF and LV volumes • NYHA I	Repeat pregnancy might be possible for some. Consultation at high-risk maternal centre should be undertaken
Valve replacement surgery	• Normal EF and LV volumes • NYHA I • Normally functioning valve	Less consensus on regurgitant lesions with ongoing dilation of LV

BB, β-blocker; CM, cardiomyopathy; EF, ejection fraction; ETOH, ethanol; GDMT, guideline-directed medical therapy; HR, heart rate; LV, left ventricle; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVC, premature ventricular contraction.

Table 13. Suggested management approach for hyperkalemia, according to severity

Severity of hyperkalemia*	Initial management	When to recheck electrolytes and potassium	When to restart and/or retitrate RAAS inhibitors
Mild (serum K^+ 5.0-5.5 mmol/L)	• Continue all RAAS unless new and major increase in K^+ (if so, stop most recently added RAAS agent) • Reinforce potassium restriction • Avoid other sources of K^+ • Ensure patient is not hypovolemic • Review all medications	• Routine measurement unless K^+ has been gradually increasing over time • If RAAS agent has been stopped, recheck within 72 hours	• Usually not applicable • If RAAS agent has been stopped, restart when serum potassium decreases to within the patients usual level, or < 5.0 mmol/L, (whichever is higher) and • Any concomitant condition contributing to recent changes is under control
Moderate (serum K^+ 5.6-5.9 mmol/L)	• Continue all RAAS at half previous dose unless K^+ has been increasing over time or major increase in K^+ (if so, stop most recently added RAAS agent) • Reinforce potassium restriction • Avoid other sources of K^+ • Ensure patient is not hypovolemic • Review all medications	• Recheck K^+ and renal function within 72 hours • With repeated $K^+ > 5.5$, stop at least 1 RAAS agent and repeat measurement within 72 hours • With a second $K^+ > 5.5$, consider calcium or sodium polystyrene 30 g administration	• When serum potassium decreases to within the patients' usual level, or < 5.0 mmol/L, (whichever is higher) and • Any concomitant condition contributing to recent changes is under control • RAAS medications should usually be reintroduced 1 at a time with intervening measurement of renal function and electrolytes
Serious or severe (serum $K^+ > 5.9$ mmol/L)	• Contact patient to proceed to health centres for clinical assessment and 12-lead electrocardiogram • Patient to undergo treatment according to local protocols for serious hyperkalemia • Hold all RAAS inhibiting agents until reassessment • Review all medications	• Within 4-24 hours, depending on local acute hyperkalemia protocol (when symptomatic or if there are electrocardiographic changes consistent with hyperkalemia) • Again approximately 72 hours later	• When serum potassium decreases to within the patients' usual level, or < 5.0 mmol/L, (whichever is higher) and • Any concomitant condition contributing to recent changes is under control • RAAS-inhibiting medications should usually be reintroduced 1 at a time with intervening measurement of renal function and electrolytes

RAAS, renin-angiotensin-aldosterone system.

*The above actions are suggested on the basis of the assumption that the potassium level is correctly measured. For instance, hemolysis of blood might occur, which falsely increases the potassium level. In this instance, a repeat measure is necessary.

RECOMMENDATION

28. We recommend an ACEi, or ARB in those with ACEi intolerance, in patients with acute MI with HF or an EF < 40% post-MI to be used as soon as safely possible post-MI and be continued indefinitely (Strong Recommendation; High-Quality Evidence).

7.1.1.3. β-Adrenergic receptor blocker (β-blocker)

β-Blockers are part of the first-line therapy in the treatment of HFrEF, because they have been proven to improve survival and decrease hospitalizations in this population of patients, in a number of large clinical trials.[101,103,116-121]

RECOMMENDATION

29. We recommend NYHA class IV patients be stabilized before initiation of a β-blocker (Strong Recommendation; High-Quality Evidence).
30. We recommend that β-blockers be initiated as soon as possible after diagnosis of HF, including during the index hospitalization, provided that the patient is hemodynamically stable. Clinicians should not wait until hospital discharge to start a β-blocker in stabilized patients (Strong Recommendation; High-Quality Evidence).
31. We recommend that β-blockers be initiated in all patients with an LVEF < 40% with previous MI (Strong Recommendation; Moderate-Quality Evidence).

7.1.1.4. MRAs

A single RCT supports the use of eplerenone (target 50 mg daily) compared with placebo post-MI.[122] The **E**plerenone **P**ost-Acute Myocardial Infarction **H**eart Failure **E**fficacy and **Su**rvival **S**tudy (EPHESUS) trial enrolled 6642 patients who had an MI 3-14 days previously with an LVEF < 40% and symptoms of HF or an LVEF < 30% and diabetes without symptoms of HF. The primary outcome included all-cause mortality and cardiovascular mortality or hospitalization for cardiovascular events. After a median follow-up of 16 months, there was a 15% relative decrease in mortality and 13% relative decrease in cardiovascular

Table 14. Potential valsartan/sacubitril dosing and titration

ACEi	ARB	Initial dose*	Titration
Higher dose of RAAS inhibitor			
Enalapril ≥ 10 mg/d	Candesartan ≥ 16 mg/d	100 mg PO BID	Over 3-6 weeks, increase to target 200 mg PO BID
Lisinopril ≥ 10 mg/d	Irbesartan ≥ 150 mg/d		
Perindopril ≥ 4 mg/d	Losartan ≥ 50 mg/d		
Ramipril ≥ 5 mg/d	Olmesartan ≥ 10 mg/d		
	Telmisartan ≥ 40 mg/d		
	Valsartan ≥ 160 mg/d		
Lower dose of RAAS inhibitor		50-100 mg PO BID	Over 6 weeks, increase to target 200 mg PO BID[96]
Higher risk of hypotension (eg. low baseline SBP, poor renal function)		50 mg PO BID	

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BID, twice per day; PO, orally; RAAS, renin-angiotensin-aldosterone system.

*Health Canada labelled dose of 50 mg BID is 24.3 mg sacubitril/25.7 mg valsartan, 100 mg BID is 48.6 mg sacubitril/51.4 mg valsartan, and 200 mg is 97.2 mg sacubitril/102.8 mg valsartan.

mortality or hospitalization for cardiovascular events in the eplerenone group. There was more hyperkalemia in the eplerenone group.

RECOMMENDATION

32. We recommend an MRA for patients with acute MI with EF < 40% and HF or with acute MI and an EF < 30% alone in the presence of diabetes (Strong Recommendation; High-Quality Evidence).

7.1.1.5. ARNI

In those who remain symptomatic despite triple therapy, consideration should be made to change an ACEi/ARB to an ARNI. Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including NPs, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodelling.[123,124] In the **P**rospective Comparison of **ARN**i With **A**CEi to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure (PARADIGM-HF) trial, the ARNI sacubitril/valsartan was

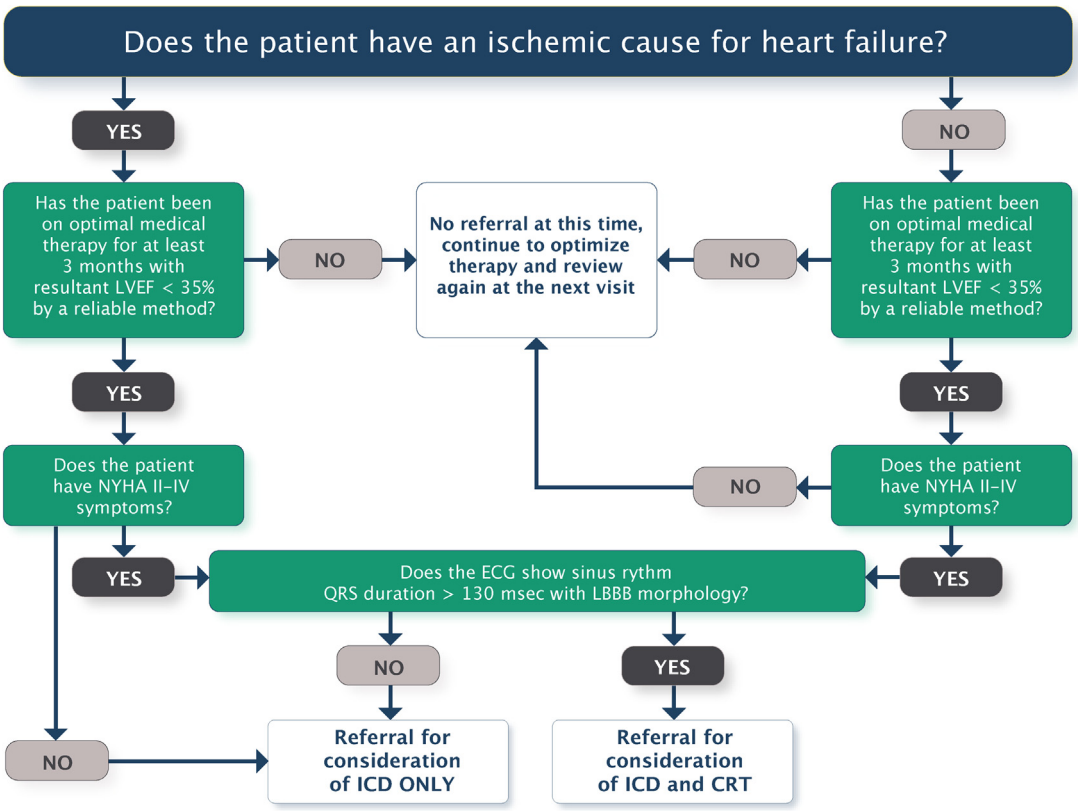

Figure 5. Referral pathway for device therapy in patients with heart failure; the referral pathway for devices should be guided by many factors as outlined in the figure, as well as patient preferences, goals, and comorbidity. CRT, cardiac resynchronization therapy; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 15. Profile descriptions for patients with advanced heart failure, according to the INTERMACS Registry[242]

INTERMACS profile description	Time frame for intervention
Profile 1: critical cardiogenic shock Patients with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. "Crash and burn"	Definitive intervention needed within hours
Profile 2: progressive decline Patient with declining function despite intravenous inotropic support, might be manifest by worsening renal function, nutritional depletion, inability to restore volume balance; "sliding on inotropes." Also describes declining status in patients unable to tolerate inotropic therapy	Definitive intervention needed within a few days
Profile 3: stable but inotrope-dependent Patient with stable blood pressure, organ function, nutrition, and symptoms receiving continuous intravenous inotropic support (or a temporary circulatory support device or both), but with repeated failure to wean from support because of recurrent symptomatic hypotension or renal dysfunction; "dependent stability"	Definitive intervention elective over a period of weeks to a few months
Profile 4: resting symptoms Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest during ADL. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which might in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients might shuttle between profile 4 and 5	Definitive intervention elective over period of weeks to a few months
Profile 5: exertion intolerant Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but might have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, the patient might be more at risk than INTERMACS 4, and require definitive intervention	Variable urgency, depends upon maintenance of nutrition, organ function, and activity
Profile 6: exertion limited The patient without evidence of fluid overload is comfortable at rest, and with ADL and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment; "walking wounded"	Variable, depends upon maintenance of nutrition, organ function, and activity level.
Profile 7: advanced NYHA III A placeholder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion	Transplantation or circulatory support might not currently be indicated

ADL, activities of daily living; INTERMACS, **Inter**agency **R**egistry for **M**echanically **A**ssisted **C**irculatory **S**upport; NYHA, New York Heart Association. Reproduced from Stevenson et al.[242] with permission from Elsevier.

compared with enalapril in patients with HFrEF.[125] A total of 8442 patients were randomized to sacubitril/valsartan 200 mg twice daily or enalapril 10 mg twice daily after a 6-8 week run-in phase. Patients were included if they were NYHA class II-IV (70% class II), LVEF $\leq$ 40% (amended to $\leq$ 35%), had a BNP $\geq$ 150 pg/mL (or NT-proBNP $\geq$ 600 pg/mL), or hospitalization for HF in the past year and BNP $\geq$ 100 pg/mL (or NT-proBNP $\geq$ 400 pg/mL). The primary outcome was a composite of death from cardiovascular causes or hospitalization for HF. The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months. The primary outcome occurred in 914 patients

Table 16. Features associated with the need for short-term vs long-term MCS

Feature	Temporary assist	Long-term assist
Time period	Emergent (< 24-72 hours) insertion; support time in days	Urgent or elective insertion; support time in weeks to years
Care setting	Intensive cardiac care setting with goal to recovery, transplantation, longer-term device, or palliative care	Post cardiovascular surgery unit, with goal toward hospital discharge
Infection control	High risk	Lower risk
Special issues	Frequently ventilated, invasive hemodynamic monitoring, and paralysis to deter device migration	Early intensive care, late noninvasive monitoring
Type of support	Might be 1 or both ventricles, partial or full support; maximum support usually less than permanent devices	Usually only left ventricular support, able to provide larger amount of support

MCS, mechanical circulatory support.

(21.8%) in the sacubitril/valsartan group and 1117 patients (26.5%) in the enalapril group, a 20% relative reduction. There was also a decrease in all-cause mortality, cardiovascular mortality, HF hospitalization, and symptoms of HF. The sacubitril/valsartan group had a higher proportion of patients with hypotension but a smaller risk of renal impairment, hyperkalemia, and cough than the enalapril group. The type of patients and magnitude of effect were similar to other landmark trials in HFrEF including ACEis, β-blockers, and MRAs. This trial also closely reflects contemporary practice with high utilization of ACEis, β-blockers, and MRAs (100%, 92%, and 55%, respectively) at baseline and had an active gold standard comparator.

RECOMMENDATION

33. We recommend that an ARNI be used in place of an ACEi or ARB, in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT to decrease cardiovascular death, HF hospitalizations, and symptoms (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation places high value on medications proven in large trials to reduce mortality, HF re-hospitalization, and symptoms. It also considers the health economic implications of new medications.

Practical tip. Drug tolerability, side effects, and laboratory monitoring with use of ARNIs is similar to that of ACEi or ARB noted previously.

Practical tip. The PARADIGM-HF trial excluded patients with a serum potassium > 5.2 mmol/L, an eGFR < 30 mL/min, and symptomatic hypotension with a systolic BP of < 100 mm Hg.

Practical tip. When switching between an ARNI and an ACEi, a washout period of at least 36 hours is required to decrease the risk of angioedema. No washout period is required for conversion between ARNIs and ARBs.

Practical tip. ARNIs should not be used in anyone with a history of angioedema.

Practical tip. Currently, there is only 1 ARNI, sacubitril-valsartan, available on the Canadian market. Initial dosing and rate of titration is dependent on pre-existing treatment and comorbidities and should be individualized (Table 14). When selecting a dose or titration schedule consideration should be given to the likelihood of tolerability and ultimately successful titration to doses shown to improve important HF outcomes.

7.1.1.6. Ivabradine

Resting heart rate independently predicts CVD events, including HF hospitalization.[126,127] Systematic reviews have shown that a major contributor to the benefits of β-blocker therapy might be their rate-lowering effect.[128-130] Despite their benefits, β-blockers are generally underused and underdosed.[129-131] Ivabradine is approved for the treatment of HF by Health Canada. The latter drug selectively inhibits the depolarizing I_f current in the sinus node. It thus requires sinus rhythm to provide its pharmacological effect. In contrast to β-blockers, ivabradine does so without lowering BP or myocardial contractility.[132,133]

Table 17. Checklist assessment for mechanical circulatory support

Issue	Assessment items
Cardiac assessment	Full assessment of ventricular, valvular function, assessment of hemodynamics with particular view to potential reversibility of condition
	Right ventricular function—will the patient require biventricular support? (higher risk)
	Rapidity of cardiac decompensation (rapid deterioration mitigates toward temporary support)
Surgical history	Previous sternotomy
	Is this early postpericardiotomy? (higher risk)
	Does the patient have a prosthetic valve, which will need replacement at the time of VAD insertion?
	Vascular access, device, and patient technical considerations
	Ability to withstand major surgical procedure
Other medical issues	Active infection, coagulopathy, liver dysfunction, renal function, cognitive/neurological status
	Are other conditions that limit operational or long-term survival present?
Cardiac transplantation eligibility	Is there time to consider cardiac transplantation eligibility?
	If not, temporary device consideration suggested
Advanced care planning issues	Patient preferences for care
	Has the patient outlined goals of care?
Psychosocial considerations	Can the patient maintain self-care at home?
	Are sufficient home or family supports available, and are they engaged in preoperative planning and decision-making?

VAD, ventricular assist device.

The first trial to assess ivabradine in CAD was the Mor**b**idity-Mortality **E**v**a**l**u**a**t**ion of the $\mathbf{I_f}$ Inhibitor Ivabradine in Patients With Coronary Disease and Left-Ventric**ul**ar Dysfunction (BEAUTIFUL) trial.[134] In this trial the effect of ivabradine 7.5 mg twice daily was evaluated in patients with CAD and LVEF $< 40\%$ in sinus rhythm with a heart rate $>$ 60 bpm in $>$ 10,000 patients. Although ivabradine did not reduce the primary composite end point of cardiovascular death, hospitalization for MI, or new-onset or worsening HF, it did reduce the incidence of the secondary end point of fatal and nonfatal MI in patients with a baseline heart rate ≥ 70 bpm.

The **S**ystolic **H**eart Failure Treatment With the $\boldsymbol{I_f}$ Inhibitor Ivabradine **T**rial (SHIFT) trial was the key trial to address the use of ivabradine in symptomatic HF.[135] Inclusion criteria were NYHA class II-IV, sinus rhythm, resting heart rate ≥ 70 bpm, LVEF $\leq 35\%$, and HF admission within 12 months. Patients were randomized to a target dose of ivabradine 7.5 mg twice daily vs placebo. The primary end point was a composite of cardiovascular death or HF admission. Ninety percent

Table 18. Exercise modalities according to clinical scenario

Exercises	Recently discharged with heart failure	NYHA I-III	NYHA IV
Flexibility exercises	Recommended	Recommended	Recommended
Aerobic exercises	Recommended	Recommended	Recommended
Suggested modality	Selected population only Supervision by an expert team needed	Walk Treadmill Ergocycle Swimming	Selected population only Supervision by an expert team needed
Intensity		Continuous training • Moderate intensity: RPE scale 3-5, or 65%-85% maximum HR, or 50%-75% peak VO_2 • Moderate-intensity aerobic interval might be incorporated in selected patients • Intervals of 15-30 minutes with an RPE scale of 3-5 • Rest intervals of 15-30 minutes	
Frequency		Starting with 2-3 days per week Goal: 5 days per week	
Duration		Starting with 10-15 minutes Goal: 30 minutes	
Isometric/resistance exercises		Recommended	
Intensity		10-20 repetitions of 5- to 10-pound free weights	
Frequency		2-3 days per week	

HR, heart rate; NYHA, New York Heart Association; RPE, rated perceived exertion; VO_2, volume of oxygen.

of patients were receiving a β-blocker, and 56% were receiving > 50% of target doses. Heart rate was 8 bpm lower in the ivabradine group at the end of the study. There was an 18% decrease in the primary outcome, which was largely driven by hospital admission for worsening HF (RRR, 26%). Treatment effect was consistent across prespecified subgroups, although the difference between treatment groups did not reach statistical significance in the subgroup with a baseline heart rate lower than the median of 77 bpm. Additionally, in those receiving > 50% of the target dose of a β-blocker, the overall trial results were similar. Ivabradine did not reduce all-cause or cardiovascular mortality. There were more withdrawals (21% vs 19%) and bradycardia in the ivabradine group (10% vs 2%). Only 1% of patients withdrew from the study as a consequence of bradycardia. Visual symptoms specific to ivabradine occurred rarely (3% vs 1% with placebo; $P < 0.0001$ and led to withdrawal in 1% of cases).

RECOMMENDATION

34. We recommend that ivabradine be considered in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT, with a resting heart rate > 70 beats per minute (bpm), in sinus rhythm, and a previous HF hospitalization within 12 months, for the prevention of cardiovascular death and HF hospitalization (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. High value is placed on the improvement of cardiovascular death and HF hospitalizations as adjunctive therapy to standard HF medication treatments in a selected HF population. The health economic implications are unknown. Differing criteria for heart rate eligibility have been approved by various regulatory authorities ranging from 70 to 77 bpm with the trial entry criteria of 70 bpm.

Practical tip. Every effort should be made to achieve target or maximally tolerated doses of β-blockers before initiation of ivabradine.

Practical tip. Ivabradine has no effect on BP or myocardial contractility.

7.1.1.7. Hydralazine and isosorbide dinitrate

Three RCTs inform the use of H-ISDN in HFrEF. The **V**asodilator in **He**art **F**ailure **T**rial (V-HeFT) trial, the first RCT, compared the effect of H-ISDN, prazosin and placebo in HFrEF on mortality (n = 642).[136] After a mean follow-up of 2.3 years, there was no difference in mortality for the entire follow-up period (primary outcome), but showed a 66% relative improvement in survival in the H-ISDN group at 2 years. This trial predated the era of ACEis and β-blockers. The second trial to evaluate H-ISDN (300 mg and 160 mg) compared with enalapril (20 mg daily) in HFrEF on the outcome of mortality (n = 804).[137] There was a reduction in mortality in the enalapril arm after a mean of 2.5 years (32.8% vs 38.2%; $P = 0.016$) and no difference in hospitalizations. Neither of these trials provide an insight into the role of H-ISDN in the face of contemporary therapy. The third trial was the **A**frican-American **He**art **F**ailure **T**rial (A-HeFT) trial, in which H-ISDN was investigated in additional to optimal therapy (ACEi/ARB, β-blocker, MRA) in self-identified black patients with NYHA class III/IV

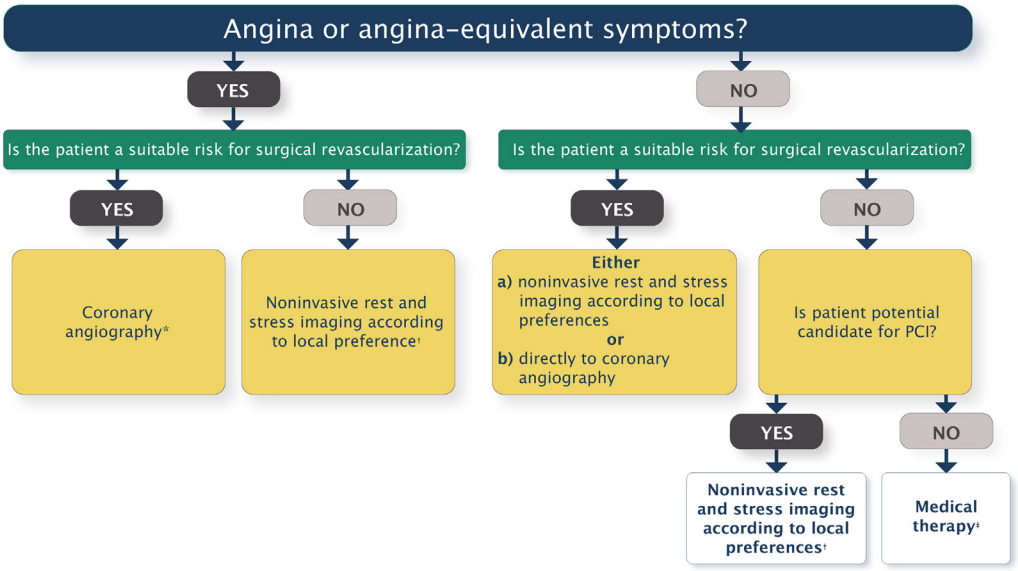

Figure 6. The approach to assessment for coronary artery disease in patients with heart failure. All patients with heart failure are expected to undergo noninvasive measurement of systolic function (not included in this algorithm). PCI, percutaneous coronary intervention. *Some centres might additionally perform noninvasive imaging, especially when coronary anatomy is not optimal. †If imaging indicates features of high risk, progression to coronary angiography is expected. ‡Noninvasive imaging might be performed in certain centres for risk stratification or diagnosis.

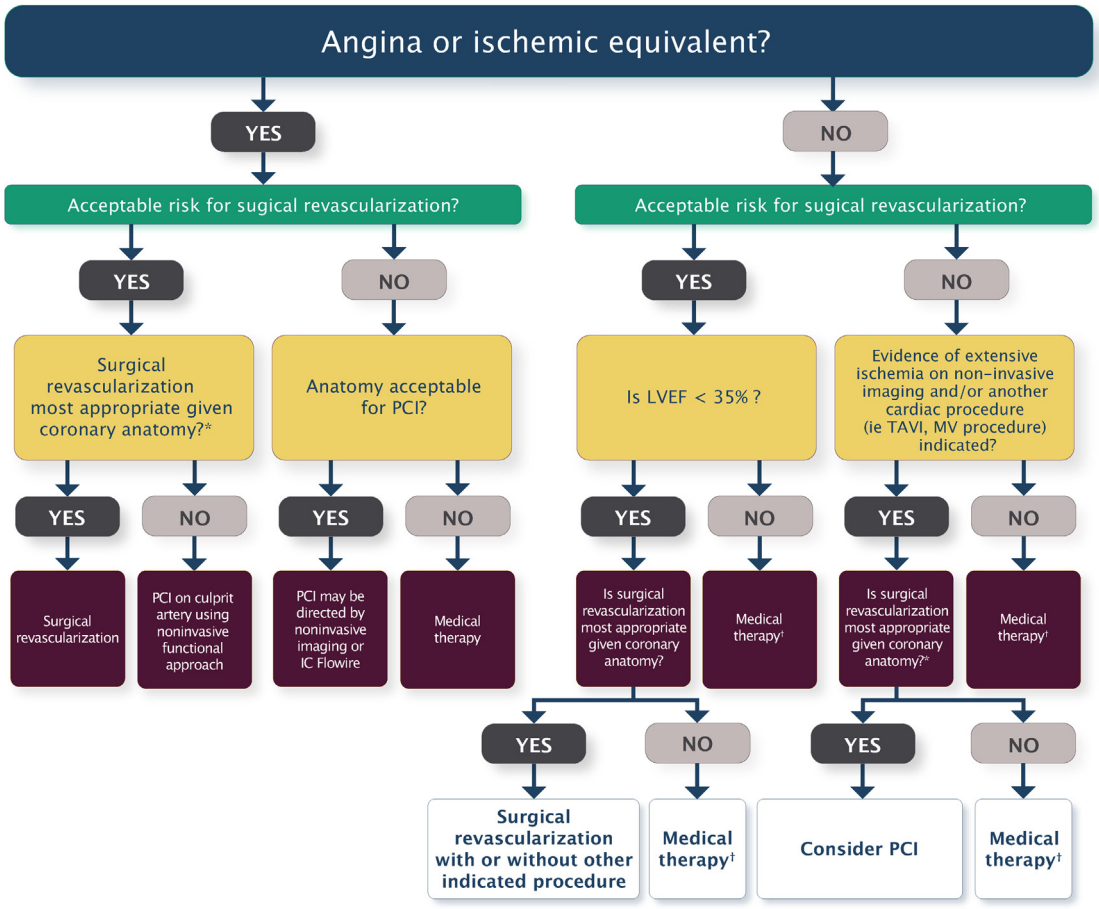

Figure 7. Decision regarding coronary revascularization in patients with heart failure. It is recommended that surgical and interventional cardiology consultation be considered early in this process. *Coronary anatomy suitable for CABG includes: multivessel disease > 70% stenosis; left main stem stenosis > 50%; or diabetes with left anterior descending artery stenosis > 70%. †In selected cases in which there is noninvasive imaging evidence of extensive cardia ischemia, PCI might be considered. CABG, coronary artery bypass grafting; IC, intracoronary; LVEF, left ventricular ejection fraction; MV, mitral valve; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.

Table 19. Causes of RHF

Etiology
Mixed
Restrictive heart disease
Congenital heart disease including surgical residual
Primary
Right-sided valvular disease
RV infarction
RV myopathic process
Secondary etiology
Pericardial disease (a mimic of RHF)
Pulmonary arterial hypertension
Left-sided heart failure

RHF, right heart failure; RV, right ventricular.

HFrEF.[138] Black patients were specifically evaluated in this trial because it had been noted that this population has a less active renin-angiotensin system and seemed to respond better to H-ISDN. In this trial H-ISDN (225 mg or 120 mg) was evaluated vs placebo (in addition to standard therapy) on the outcome of all-cause mortality, first hospitalization for HF, and quality of life. A total of 1050 black patients were enrolled and followed for a mean of 10 months. The study was terminated early secondary to higher mortality in the placebo group. The primary outcome was a weighted score, but individual components of the outcome showed a difference favouring H-ISDN for all-cause mortality, first hospitalization for HF, and change in quality of life score. It is unclear if these results can be extrapolated to other groups.

RECOMMENDATION

35. We recommend the combination of hydralazine and isosorbide dinitrate (H-ISDN) be considered in addition to standard GDMT at appropriate doses for black patients with HFrEF and advanced symptoms (Strong Recommendation; Moderate-Quality Evidence).
36. We recommend that H-ISDN be considered in patients with HFrEF who are unable to tolerate an ACEi, ARB, or ARNI because of hyperkalemia or renal dysfunction (Strong Recommendation; Low-Quality Evidence).

Values and preferences. There is limited high-quality clinical trial evidence in the modern era from which to base an H-ISDN recommendation without considering the tolerability and adverse effects. Adverse effects related to H-ISDN are frequent, limit uptitration, and result in discontinuation in a significant proportion of patients. Every effort should be made to use ACEi/ARB/ARNI therapy including a low dose and/or rechallenge therapy before changing to H-ISDN.

Practical tip. Renal dysfunction warranting a trial of H-ISDN includes those who have a significant change in creatinine from baseline with ACEi/ARB/ARNI therapy that

Table 20. Common symptoms, signs, and test results in RHF without pulmonary hypertension and in cor pulmonale

Common features	RHF without pulmonary hypertension	Cor pulmonale
Symptoms	Fatigue	Fatigue
	Hepatic congestion	*Hemoptysis*
	Right upper quadrant discomfort	*Hoarseness*
	Anorexia/early satiety	Hepatic congestion
	Peripheral edema	Right upper quadrant discomfort
	Cough	Anorexia/early satiety
	Shortness of breath/orthopnea*	Peripheral edema
		Cough
		Shortness of breath/orthopnea*
Physical signs	Elevated jugular venous pulsation, positive hepatojugular reflux or Kussmaul sign	Elevated jugular venous pulsation, positive hepatojugular reflux or Kussmaul sign
	Peripheral or sacral edema	Peripheral or sacral edema
	Ascites	Ascites
	Hepatomegaly or liver tenderness	Hepatomegaly or liver tenderness
	Right-sided third heart sound	Right-sided third heart sound, *increased pulmonary closure sound, pulmonary ejection click*
	Murmur of tricuspid regurgitation	Murmur of tricuspid regurgitation
	Signs of right ventricular enlargement	Signs of right ventricular enlargement
		Evidence of coexisting underlying pulmonary cause of cor pulmonale
Diagnostic testing	ECG: right axis deviation, right ventricular hypertrophy, p pulmonale pattern low-voltage QRS, incomplete or complete right bundle branch block	ECG: right axis deviation, right ventricular hypertrophy, p pulmonale pattern low-voltage QRS, incomplete or complete right bundle branch block
	Chest x-ray: right-sided cardiac enlargement, enlargement of pulmonary arteries (uncommon), oligemic peripheral lung fields (rare), right-sided pleural effusion*	Chest x-ray: right-sided cardiac enlargement, enlargement of pulmonary arteries, oligemic peripheral lung fields, right-sided pleural effusion*
	Echocardiography: evidence of abnormal right ventricular structure and/or function. No evidence of increased pulmonary pressure. *Septal flattening during diastole but not systole*	Echocardiography: evidence of abnormal right ventricular structure and/or function. *Evidence of increased pulmonary pressure. Septal flattening during systole*

Items italic occur in the setting of cor pulmonale but are very uncommon in its absence.
ECG, electrocardiogram; RHF, right heart failure.
*Less commonly found, but may occur.

Table 21. Comparison of original and revised Task Force criteria

Original task force criteria	Revised task force criteria
I. Global or regional dysfunction and structural alterations*	
Major	
• Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment • Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) • Severe segmental dilatation of the right ventricle	Using 2-dimensional echocardiography: • Regional RV akinesia, dyskinesia, or aneurysm • and 1 of the following (end diastole): —PLAX RVOT $\geq$ 32 mm (corrected for body size [PLAX/BSA] $\geq$ 19 mm/m^2) —PSAX RVOT $\geq$ 36 mm (corrected for body size [PSAX/BSA] $\geq$ 21 mm/m^2) —or fractional area change $\leq$ 33% Using MRI: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • and 1 of the following: —Ratio of RV end-diastolic volume to BSA $\geq$ 110 mL/m^2 (male) or $\geq$ 100 mL/m^2 (female) —or RV ejection fraction $\leq$ 40% Using RV angiography: • Regional RV akinesia, dyskinesia, or aneurysm
Minor	
• Mild global RV dilatation and/or ejection fraction reduction with normal left ventricle • Mild segmental dilatation of the right ventricle • Regional RV hypokinesia	Using 2-dimensional echocardiography: • Regional RV akinesia or dyskinesia • and 1 of the following (end diastole): —PLAX RVOT $\geq$ 29 to $<$ 32 mm (corrected for body size [PLAX/BSA] $\geq$ 16 to $<$ 19 mm/m^2) —PSAX RVOT $\geq$ 32 to $<$ 36 mm (corrected for body size [PSAX/BSA] $\geq$ 18 to $<$ 21 mm/m^2) —or fractional area change $>$ 33% to $\leq$ 40% Using MRI: • Regional RV akinesia or dyskinesia or dys-synchronous RV contraction • and 1 of the following: —Ratio of RV end-diastolic volume to BSA $\geq$ 100 to $<$ 110 mL/m^2 (male) or $\geq$ 90 to $<$ 100 mL/m^2 (female) —or RV ejection fraction $>$ 40% to $\leq$ 45%
II. Tissue characterization of wall	
Major	
• Fibrofatty replacement of myocardium on endomyocardial biopsy	• Residual myocytes $<$ 60% using morphometric analysis (or $<$ 50% if estimated), with fibrous replacement of the RV free wall myocardium in $\geq$ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor	• Residual myocytes 60%-75% using morphometric analysis (or 50%-65% if estimated), with fibrous replacement of the RV free wall myocardium in $\geq$ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	
Major	• Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals older than 14 years of age (in the absence of complete right bundle branch block QRS $\geq$ 120 ms)
Minor	
• Inverted T waves in right precordial leads (V_2 and V_3) (people aged older than 12 years, in absence of right bundle branch block)	• Inverted T waves in leads V_1 and V_2 in individuals older than 14 years of age (in the absence of complete right bundle branch block) or in V_4, V_5, or V_6 • Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals older than 14 years of age in the presence of complete right bundle branch block

Diagnostic terminology for original criteria: this diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; and possible: 1 major or 2 minor criteria from different categories.

BSA, body surface area; LV, left ventricular; MRI, magnetic resonance imaging; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RV, right ventricular; RVOT, RV outflow tract.

*Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

Modified from Marcus et al.[308] with permission from Wolters Kluwer Health, Inc.

Table 22. Commonly available tests for the work-up of anemia and iron deficiency

Test	Suspected etiologies	Remarks
Transferrin saturation, ferritin, serum iron	Iron deficiency	Ferritin might be artificially elevated in chronic inflammatory states; transferrin saturation might be low in patients with cachexia
Fecal occult blood; upper and lower endoscopy	Gastrointestinal-related blood loss	Referral to gastroenterology
TSH	Thyroid-related disorders	
Peripheral smear, reticulocyte count/index, LDH, haptoglobin, bone marrow biopsy	Multiple	
B12	Nutritional deficiency	Uncommon in Canada
Hemoglobin electrophoresis	Thalassemia; sickle cell disease	Target testing to those in high prevalence population
Serum and urine protein electrophoresis	Multiple myeloma, amyloidosis, and other protein disorders	

LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

persists despite modification of dose, rechallenge, and/or removal of other potentially nephrotoxic agents. It may also be considered in those with a serum creatinine (Scr) > 220 μmol/L who experience significant worsening in renal function with the use of ACEi/ARB/ARNI therapy, or in a trial of these agents (eg, potential worsened renal function requiring renal replacement therapy) is thought to outweigh benefits.

Practical tip. Hyperkalemia warranting a trial of H-ISDN includes those with persistent hyperkalemia (K > 5.5 mmol/L) despite dietary intervention, dosage reduction of ACEi/ARB/ARNI, and removal of other agents known to increase potassium levels.

Practical tip. Nitrates alone might be useful to relieve orthopnea, paroxysmal nocturnal dyspnea, exercise-induced dyspnea, or angina in patients when used as tablet, spray, or transdermal patch, but continuous (ie, around the clock) use should generally be avoided because most patients will develop tolerance.

7.1.1.8. Digoxin

The effect of digoxin on mortality and morbidity in patient with heart failure (**D**igitalis **I**nvestigation **G**roup [DIG-trial])[139] enrolled 6800 patients with HF and a LVEF ≤ 45% and were randomized to digoxin (median dose 0.25 mg/d) or placebo. The primary outcome was mortality over a mean follow-up of 37 months. Fifty-four percent were NYHA class II and 94% of patients were receiving an ACEi. There was no difference in all-cause mortality. There was a decrease in HF-related deaths but an increase in "other cardiac deaths," which has led to speculation that it might be due to arrhythmic death and led to an overall neutral effect on mortality. There were fewer patients hospitalized for HF in the digoxin group. Suspected digoxin toxicity was higher in the digoxin group (11.9% vs 7.9%). A systematic review included 13 studies (n = 7896, 88% of participants from the DIG-trial) showed similar results.[140] None of these studies provide much insight into the relative benefit or harm of digoxin in light of contemporary therapy with β-blockers and MRAs, however, many landmark trials of these agents had a substantial background therapy of digoxin with no apparent change in the overall results if a patient was or was not receiving digoxin.

RECOMMENDATION

37. We suggest digoxin be considered in patients with HFrEF in sinus rhythm who continue to have moderate to severe symptoms, despite appropriate doses of GDMT to relieve symptoms and reduce hospitalizations (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. These recommendations place a high value on the understanding that the use of cardiac glycosides in HFrEF remains controversial in light of contemporary therapy, and digoxin had no effect on mortality, cardiovascular hospitalizations, exercise, or the primary end point in DIG-trial. Digoxin can cause atrial and ventricular arrhythmias particularly in the presence of hypokalemia or in the presence of worsening of renal function (with increased digoxin levels).

Practical tip. In patients receiving digoxin, serum potassium and creatinine should be measured with increases in digoxin or diuretic dose, the addition or discontinuation of an

Table 23. Acute Dialysis Quality Initiative (ADQI) classification system of the cardiorenal syndrome

Cardiorenal syndrome type	Inciting event	Secondary disturbance
1	Acute decompensated heart failure	Acute kidney injury
2	Chronic heart failure	Chronic kidney disease
3	Acute kidney injury	Acute heart failure
4	Chronic kidney disease	Chronic heart failure
5	Codevelopment of heart failure and	chronic kidney disease

Modified from Ronco et al.[372] with permission from Oxford University Press.

Table 24. Standard definition of renal function

Stage	Descriptor	Creatinine clearance in mL/min/1.73 m^2
1	Normal renal function	> 90
2	Mild renal insufficiency	60-89
3	Moderate renal insufficiency	30-59
4	Severe renal insufficiency	15-29
5	Chronic renal failure	< 15 or receiving dialysis

Data from the National Kidney Foundation.[369]

Table 25. Major precipitants of decompensation from established heart failure

Major category	Examples		
Ischemia	Worsening of known CAD	New-onset CAD	Infarction
Electrical	Atrial arrhythmia	Ventricular arrhythmia	RV pacing or ICD discharge
Provider	Inappropriate medication	Diuretic withdrawal	Nutraceutical addition
Patient nonadherence	Medication	Diet	Illicit drug or alcohol use
Surgical	Post noncardiac surgery	Post CV surgical procedure	
Endocrine	Thyroid function	Addition/withdrawal of steroids	
Renal/hematologic	Worsening renal function	Anemia	
Infectious	Pneumonia, influenza	Endocarditis	Reactivation of myocarditis
Social/mental health	Depression/anxiety	Social stressors	Living conditions

CAD, coronary artery disease; CV, cardiovascular; ICD, implantable cardioverter-defibrillator; RV, right ventricular.

interacting drug, or during a dehydrating illness, to reduce the risk of digoxin toxicity. Patients with reduced or fluctuating renal function, elderly patients, those with low body weight, and women are at increased risk of digoxin toxicity and might require more frequent monitoring including digoxin levels.

Practical tip. Routine digoxin levels are not required other than to assess for digoxin toxicity. Digoxin levels should not be used to guide chronic therapy. Titration to digoxin levels has not been tested in clinical trials.

7.1.1.9. Omega-3 polyunsaturated fatty acid

The **G**ruppo **I**taliano per lo **S**tudio della **S**opravvivenza nell'**I**nsufficienza cardiaca-**H**eart **F**ailure (GISSI-HF) study was an RCT designed to assess the effects of omega-3 polyunsaturated fatty acids (n-3 PUFAs) in HF.[141] More than 4600 patients with NYHA class II to IV HF, irrespective of etiology or EF, were randomly assigned to a fish-based n-3 PUFA (daily 850 mg to 882 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the average ratio of 1:1.2) or placebo. The primary end points were time to death, and time to death or admission to hospital for cardiovascular reasons. After a median 3.9-year follow-up, there was a decrease in both primary outcomes favouring n-3 PUFA (9% relative reduction in all-cause death and an 8% relative reduction in death or admission to hospital). The therapy was well tolerated with primarily gastrointestinal side effects, and fewer than 10% of patients required study drug withdrawal.

Current sources of n-3 PUFA in Canada are food supplements, therefore, are not subject to the regulatory review (including predefined tolerances for drug content) that is required for any drug approval. As such, it is difficult to be certain of the amount of n-3 PUFA present in any given commercial preparation. Indeed, evidence suggests a large degree of variability between different available forms of n-3 PUFA.[142] Patients and caregivers who wish to use n-3 PUFA are therefore referred to a local medical practitioner, pharmacy, or other reputable source of information to determine their best source of n-3 PUFA. Reports of excessive bleeding have been associated with doses < 3 g/d, but this remains controversial.[143,144]

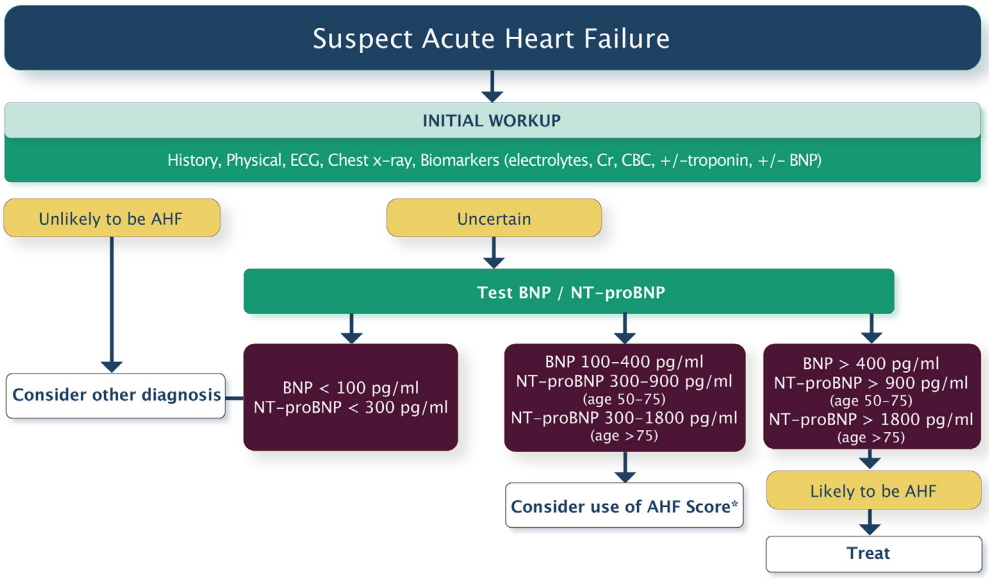

Figure 8. Diagnosis of heart failure in the acute care setting. If acute heart failure (AHF) is suspected, the initial work-up may be supplemented by natriuretic peptide testing and/or an AHF diagnosis score. ***Pr**oBNP **I**nvestigation of **D**yspnea in the **E**mergency Department (PRIDE) or other scoring system. BNP, B-type natriuretic peptide; CBC, complete blood count; Cr, creatinine; ECG, electrocardiogram; NT-proBNP, N-terminal propeptide B-type natriuretic peptide.

Table 26. Clinical scoring system for the diagnosis of acute heart failure

Predictor	Possible score	Your patient's score
Age older than 75 years	1	
Orthopnea present	2	
Lack of cough	1	
Current loop diuretic use (before presentation)	1	
Rales on lung exam	1	
Lack of fever	2	
Elevated NT-proBNP*	4	
Interstitial edema on chest x-ray	2	
	14	Total =
Likelihood of heart failure	Low	0-5
	Intermediate	6-8
	High	9-14

NT-proBNP, N-terminal propeptide B-type natriuretic peptide.
*Elevated NT-proBNP was defined as > 450 pg/mL if age younger than 50 years and > 900 pg/mL if age older than 50 years.

RECOMMENDATION

38. We suggest n-3 PUFA therapy at a dose of 1 g/d be considered for reduction in morbidity and cardiovascular mortality in patients with HFrEF (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. Although there is an effect of fish oils on important HF outcomes, this recommendation also considers the modest effect size and issues surrounding the lack of standardization of commercial preparations in Canada.

Practical tip. With most data, the dose of n-3 PUFA is 1 g/d. It is unknown whether higher or lower doses would confer clinical benefit and they are therefore not suggested. Doses greater than 3 g/d are associated with excessive bleeding.

Practical tip. n-3 PUFA therapy might affect measures of anticoagulation. Close monitoring of the international normalized ratio (INR) in patients receiving warfarin after institution of n-3 PUFA is suggested.

Practical tip. There is evidence of significant variability in the content of n-3 PUFA. Patients considering n-3 PUFA should consult with their pharmacist to select a reliable supplement brand that most closely matches formulations shown to be effective in clinical trials.

7.1.1.10. 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins)

Many patients with HF have coexistent ischemic heart disease; however, these patients were systematically excluded from many of the early landmark statin trials. Two RCTs give insight into the benefit of statins specifically in patient with HF.

The **Co**ntrolled **Ro**suvastatin Multi**na**tional Trial in Heart Failure (CORONA) study was an RCT of 5011 patients with HF that compared rosuvastatin 10 mg/d with placebo.[145] There was no difference in the primary end point of cardiovascular mortality, nonfatal MI, or nonfatal stroke. There was an 8% relative reduction in the secondary outcome of cardiovascular hospitalizations, but not HF hospitalizations. Rosuvastatin was well tolerated, with fewer withdrawals from therapy than with placebo. Despite achieving the expected low-density lipoprotein cholesterol-lowering of rosuvastatin, there was little benefit in this cohort of patients with CAD.[146]

The second trial was the GISSI-HF study; 4574 patients with chronic HF, NYHA class II-IV, irrespective of cause and LVEF, were randomly assigned to rosuvastatin 10 mg/d or placebo, and followed for a median of 3.9 years.[147] There was

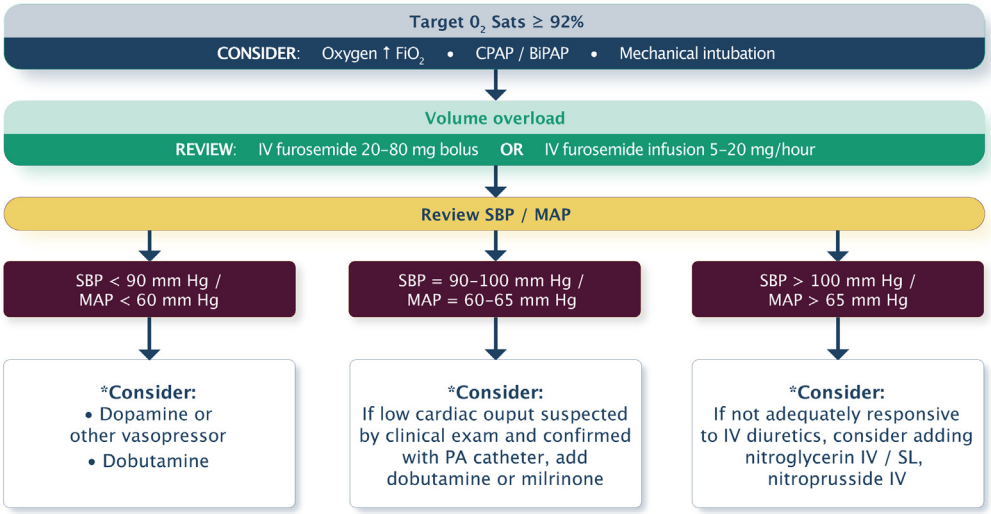

Figure 9. Treatment algorithm for acute heart failure. Decisions regarding the additional use of inotropes or vasodilators should be done in consultation with individuals with experience and expertise in the management of patients with acute heart failure, and placed in clinical context. *See Table 27 for dosing. BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; I.V., intravenous; MAP, mean arterial pressure; PA, pulmonary artery; SBP, systolic blood pressure; SL, sublingual.

Table 27. Diuretic dosing for the treatment of acute heart failure

eGFR	Patient	Initial I.V. dose*	Maintenance oral dose
$\geq$ 60 mL/min/1.73 m^2	New onset HF or no current diuretic therapy	Furosemide 20-40 mg 2-3 times daily	Lowest diuretic dose that allows for clinical stability is the ideal dose
	Established HF or chronic oral diuretic therapy	Furosemide dose I.V. equivalent of oral dose	
< 60 mL/min/1.73m^2	New-onset HF or no current diuretic therapy	Furosemide 20-80 mg 2-3 times daily	
	Established HF or chronic oral diuretic therapy	Furosemide dose I.V. equivalent of oral dose	

eGFR is calculated from the Cockroft-Gault, CKD-EPI, or Modification of Diet in Renal Disease formula. See section *7.4.2. Initial and Ongoing Treatment* for details.

CKD-EPI, **C**hronic **K**idney **D**isease**Epi**demiology Collaboration; eGFR, estimated glomerular filtration rate; HF, heart failure; I.V., intravenous.

*I.V. continuous furosemide at doses of 5-20 mg/h is also an option.

no difference in the primary end points of time to death, and time to death or admission to hospital for cardiovascular reasons. There was no difference in any other outcomes or subgroups.

RECOMMENDATION

39. We recommend against statins used solely for the indication of HF in the absence of other indications for their use. Statin treatment should be in accordance with primary and secondary prevention guidelines for CVD (Strong Recommendation; High-Quality Evidence).

Practical tip. Routine statin therapy is unlikely to provide clinical benefit for patients with HF due to nonischemic causes and in the absence of a very high risk of vascular events (such as recent MI, diabetes, and known vascular disease).

Practical tip. In those already receiving statin therapy, it is reasonable to consider statin withdrawal in patients with advanced HF, in polypharmacy where risks outweighs benefits, or when palliative care is an overriding concern.

7.1.1.11. Anticoagulation and antiplatelet therapy

There are no RCTs that evaluate the role of ASA in comparison with placebo in patients with HF. A meta-analysis showed a reduction in serious vascular events, stroke, and coronary events with ASA therapy in secondary prevention trials.[148]

The 2 largest RCTs both compared warfarin with ASA (with or without clopidogrel) rather than placebo. The **W**arfarin and **A**ntiplatelet **T**herapy in **C**hronic **H**eart Failure (WATCH) trial compared warfarin (INR, 2.5-3), ASA (162 mg) and clopidogrel (75 mg) in patients with HFrEF in sinus rhythm. A total of 1587 patients were followed for a mean of 1.9 years.[149] The study was stopped early secondary to poor recruitment. There was no difference in the primary end point of all-cause mortality, nonfatal MI, or nonfatal stroke in any of the groups. However, there was a reduction in stroke in the warfarin arm compared with the antiplatelet

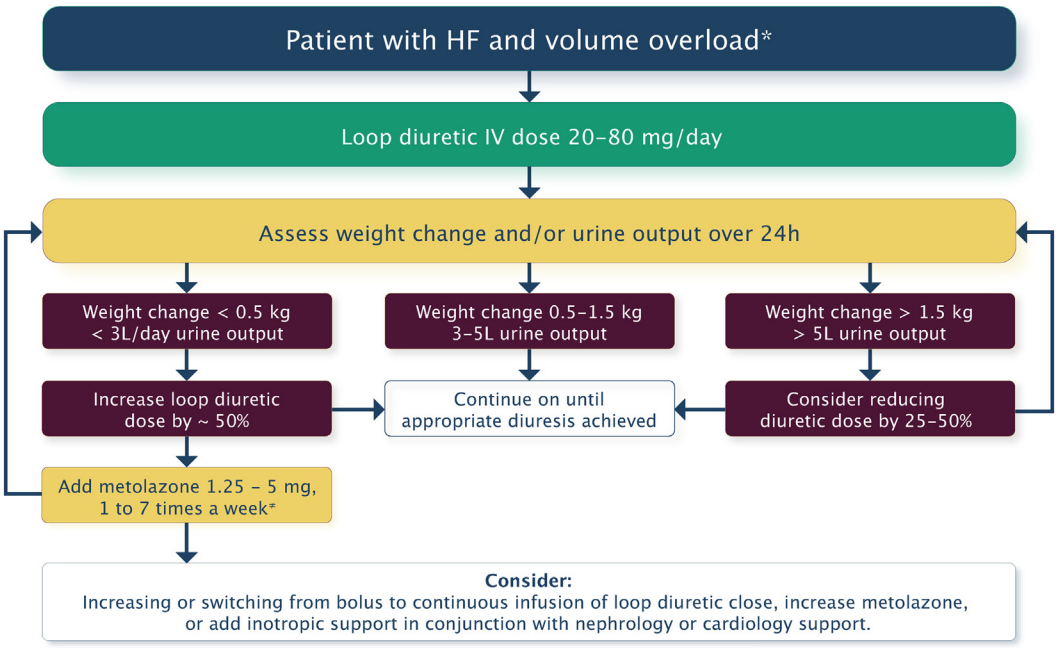

Figure 10. Stepped pharmacological care; treatment algorithm for patients with heart failure (HF) and volume overload. At each decision, clinical assessment should include an assessment of symptoms, volume assessment, and appropriate monitoring of vital signs, electrolytes, and creatinine. Daily weights are more easily and accurately assessed than urine output. *Assumes: (1) volume assessment with each step; (2) monitoring of electrolytes, renal function, symptoms, and vital signs; (3) daily weights; and (4) urine output not often accurate or obtainable. †Titrate progressively, according to the degree of hypervolemia, furosemide doses, and creatinine/kidney function. I.V., intravenous.

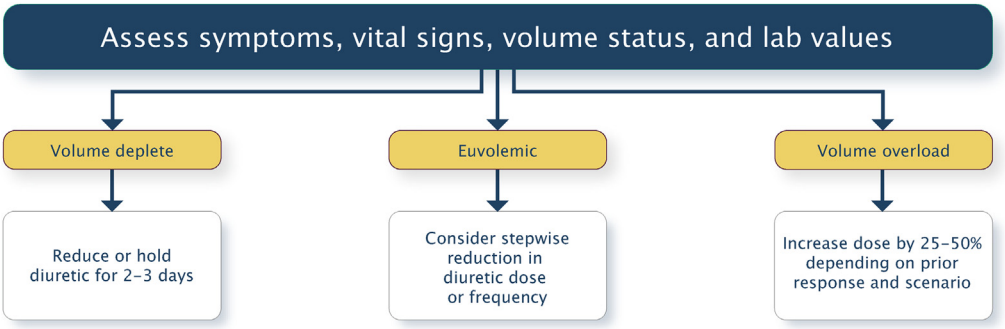

Figure 11. Outpatient diuretic management algorithm for patients with heart failure. At each decision, clinical assessment should include an assessment of symptoms, volume assessment, and appropriate monitoring of vital signs, electrolytes, and creatinine. Daily weights are more easily and accurately assessed than urine output. Reassess serum potassium and creatinine 3-5 days after each diuretic dose change, earlier if concerned, other medication changes, or significant volume changes. Lowest dose of a diuretic that allows for optimal symptoms is the ideal dose. Dose reductions or increases should take into account previous response if known, and clinical scenario. See section *7.4.2. Initial and Ongoing Treatment* and Canadian Cardiovascular Society Apps for further practical guidance.

arms, but there was also a higher risk of bleeding in the warfarin group compared with the clopidogrel group. The **W**arfarin versus **A**spirin in **R**educed **C**ardiac **E**jection **F**raction (WARCEF) trial, the largest trial to date, had similar results with a single comparison arm of ASA 325 mg daily vs warfarin (INR, 2-3.5). A total of 2305 patients were enrolled with a mean follow-up of 42 months.[150] There was no difference in the primary outcome of ischemic stroke, intracerebral hemorrhage, or all-cause mortality, but there was a decrease in ischemic stroke and an increase in major hemorrhage for patients who received warfarin. In a meta-analysis of the 4 main RCTs, there was no difference in all-cause mortality, HF-related hospitalization, or nonfatal MI.[151] There was a decrease in all cause stroke and ischemic stroke and an increase in major bleeding for patients who received warfarin.[152] The ongoing A Randomized, Double-blind, Event-driven, Multicenter Study Comparing the Efficacy and Safety of Rivaroxaban With Placebo for Reducing the Risk of Death, Myocardial Infarction or Stroke in Subjects With Heart Failure and Significant Coronary Artery Disease Following an Episode of Decompensated Heart Failure (COMMANDER-HF) trial is testing the additional use of rivaroxaban vs placebo in patients with sinus rhythm, HFrEF, and a recent hospital admission (NCT01877915).

RECOMMENDATION

40. We recommend acetylsalicylic acid (ASA) at a dose of between 75 and 162 mg be considered only in patients with HFrEF with clear indications for secondary prevention of atherosclerotic cardiovascular events (Strong Recommendation; High-Quality Evidence).
41. We recommend against routine anticoagulation use in patients with HFrEF who are in sinus rhythm and have no other indication for anticoagulation (Strong Recommendation; High-Quality Evidence).

Anterior ST-elevation myocardial infarction (STEMI) and LV dysfunction has been associated with increased rates of LV thrombus and subsequent thrombotic complications. The rate of LV thrombus associated with anterior STEMI has decreased with more contemporary reperfusion strategies and DAPT. Historical rates range from 3% to 27%, depending on LV function.[153-155] However, rates of embolization are much more difficult to quantify. There are no prospective RCTs that address the role of anticoagulation in MI with low EF.

Table 28. Should the patient be admitted to hospital or discharged home?

Variable	Consider for hospital admission	Consider for discharge home with close follow-up
Current clinical status	NYHA III/IV	NYHA II
Amount of improvement	Minimal or modest	Significant
O_2 saturation in room air	< 91%	≥ 92%
Systolic blood pressure	< 90-100 mm Hg	>100 mm Hg or similar to previous
Heart rate	≥ 90 bpm	< 90 bpm
Respiratory rate	> 20 breaths per minute	≤ 20 breaths per minute
ECG findings	Active ischemia; ventricular arrhythmia; atrial arrhythmia not under control	Baseline
Renal function	Worsening	Stable
Comorbidity	Other comorbid condition requiring admission; syncope; pneumonia	
Other	New diagnosis of HF	Established etiology and precipitant
Follow-up	Uncertain	Established/organized

All of the features should be considered in disposition decisions.
bpm, beats per minute; ECG, electrocardiogram; HF, heart failure; NYHA, New York Heart Association.

Table 29. Is my patient ready for discharge from hospital?

Symptoms and disease	Stability	Transition
Intercurrent cardiac illness adequately diagnosed and treated	Returned to "dry" weight and stable for > 24 hours	Communication to primary care provider and/or specialist physician and/or multidisciplinary disease management program
Presenting symptoms resolved	Vital signs resolved and stable for > 24 hours, especially blood pressure and heart rate	Clear discharge plan for laboratory tests, follow-up, and other testing
Chronic oral HF therapy initiated, titrated, and optimized (or plan for same)	> 30% decrease in natriuretic peptide level from time of admission and relatively free from congestion	Education initiated, understood by patient, continued education planned

HF, heart failure.

A retrospective study of 460 patients done in 2015 evaluated the role of warfarin after primary PCI for anterior STEMI.[156] Warfarin use was at the discretion of the attending physician and 131 patients were discharged receiving warfarin; 99% were discharged receiving DAPT. The rate of death, stroke, need for transfusion, and major bleeding was higher in the warfarin group. Other cohorts have shown similar results.[157] These data should be placed in context with emerging evidence for the use of DAPT as well as non-vitamin K antagonist oral anticoagulants in the setting of an ACS.

RECOMMENDATION

42. We recommend against routine anticoagulation after large anterior MI and low EF, in the absence of intracardiac thrombus or other indications for anticoagulation (Weak Recommendation; Low-Quality Evidence).

Values and preferences. High value is placed on the paucity of compelling evidence supporting efficacy and the potential for harm from bleeding according to the contemporary treatment recommendations with dual antiplatelet therapy (DAPT) post-MI, the emerging efficacy of direct oral anticoagulants after percutaneous coronary intervention (PCI), and the lack of high-quality trial evidence for anticoagulation with warfarin post-MI.

Practical tips. Anticoagulation may be considered in those with an LV thrombus.

Practical tip. If anticoagulation is used, a duration of 3 months before re-evaluating is reasonable.

Practical tip. Either warfarin or a direct oral anticoagulant could be used for LV thrombus on the basis of the lack of trial evidence and mechanism of action.

7.1.1.12. Anti-inflammatory medications

Several studies have shown that nonsteroidal anti-inflammatory drugs increase the risk of HF. This includes new-onset HF as well as worsening HF outcomes such as hospitalizations and even mortality. There are inconsistent data regarding the safety of individual agents in HF, however most have been associated with negative cardiovascular effects.[158-163]

RECOMMENDATION

43. We recommend against the use of nonsteroidal anti-inflammatory drugs as well as cyclooxygenase-2 (COX-2) inhibitors in patients with HFrEF (Strong Recommendation; High-Quality Evidence).

Values and preferences. These agents might cause sodium and water retention, worsen renal function, interact with HF medication (ACEi/ARB), increase cardiovascular events, and worsen HF. Preference is given to reducing drug-related adverse outcomes and should take into account patient preference for pain control and quality of life.

Table 30. Cardiac hypertrophy including hypertrophic cardiomyopathy vs restrictive cardiomyopathy

	Cardiac hypertrophy	Restrictive cardiomyopathy
Prevalence	High	Low
Onset	Late	Early
Sex	Female > male	Male = female
Family history	Uncommon except in hypertrophic cardiomyopathy	Approximately 30%
Hypertension	Common	Uncommon
Obesity	Common	Uncommon
Hypertrophy	Moderate/marked	None/mild
Echocardiographic/magnetic resonance imaging findings	Diastolic dysfunction grade 1-2, mild left atrial enlargement, usually preserved ejection fraction	Diastolic dysfunction grade 3, severe biatrial enlargement, preserved ejection fraction
Hemodynamics	Elevated left ventricular end-diastolic pressure	Steep "Y" descent, dip and plateau pattern
Coronary heart disease	Common comorbid condition	Uncommon
Natriuretic peptide	Variable	Elevated
Endomyocardial biopsy	Nonspecific	Specific findings

Table 31. Classification of etiologies of restrictive cardiomyopathy

Noninfiltrative	Infiltrative
Myocardial	
Idiopathic,* familial, hypertrophic or diabetic cardiomyopathy, scleroderma, pseudoxanthoma elasticum	Amyloidosis,* sarcoidosis,* fatty infiltration, Gaucher or Hurler disease, Storage disease, hemochromatosis, Fabry or glycogen storage disease
Endomyocardial	
Endomyocardial fibrosis,* hypereosinophilic syndrome, carcinoid heart disease, metastatic cancers, radiation,* toxic effects of anthracycline,* drugs causing fibrous endocarditis (serotonin, methysergide, ergotamine, mercurial agents, busulfan)	

* Frequently encountered in clinical practice.

Practical tip. High doses of ASA might share the same risks as nonsteroidal anti-inflammatory drugs and might aggravate HF, especially in unstable patients.

7.1.1.13. Calcium channel blockers

Most studies on the role of CCBs in HF have shown worsening in HF outcomes.[164-167] The **P**rospective **R**andomized **A**mlod**i**pine **S**urvival **E**valuation (PRAISE) and PRAISE-2 trials were RCTs that evaluated the effect of amlodipine vs placebo on all-cause mortality and/or cardiovascular hospitalization. There was no difference in either trial in terms of all-cause mortality, cardiovascular death, or hospitalizations.[168,169] In PRAISE, there was no overall difference between placebo and amlodipine, however, a subgroup analysis showed a reduction on cardiovascular events in patients with a nonischemic etiology of HF.[168] In PRAISE-2, there was no significant difference between amlodipine and placebo in efficacy. The results together suggest caution when using amlodipine.

RECOMMENDATION

44. We recommend against the routine use of calcium channel blockers (CCBs) in patients with HFrEF (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. Several RCTs have shown no benefits on, or worsening of, HF outcomes in patients treated with CCBs. Diltiazem, verapamil, nifedipine, and felodipine should be avoided. Amlodipine may be considered for other indications such as persistent hypertension or angina symptoms despite use of GDMT.

Practical tip. Amlodipine causes dose-related peripheral edema and should be considered when assessing peripheral edema potentially related to HF.

7.1.1.14. Antiarrhythmic drugs

Most anti-arrhythmic drugs (eg, amiodarone) have significant concerns related to their safety profile, especially in HFrEF, and although effective at suppressing atrial or ventricular arrhythmias, might also provoke HF decompensation and cause other adverse effects. When considering these drugs, consultation with an electrophysiologist or individual with appropriate experience and expertise in the use of these drugs is generally advisable.

RECOMMENDATION

45. We recommend antiarrhythmic drug therapy in patients with HFrEF only when symptomatic arrhythmias persist despite optimal medical therapy with GDMT, and correction of any ischemia or electrolyte and metabolic abnormalities (Strong Recommendation, Moderate Evidence).

Practical tip. Only amiodarone has been proven to be acceptable in the HFrEF population.

7.1.2. HFpEF pharmacological treatment

Principles underpinning the pharmacological management of HFpEF include: (1) identification and treatment of underlying etiological factors implicated in the development of HFpEF; (2) identification and treatment of comorbid conditions that might exacerbate the HF syndrome; (3) control of symptoms; and (4) realization of clinically meaningful cardiovascular end points such as HF hospitalization and mortality. There remains a paucity of clinical trial data regarding specific pharmacological therapy in the HFpEF population at this time. Comorbid conditions including other chronic medical diseases are common in the HFpEF population and frequently implicated as triggers for HF decompensation, thus optimal management of these coexistent disorders, including

Table 32. Four common ethnic minority groups in Canada

Ethnic population	Risk factors for HF prevention	Language spoken and ethnocultural considerations	Treatment of HF
South Asian	Obesity, diabetes, and metabolic syndrome	Predominantly English, family involvement important	Follow guidelines
Chinese	Hypertension, however, coronary heart disease and diabetes increasingly prevalent	Mostly Cantonese and Mandarin, family involvement very important	Follow guidelines; beware of concurrent traditional Chinese medicine
Black	Hypertension	English or French	Follow guidelines; consider in addition using hydralazine-nitrate in those with HF and reduced ejection fraction; uncertainty remains if A-HeFT results apply to all self-identified black populations
Aboriginal	Obesity and diabetes	English, Cree, and Ojibwe are among many languages spoken in Canada. Might need to involve family members and community representatives	Follow guidelines

A-HeFT, **A**frican-American **H**eart **F**ailure **T**rial; HF, heart failure.

Table 33. Hemodynamic changes in normal pregnancy

Parameter	Trimester			
	First	Second	Third	Peripartum
Blood volume	Rises	Rises	Maximum at 45%-50% early on, additional 33% increase in twin gestation	Potential rapid autotransfusion from placenta due to sympathetic stimulation and uterine contraction
Peripheral vascular resistance and blood pressure	Gradual decrease, diastolic more such that pulse pressure increases	At lowest point in midpregnancy	Gradual reversion to normal	Variable changes depending on stage and sympathetic stimulation
Heart rate	Increases	Peaks at 20% late	20% increase	Further increase
Cardiac output	Increases	Increases	Maximal 30%-50% increase early	Further increase up to 31% in labour, 49% in second stage; return to third trimester values within 1 hour of delivery

pharmacological and nonpharmacological therapies, should be aggressively pursued.

7.1.2.1. ACEis and ARBs in HFpEF

There is, however, evidence to support the use of ARBs to reduce HF hospitalizations that draws upon secondary end point analysis from the **C**andesartan in **H**eart Failure **A**ssessment of **R**eduction in **M**ortality and Morbidity (CHARM)-Preserved trial.[170] Among 3025 previously hospitalized NYHA class II-IV patients with an LVEF $\geq$ 40%, candesartan reduced the relative risk of time to first HF hospitalization by 26% compared with placebo. Moreover, a recurrent event analysis of CHARM-Preserved confirmed that this benefit extended to subsequent hospitalizations as well.[171] Reduction in HF hospitalization has also been shown with ACEis, although the evidence is less robust and limited to data from the PEP-CHF study,[172] which included patients 70 years of age or older with an LVEF $\geq$ 45%. The trial, which had a lower than anticipated event rate and high open-label crossover, did show that perindopril reduced the secondary end point of HF hospitalization by 37% at 1 year although this benefit did not persist over a mean follow-up period of 2.1 years. The I-PRESERVE trial did not show a similar benefit.[173] The ongoing **P**rospective Comparison of **ARNI** with **A**RB **G**lobal **O**utcomes in Heart Failure With Preserved Ejection Fraction (PARAGON-HF) trial is comparing sacubitril-valsartan with valsartan on clinical outcomes in patients with HFpEF (NCT01920711).

7.1.2.2. MRAs in HFpEF

The TOPCAT trial[174] randomized 3445 symptomatic high-risk HFpEF patients, characterized by elevations in NP levels or HF hospitalization within the previous year, to receive spironolactone (mean dose of approximately 25 mg and target dose 45 mg daily) or placebo. Patients were generally older (age older than 50 years) with relatively preserved renal function (eGFR $>$ 30 mL/min) and serum potassium levels ($K^+ < 5.0$ mmol/L). After a mean follow-up period of 3.3 years, there was no difference in the combined primary end point of cardiovascular death, aborted cardiac arrest, or HF hospitalization between groups. When considering the constituent components of the primary end point, only HF hospitalization was decreased in spironolactone-treated patients (HR, 0.83; 95% CI, 0.69-0.99). Although elevated potassium levels were more prevalent in the spironolactone arm of the trial (9.1% for placebo vs 18.7% for spironolactone) this did not translate into clinical adverse events including need for dialysis or death due to hyperkalemia.

Table 34. Cardiovascular symptoms and signs, and the pregnant state

Findings	Noted in normal pregnancy	Not seen in normal pregnancy
Dizziness, palpitations	Common	Syncope on exertion
Dyspnea	Common (75%) if mild, not progressive	Progressive or New York Heart Association functional class IV
Orthopnea	Common, especially late in term	
Decreased exercise capacity	Mild, not progressive	New York Heart Association functional class IV symptoms
Chest pain	Common, may be musculoskeletal in origin, not progressive. Not typically anginal	Typical angina pain, severe or tearing pain may be dissection, especially late in term/peripartum
Pulse	Increased volume, rate	Decreased volume or upstroke
Peripheral edema	Mild, common	Severe or progressive edema
Apical beat	Mildly displaced laterally, hyperdynamic	Double or triple apex beat, thrill
Heart rate	Sinus tachycardia common	Atrial fibrillation, persistent supraventricular tachycardia, symptomatic ventricular arrhythmias
Neck veins	May be mildly distended	Progressively distended with dominant V wave
Heart sounds	Increased S1, S2, S3 common	Opening snap, pericardial rub, S4
	Systolic ejection murmur common; continuous murmur (venous hum, mammary souffle) not common	Late peaking systolic murmur, diastolic murmur, other continuous murmurs

Table 35. Medications that might be useful for pregnant women with HF

Medication	Use in pregnancy*
β-Blockers	Should be continued or initiated during pregnancy Requires close fetal monitoring for growth retardation B-1 selective antagonists preferred to avoid potential increased uterine tone and decreased uterine perfusion
Digoxin	May be used if volume overload symptoms persist despite vasodilator and diuretic therapy
Diuretics	May be used, but with caution regarding excessive volume contraction leading to reduced placental perfusion
Hydralazine	May be used for management of HF symptoms or elevated blood pressure
Nitrates	May be used to treat decompensated HF pregnancy

HF, heart failure.

*Avoid all renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, angiotensin receptor neprilysin inhibitors, renin inhibitors).

Numerous prespecified and post hoc analyses of the TOPCAT trial have been performed to guide the clinical interpretation and application of these data. Notably, 28.5% of participants were enrolled in the trial on the basis of elevated NP levels. In this group, participants randomized to spironolactone had a 35% reduction in the primary end point compared with those who received placebo. This benefit of spironolactone was not observed among patients who entered the trial on the basis of a previous HF hospitalization. Marked differences in baseline demographic characteristics were observed between inclusion criteria groups; those enrolled on the basis of elevated NP levels were older, had worse renal function at baseline (higher serum creatinine and lower eGFR), and were less likely to be recruited at centres in Russia or Georgia. A significant proportion of patients recruited in the latter region might not have received the assigned study treatment and thus reliable results from TOPCAT might come mainly from the Americas.[175] The observed geographic variation analysis showed a 15% RRR in the primary end point favouring spironolactone in patients enrolled in the Americas vs those enrolled in Russia or Georgia.[86]

7.1.2.3. β-Blockers in HFpEF

Although β-blockers provide a plausible physiological mechanism of action for improved outcomes by prolongation of diastolic filling time, reduction of myocardial ischemia, control of hypertension, and arrhythmia prophylaxis, the available quality of evidence and heterogeneity of findings from meta-analyses precludes a firm recommendation for use of this medication class in HFpEF at this time.[176-179] As an example, an LVEF subgroup analysis of the **S**tudy of the **E**ffects of **N**ebivolol **I**ntervention on **O**utcomes and **R**ehospitalization in **S**eniors With Heart Failure (SENIORS) trial[180] showed a 19% reduction in the combined primary end point of all-cause mortality and cardiovascular hospitalization (HR, 0.81; 95% CI, 0.63-1.04; *P* for subgroup interaction = 0.043) among study participants with an LVEF ≥ 35% who received nebivolol compared with placebo. However, because of the small effect size of nebivolol in the main SENIORS trial, this analysis lacks power to definitively rule out a significant interaction between outcomes of interest and EF. High dropout rates in the main trial, small sample size, and low event rate in the nonreduced EF group raise further questions about the reproducibility of these findings.

7.1.2.4. Nitrates in HFpEF

Nitrates have been broadly used in patients with established CVD, however, the role of long-acting nitrates in patients with HFpEF is unclear. The **N**itrate's **E**ffect on **A**ctivity **T**olerance in **H**eart **F**ailure With **P**reserved **E**jection **F**raction (NEAT-HFpEF) trial[181] enrolled 110 patients to a long-acting nitrate (isosorbide mononitrate 120 mg/d) or placebo into a 6-week crossover trial to test the efficacy and safety of this approach. There was no beneficial effect of nitrates seen in this group on biomarkers, exercise tolerance, activity level, or clinical events—and there was a nonsignificant trend toward a lower rate of daily activity for patients who received long-acting nitrates.

RECOMMENDATION

46. We suggest candesartan be considered to reduce HF hospitalizations in patients with HFpEF (Weak Recommendation; Moderate-Quality Evidence).
47. We recommend systolic/diastolic hypertension be controlled according to current Canadian Hypertension Education Program hypertension guidelines (2017) (http://www.onlinecjc.ca/article/S0828-282X(17)30110-1/abstract) to prevent and treat HFpEF (Strong Recommendation; High-Quality Evidence).
48. We recommend loop diuretics be used to control symptoms of congestion and peripheral edema (Strong Recommendation; Moderate-Quality Evidence).
49. We suggest that in individuals with HFpEF, serum potassium < 5.0 mmol/L, and an eGFR > 30 mL/min, an MRA like spironolactone should be considered, with close surveillance of serum potassium and creatinine (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. These recommendations place a high value on the known etiologic factors for HFpEF and less on known outcome-modifying treatments which, unlike in HFrEF, are still limited.

The MRA recommendation is on the basis of post hoc geographic subgroup analyses of the TOPCAT trial conducted within North and South America mentioned previously.

Practical tip. Excessive diuretic use can lead to decreased cardiac output and compromise of renal function. Every attempt should be made to use the lowest possible dose of diuretic to achieve and maintain euvolemia.

Practical tip. There is insufficient quality of data to provide strong recommendations regarding statin therapy in HFpEF, so the decision to treat should be customized and on the basis of existing guidelines for primary and secondary prevention of CVD.

Practical tip. After an MRA or ARB is initiated and with a change in dose, serum potassium and creatinine should be

Table 36. Cancer therapies associated with LV dysfunction

Anticancer therapy	Major mechanisms	Signs and symptoms of toxicity	Therapy-associated risk factors	References
Anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone)	Proposed mechanisms: (1) Reactive oxygen/free radical generation (2) Transcriptional change in myocyte ATP pathway (3) Decreased mRNA expression, reduced contractility (4) Topoisomerase IIβ interference	Classified into: (1) Acute toxicity: reversible, shortly after infusion; toxicities include arrhythmias, QT prolongation with or without HF (2) Early-onset chronic progressive: during treatment and up to 1 year after, not reversible, clinically resembles myocarditis, accompanying diastolic dysfunction (3) Late-onset chronic progressive: > 1 year from treatment, not reversible, clinical decompensation is usually preceded by occult LVD	(1) Greater risk for doxorubicin than for idarubicin or epirubicin (2) Intravenous bolus administration (3) High peak concentrations in some studies (4) History of irradiation (5) Concurrent administration of cyclophosphamide, trastuzumab, and/or paclitaxel (6) Time from therapy completion (7) Most important risk factor is cumulative dose Rates of HF: Doxorubicin 400 mg/m^2 = 3%-5% 550 mg/m^2 = 7%-26% 700 mg/m^2 = 18%-48% Maximal cumulative doses (mg/m^2): Doxorubicin: 400-450 Daunorubicin: 600 Idarubicin: 100 Epirubicin: 800-900 Mitoxantrone: 160	3-5,16-22
Cyclophosphamide	Proposed mechanisms: (1) Direct endothelial injury (2) Toxic metabolites resulting in myocardial injury (3) Ischemia from intracapillary microemboli (4) Coronary vasospasm	Include: (1) Arrhythmias (2) Nonspecific ST-T abnormalities (3) Pericardial effusion (4) Hemorrhagic myopericarditis (5) Symptomatic HF Occurs within 1-14 days of dose administration and often lasts for a few days	(1) High-dose cyclophosphamide: 120-200 mg/kg or > 1.5 g/m^2/d (2) History of anthracyclines or mitoxantrone therapy (3) Mediastinal radiation Toxicity related to single rather than cumulative drug dose	20-22
Ifosfamide	Proposed mechanisms similar to that of cyclophosphamide because of structural and mechanistic similarities	(1) Arrhythmias (2) Nonspecific ST-T changes on electrocardiogram (3) HF Acute HF typically presents within 6-23 days of first ifosfamide dose	(1) Potentially dose related: doses > 150 mg/kg or > 12.5 g/m^2 Toxicity related to single rather than cumulative drug dose	20,22
Docetaxel	Myocyte damage	(1) HF (2) Ischemia		20,22,24
Sunitinib	Multiple proposed mechanisms: (1) Myocyte mitochondrial damage (2) Impairs myocyte function in setting of hypertensive stress (3) Reduction in nitric oxide production through VEGF inhibition (4) AMPK inhibition Toxicity likely reversible with stopping therapy and implementing medical management	(1) Hypertension (2) Asymptomatic decline in LVEF (3) Symptomatic HF Variable time to presentation (days to months)	(1) Concurrent anthracycline therapy	16,20,21,23-25
Sorafenib	Mechanism similar to sunitinib Toxicity is generally reversible and responsive to medical treatment	(1) MI (2) Hypertension (3) HF/LV dysfunction Less cardiac dysfunction than Sunitinib		16,20,23,26,27
Imatinib	Proposed mechanisms: (1) Mitochondrial damage (2) Protective mitochondrial pathway inhibition	(1) LV dysfunction		23,25

Table 36. Continued.

Anticancer therapy	Major mechanisms	Signs and symptoms of toxicity	Therapy-associated risk factors	References
Dasatinib	Proposed mechanisms: (1) Mitochondrial damage (2) Protective mitochondrial pathway inhibition	(1) HF/LV dysfunction		23,24
Lapatinib	Proposed mechanisms: (1) Targeting of HER1/EGFR and HER2 receptors	(1) LV dysfunction (2) Symptomatic HF (3) QTc prolongation Relatively low incidence of adverse cardiac events	(1) Previous anthracycline or trastuzumab therapy	21,24
Trastuzumab	Proposed mechanisms: (1) Inhibition of HER2 (Erbβ2) signalling might interfere with growth and signalling of cardiomyocytes and might induce mitochondrial damage Toxicity is generally reversible	(1) HF/LV dysfunction	(1) Concurrent paclitaxel- or anthracycline-based therapy (2) Cumulative anthracycline dose > 300 mg/m^2) (3) Concomitant use of antihypertensive drugs Toxicity is generally not dose-related	20,21
Bevacizumab	Proposed mechanisms: (1) Inhibition of VEGF signalling resulting in uncontrolled HTN (2) Risk of HF through impaired adaptive response to pressure overload (3) Decreased nitrous oxide and prostacyclin production and exposes vascular collagen to tissue factor increasing risk of thrombosis	(1) HTN (2) HF (3) MI/angina (4) ATE	(1) Concurrent anthracycline therapy ATE events not believed to be associated with dose or cumulative exposure	20,21,28-31
Radiation therapy		(1) Coronary artery disease (2) Valvular disease (3) Pericardial disease (4) Restrictive cardiomyopathy (5) Conduction system disease		16,17

AMPK, adenosine monophosphate-activated protein kinase; ATE, arterial thrombotic event; ATP, adenosine triphosphate; EGFR, epidermal growth factor receptor; HER1 and HER2, human epithelial growth factor receptor 1 and 2; HF, heart failure; HTN, hypertension; LV, left ventricular; LVD, LV dysfunction; LVEF, LV ejection fraction; MI, myocardial infarction; VEGF, vascular endothelial growth factor.

Modified from Virani et al.[56] with permission from Elsevier.

monitored in the first week, fourth week, and then fourth month, and whenever clinically indicated.

7.1.3. Implantable cardiac devices

7.1.3.1. Implantable cardioverter-defibrillator therapy

The evidence for the recommendations for implantable cardioverter-defibrillator (ICD) therapy in HF management has been discussed extensively in previous CCS HF guidelines.[182-184] Since the publication of these updates, no new indications for ICD therapy have arisen for the general HF population; however, it is worth highlighting some of the most salient points.

7.1.3.1.1. ICD therapy in patients with HF and previous occurrence of sustained ventricular arrhythmia (secondary prevention)

Three large RCTs[185-187] (and a subsequent meta-analysis[188]) have compared the use of an ICD with antiarrhythmic drug therapy (primarily amiodarone) in patients with a history of life-threatening ventricular arrhythmias. Most of the patients in these trials had LVSD, and many had symptomatic HF. Although HF symptoms were not often specified as inclusion criteria in many of the trials, most patients had CAD with previous MI or nonischemic cardiomyopathy, with a mean LVEF of 30%-35%. As a primary end point, all-cause mortality was reduced in all studies in the defibrillator-treated patients compared with in the antiarrhythmic drug-treated patients (significantly lower in the **A**ntiarrhythmics **V**ersus **I**mplantable **D**efibrillators [AVID] study[186] and in the meta-analysis[188]); in the secondary analyses of the studies and the meta-analysis, patients with lower EFs (< 35%), higher NYHA class (classes III or IV), and older age had a higher absolute risk of death and received greater relative and absolute benefits from ICD therapy than did patients without these risk factors. ICDs are the therapy of choice for the prevention of sudden death and all-cause mortality in patients with a history of sustained ventricular tachycardia or ventricular fibrillation, cardiac arrest, or unexplained syncope in the presence of LVSD patients with symptomatic HF, especially with LVEF < 35%, are at particularly high risk of death and stand to

Table 37. Additional symptoms experienced by patients with advancing heart failure

Symptom class	Specific symptoms
Physical	Gout, pruritus, muscle cramps, pain, anorexia, abdominal fullness, nausea, constipation
Social/functional	Falls, incontinence, trouble walking, loss of independence in performing activities of daily living, isolation
Psychological/spiritual	Panic attacks, anxiety, depression, cognitive impairment, insomnia, loss of confidence, feelings of uselessness or hopelessness

receive at least as much benefit as patients not meeting these clinical criteria.

RECOMMENDATION

50. We recommend an ICD be implanted in patients with HFrEF and a history of hemodynamically significant or sustained ventricular arrhythmia (secondary prevention) (Strong Recommendation; High-Quality Evidence).

7.1.3.1.2. ICD therapy in patients with HF without a history of sustained ventricular arrhythmia (primary prevention)

On the basis of the available evidence, ICD therapy for primary prevention improves survival in patients with NYHA II-III ischemic and nonischemic HF with EF < 35% and in patients with a previous MI with EF < 30% irrespective of symptom status. In contrast, ICD therapy does not provide any survival benefit early after an MI.[189-192]

Landmark clinical trials of ICD therapy in the primary prevention setting selected patients with low LVEF; the most common LVEF cutoff was 35%, although the **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial II (MADIT II)[190] used < 30%. Although most studies did not specifically select patients with symptomatic HF, the largest study, the **S**udden **C**ardiac **D**eath in **He**art **F**ailure **T**rial (SCD-HeFT),[189] included patients with current NYHA class II or III symptoms, and a history of HF for more than 3 months.

When considering the risk of sudden death and potential benefit from an ICD, the contribution of systolic dysfunction per se vs HF symptoms has not been fully defined. Secondary analyses of most studies have indicated that the absolute risk of sudden death, as well as the relative and absolute mortality benefits of an ICD, was greater for patients with lower LVEF (< 30%).

Table 38. Palliative care for HF defined

Palliative care for HF defined
Palliative care is a patient-centred and family-centred approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual. It is applicable early, as well as later, in the course of illness, in conjunction with other therapies that are intended to prolong life, including but not limited to in the setting of HF, oral pharmacotherapy, surgery, implantable device therapy, hemofiltration or dialysis, the use of intravenous inotropic agents, and mechanical circulatory support

HF, heart failure.

Adapted from the World Health Organization definition for palliative care (http://www.who.int/cancer/palliative/definition/en).

Table 39. Tools to assess the quality of life or symptom burden in patients with heart failure

Tool name	Description
Disease-specific patient QOL	
Minnesota Living with Heart Failure Questionnaire	21-Item, Likert scale, self-administered, overall rating, physical and emotional
Kansas City Cardiomyopathy Questionnaire	23-Item, Likert scale, self-administered, physical function, symptoms social function, self-efficacy, and QOL
Generic QOL tools: patient and caregiver	
Short Form 12	12 Items with 7 domains (physical function, role emotion, bodily pain, general health, social function, mental health, vitality); self-administered, Likert scale response format
Short Form 36	36 Items with 8 scales in physical and mental health
Euro QOL and EQ-VAS	EQ-5D: 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). EQ-5D-3 Level or EQ-5D-5 Level: Likert scale response format available, self-administered. EQ-VAS: 20-cm scale from best health to worst health you can imagine- indicate how you feel today
Symptom burden for patient	
Edmonton Symptom Assessment Scale	10 Items, 10-point scale, somatic (6) and psychological symptoms (3), other (1); developed for cancer
InterRAI instruments	Standardized comprehensive assessments widely implemented across Canada in home care, long-term care, as well as other sectors
Disease-specific and generic caregiver burden	
Caregiver Reaction Assessment	Generic, 24 items, multidimensional tool, positive and negative caregiver reactions. Five dimensions (schedule, financial, family, health, self-esteem)
Dutch Objective Burden Inventory	Disease specific. Multidimensional (personal care, practical care, motivational support, emotional support)
Caregiver Burden Scale	Generic, 15-item, self-administered, difficulty and demand summary scores
Zarit Burden Inventory	Generic, unidimensional tool, 22 items

Disclaimer: This table is not intended to be an exhaustive list of such instruments, but identifies those most used and evaluated in the context of heart failure.

EQ-5D, Euro QOL 5 dimensions; EQ-VAS, Euro QOL-Visual Analogue Scale; QOL, quality of life.

Table 40. Managing the symptoms of advancing HF

Symptom	Pharmacological	Nonpharmacological
Dyspnea	Optimized CCS HF guideline therapy • Inotropic agents or mechanical circulatory support devices if consistent with advance care plans (inotropes might hasten death) • Subcutaneous furosemide (observational data) Psychotropic: • First line: low dose opioids • Second-line: benzodiazepines	Rehabilitation/physical activity Energy conservation Positioning Supplemental oxygen if hypoxia Fan to circulate air
Fatigue	Optimized CCS HF guideline therapy	Rehabilitation/physical activity Consider depression, sleep disordered breathing, or other comorbidities
Edema	Optimized CCS HF guideline therapy	Attention to skin care
Disability	Optimized CCS HF guideline therapy	Rehabilitation/physical activity occupational therapy, social work
Pain	Apply World Health Organization ladder (avoiding nonsteroidal anti-inflammatory drugs) Opioids	Physical therapy, occupational therapy, massage If related to implantable cardioverter-defibrillator discharge, consider adjusting settings or deactivation
Gastrointestinal	Consider ascites, digoxin toxicity	
Nausea	Promotility agents (eg, metoclopramide 10 mg orally or subcutaneous 3 times per day with meals) Target chemoreceptor trigger zone: haloperidol 0.5 mg every 12 hours; ondansetron 4 mg	Small frequent meals
Constipation	Stimulant laxative: sennosides	Relax fluid restriction Prune juice
Depression	Optimized CCS HF guideline therapy Selective serotonin reuptake inhibitors (sertraline, citalopram) Avoid tricyclic antidepressants	Psychotherapy Cognitive behaviour therapy Rehabilitation/physical activity
Anxiety	Consider and treat concomitant depression Benzodiazepines	Supportive/psychotherapy Breathing exercises Relaxation therapy
Sleep disturbance	Optimized CCS HF guideline therapy Consider and treat concomitant depression, anxiety, agitated delirium, nocturia, sleep apnea	Attention to sleep hygiene
Agitated delirium	Consider underlying precipitants (eg, HF or other cardiac event, metabolic disturbance, infection or medication side effect) Minimize anticholinergic drugs Low-dose antipsychotic if symptoms lead to risk to patient or caregivers	Senior-friendly approaches, including attention to vision and hearing impairment, cognitive stimulation and reorientation, physical activity and mobilization, and nutrition and hydration
Considerations at the end of life Myoclonus or seizures	Consider discontinuation of medications no longer consistent with goals of care (eg, statins) Consider and treat underlying precipitants Terminal sedation	Consider discontinuation of shock therapies, inotropic agents, or mechanically assisted circulation

Disclaimer: This table is intended to provide practical tips or examples of medications that might provide symptom relief. It should be used by clinicians with an understanding of the medication characteristics and their patients' specific clinical conditions and limitations inherent in the location of care. These suggestions are not intended to replace specialist consultation for physicians unfamiliar with the use of these therapies.

CCS, Canadian Cardiovascular Society; HF, heart failure.

The contribution of HF symptoms (as distinct from LVEF) to the absolute and relative benefit of an ICD remains unclear. In MADIT II, in which patients with NYHA class I, II, or III could be enrolled, patients with greater symptoms of HF appeared to derive relatively greater benefit from an ICD.[190] In contrast, patients in SCD-HeFT with class III HF appeared to have a smaller RRR) than those with NYHA class II symptoms.[189]

Results on the basis of 12 RCTs (8516 patients) and 76 observational studies (96,951 patients), showed that ICD therapy was associated with a 1.2% implantation mortality and a total 3.5% annual likelihood of complications including device malfunction, lead problems, or infections. There was a 4%-20% range of annual inappropriate discharge rates.[193]

It is important to note that in RCTs that specifically selected patients early (< 40 days) after a MI, there was no significant benefit from the ICD compared with control therapy.[191,192]

Finally, recent evidence has called into question the benefit of ICDs for primary prevention in patients with nonischemic cardiomyopathy. Historically, the data supporting ICD use in this population have been less robust, and guideline recommendations have been largely on the basis of older systematic reviews and RCTs, including the **Defi**brillators in **N**on-**i**schemic Cardiomyopathy **T**reatment **E**valuation (DEFINITE)[194] and SCD-HeFT trials, that have shown a reduction in sudden death with ICDs in patients with nonischemic cardiomyopathy. However, the recently published **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 randomized 1116 patients with nonischemic HF, LVEF ≤ 35%, NYHA II-IV symptoms, and elevated NT-proBNP

Table 41. Recommended frequency of follow-up for patients with HF, according to risk

Risk group	Features defining risk of group	Suggested frequency of follow-up
Lower risk	NYHA class I or II No hospitalizations in past year No recent changes in medications Receiving optimal medical/device HF therapies	At least yearly In certain cases might consider discharge of patient from HF clinic to specialist office (in addition to primary care)
Intermediate	No clear features of high or low risk	1-6 months
Higher risk	NYHA IIIb or IV symptoms Frequent symptomatic hypotension More than 1 HF admission (or need for outpatient intravenous therapy) in past year Recent HF hospitalization especially in past month Increasing creatinine level, especially GFR < 30 mL/min Nonadherence to therapy for any reason During titration of HF medications (ACEi/BB/ARB/MRA) New-onset HF Complication of HF therapy Need to downtitrate or discontinue BB or ACEi/ARB Concomitant and active illness (eg, high-grade angina, severe COPD, frailty) Frequent ICD firings	1-2 visits per month In some cases might be weekly assessments or even more frequent—especially if patient willing to undergo multiple visits to potentially avoid a hospitalization

Many of these visits might be performed by telehealth or with allied health professionals supported in a multidisciplinary environment. The exact composition will vary according to local resources, personnel, and practice standards.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable converter defibrillator; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

to ICD vs no ICD in addition to contemporary HF therapy.[195] In this study, there was no difference between groups with respect to the primary outcome of all-cause mortality after a median follow-up of approximately 5.5 years. Importantly, ICD use was associated with a reduction in sudden cardiac death (SCD) in the overall study population, and a reduction in all-cause mortality in the subgroup of patients younger than 68 years of age. DANISH also included a very high proportion of patients treated with CRT (58%), which might have offset some of the benefits of ICD therapy. Indeed, the degree of benefit of ICDs in the setting of nonischemic cardiomyopathy is the subject of ongoing investigation; in an updated meta-analysis of primary prevention ICDs in nonischemic cardiomyopathy that included the DANISH trial a significant 23% risk reduction in all-cause mortality favouring ICD use was reported.[196] In balance, the weight of evidence appears to favour the use of ICDs for primary prevention in nonischemic HF, however, recent data highlight the need to individualize decision-making and recommendations around ICDs, and further informs the discussion between clinicians and patients regarding the anticipated effects of this therapy.

The assessment of LVEF for ICD consideration should be performed after titration and optimization of medical therapy. It is reasonable to evaluate response to therapy and LV function at least 3 months after titration of medical therapy. In addition to cardiac status, consideration of other comorbid conditions, patient desires, and goals of therapy are essential components in the assessment for prescription of ICD therapy in this group of patients. In addition, close collaboration between the referring or HF physician and the arrhythmia specialist is essential, not only in the initial assessment of these patients, but in their follow-up. Additional considerations and related guidance is available in the CCS/Canadian Heart Rhythm Society 2016 ICD guidelines.[197]

RECOMMENDATION

51. We recommend consideration of primary ICD therapy in patients with:
    i. Ischemic cardiomyopathy, NYHA class II-III, EF $\leq$ 35%, measured at least 1 month post MI, and at least 3 months post coronary revascularization procedure (Strong Recommendation; High-Quality Evidence); or
    ii. Ischemic cardiomyopathy, NYHA class I, and an EF $\leq$ 30% at least 1 month post MI, and at least 3 months post coronary revascularization procedure (Strong Recommendation; High-Quality Evidence); or
    iii. Nonischemic cardiomyopathy, NYHA class II-III, EF $\leq$ 35%, measured at least 3 months after titration and optimization of GDMT (Strong Recommendation; High-Quality Evidence).
52. We recommend against ICD implantation in patients with NYHA class IV symptoms who are not expected to improve with any further therapy and who are not candidates for cardiac transplantation or mechanical circulatory support (MCS) (Strong Recommendation; Moderate-Quality Evidence).

7.1.3.2. Device considerations in patients with HF after cardiac surgery

The rationale and evidence supporting the use of devices, ICD and CRT, in patients with HF and reduced EF have been addressed in detail in previous HF and CRT guideline updates.[184,198]

Although no studies to date have directly assessed the optimal timing of ICD implantation in the setting of ischemic cardiomyopathy, evidence from primary prevention trials suggests that ICDs do not confer an overall mortality benefit when implanted during, or immediately after, an acute event

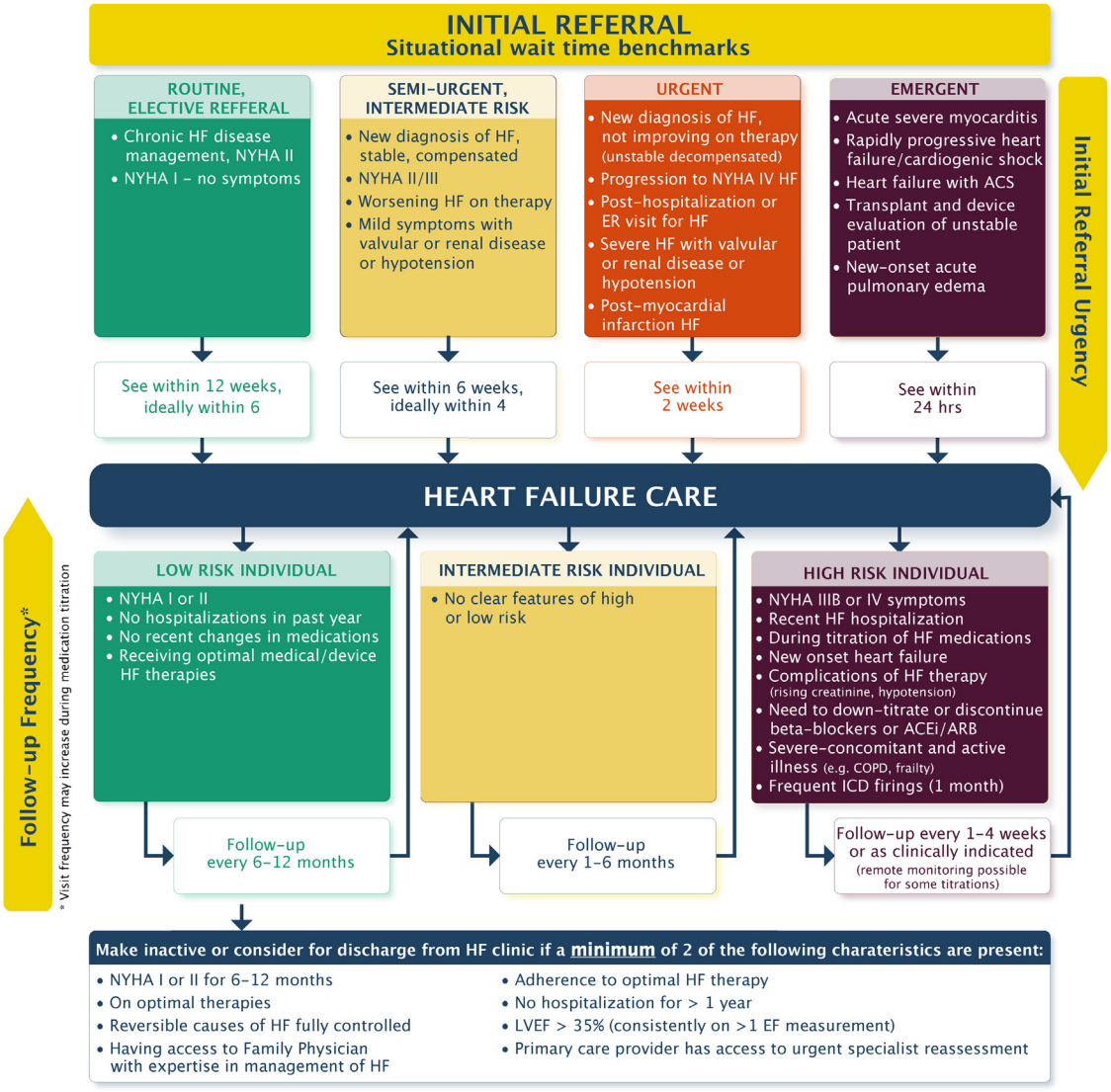

Figure 12. Referral and follow-up frequency for patients with heart failure (HF). Recommended initial referral wait time and follow-up frequency. *Visit frequency might increase during medication titration. ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; ED, emergency department; EF, ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

or revascularization.[191] The Coronary Artery Bypass Graft (CABG) Patch trial was designed to assess whether an ICD is associated with additional survival benefit in patients at high risk for SCD who undergo coronary artery bypass graft (CABG) surgery.[199] The negative findings in this trial were essentially mirrored in other studies of ICD after acute MI and reinforce the role of ICD therapy to be one for chronic LV dysfunction.[191,192,200]

After revascularization, the risk of SCD continues over time,[201] while systolic function might not improve substantially,[202] posing a challenge in defining the optimal timing for ICD therapy.

Similarly, the optimal timing for CRT implantation in suitable candidates with ischemic cardiomyopathy has not been well defined. Key clinical trials reporting a mortality benefit with CRT excluded patients with a recent (1-6 months) MI or revascularization procedure.[203-205] However, data from observational studies provide a rationale for considering epicardial LV lead placement at the time of CABG surgery in patients who might otherwise have an indication for CRT. Transvenous LV lead delivery via the coronary sinus is technically not feasible in approximately 10% of cases[206]; surgical lead placement can overcome anatomical limitations imposed by the coronary sinus, with acceptable long-term lead performance and rates of clinical response similar to conventional transvenous implantation.[207] Additionally, surgical revascularization might not have any effect on dyssynchrony, which is associated with a worse prognosis.[208] Data from one RCT[209] suggest that CRT using an epicardial lead implanted concomitantly with CABG is associated with improved systolic function and survival compared with CABG alone in patients with poor systolic

Table 42. Potential approaches to treatment of acute gout in patients with heart failure

Type of therapy	Type of gout	Dosage and duration of therapy	Dosage adjustment
Acute gouty attack			
Oral colchicine	Any type	1.0-1.2 mg then 0.5-0.6 mg every 2 hours until pain relief with maximum of 3 mg per 24-hour period May be used to abort gouty attack if used early enough	Not recommended for GFR < 15 mL/min High rate of diarrhea with aggressive dosing. Many will use only a single dose of 0.6 mg after first dose
Oral prednisone	Polyarticular gout, or inability to treat with colchicine	Prednisone, 0.5 mg/kg/d with rapid taper over 7-14 days	No adjustment needed Can be given intravenously or orally and might not worsen acute HF
IA steroid injection	Monoarticular gout. Not suitable for polyarticular gout	IA triamcinolone 20 mg once IA cortisone 100 mg once	None required
Chronic prevention of gouty attacks			
Colchicine	Can reduce attack frequency	0.6 mg daily or twice per day in function of GFR	Not recommended for GFR < 15 mL/min
Allopurinol	First-line agent for reduction of uric acid	300 mg daily orally	Dose reduction for renal disease 200 mg daily for GFR < 30 mL/min 100 mg daily for GFR < 20 mL/min 50 mg daily or 3 times weekly if ESRD
Probenecid	Second- or third-line agent	250 mg orally twice per day to maximum 1000 mg twice per day	Multiple drug interactions Avoid if GFR < 30 mL/min

ESRD, end-stage renal disease; IA, intra-arterial; GFR, glomerular filtration rate.

function and evidence of preoperative device candidacy. Therefore, epicardial LV lead placement might be considered in selected patients who undergo surgical revascularization for ischemic cardiomyopathy who are likely to remain candidates for CRT after surgery.

Perioperative management of existing devices remains an important component of care; in keeping with existing guidelines, which state device deactivation is necessary before any procedure in which electrocautery, or potential for electrical interference with the device might occur.[210] Postoperatively, re-establishment of appropriate device threshold determination and programming are recommended.

RECOMMENDATION

53. We recommend that after successful cardiac surgery, patients with HF undergo assessment for implantable cardiac devices within 3-6 months of optimal treatment (Strong Recommendation; High-Quality Evidence).
54. We recommend that patients with implantable cardiac devices in situ should be evaluated for programming changes before surgery and again after surgery, in accordance with existing CCS recommendations[197] (Strong Recommendation; Low-Quality Evidence).

Practical tip. During surgical revascularization, consideration can be given to implantation of epicardial LV leads to facilitate biventricular pacing in eligible patients who might be candidates for CRT, especially if the coronary sinus anatomy is known to be unfavourable for lead placement.

7.1.3.2.1. ICD therapy to prevent sudden death in patients with hypertrophic cardiomyopathy

Although a detailed review of specific cardiomyopathies is beyond the scope of this document, prevention of SCD in patients with an established diagnosis of HCM in particular has been an area of active study discussed elsewhere.[211,212] Cardiovascular death, frequently due to sudden death, is a well-recognized complication of HCM, at approximately 1%-2% per year.[211,212] Well established clinical risk factors for sudden death include: previous cardiac arrest, ventricular fibrillation, or sustained ventricular tachycardia, a history of sudden death in close relatives (particularly at a young age), a history of unexplained syncope, LV wall thickness $\geq$ 30 mm, nonsustained ventricular tachycardia ($\geq$ 3 beats at $\geq$ 120 bpm) on Holter monitoring, and blunted BP response to exercise.[211] Although patients with multiple risk factors are at higher risk, the relative weight or importance of individual risk factors for clinical decision-making in the primary prevention setting remains the subject of ongoing study. Current guideline-based risk stratification approaches appear to have limited ability to discriminate high- vs lower-risk patients.[213]

More recently, the HCM Risk-SCD Prediction Model[214] is a retrospectively derived risk score that provides an absolute estimate of 5-year risk of sudden death. Attempts at validating the HCM Risk-SCD Prediction Model have yielded conflicting results in different patient populations and in different practice settings.[215,216] It is therefore important to recognize that current approaches to risk stratification for SCD in HCM have limitations; patient factors and other markers of risk (including specific genetic mutations, identification of LGE on CMR imaging, for example) might modify the assessment of risk in an individual patient.

There is no evidence that drug therapy reduces the risk of sudden death, even in high-risk patients. An ICD is indicated for patients with HCM who survive a cardiac arrest or have had sustained ventricular tachycardia. Although there are no

Table 43. Necessary features of successful health system integration

Feature	Description
Program integration and care coordination	Shared and standardized information system accessible from any point in the care network Shared care plan with clearly defined patient-centred goals of care, and mutually understood and agreed-upon provider (formal and informal) responsibilities An organizational framework clearly specifying the linkages between constituents of the care network and community-based services Clearly defined protocols to facilitate seamless transitions and navigation for patients and providers between levels and sites of care, and are anchored in primary care
Human resource elements	In addition to clinical staff, additional resources should include • Program to support coordination, commensurate with its size and scope; • Access to continuing medical education to support knowledge translation
Access to care	Standardized risk stratification criteria to ensure timely referral and access to appropriate care; Access to other services: • Specialists: cardiology, geriatrics, psychiatry, internal medicine, rehabilitation; • Palliative care, spiritual care; and • Home care and community support services
Quality improvement and outcome measurement	Measurement and submission of mandated quality measures to appropriate authority; Measurement of Quality Indicators, as defined according to the Canadian Cardiovascular Society Quality Indicators Working Group for Heart Failure[640] (http://ccs.ca/images/Health_Policy/Quality-Project/Definition_HF.pdf)

prospective RCTs to guide therapy for primary prevention, there is consensus that consideration should be given to implantation of an ICD in patients with multiple high-risk factors and in patients whose estimated absolute risk (of SCD) is high.[211,212] Patients with a single high-risk factor should be individually assessed for ICD implantation, including a discussion of the level of risk acceptable to the individual and potential adverse effects with an ICD, such as inappropriate ICD discharges, lead complications, and infection.

RECOMMENDATION

55. We recommend patients with hypertrophic cardiomyopathy (HCM) who survive a cardiac arrest should be offered an ICD (Strong Recommendation; Moderate-Quality Evidence).
56. We recommend patients with HCM who have sustained ventricular tachycardia should be considered for an ICD (Strong Recommendation; Moderate-Quality Evidence).
57. We suggest an estimate of risk for SCD in patients with HCM should be determined on the basis of validated risk scores and/or the presence of one or more high-risk clinical factors to select appropriate candidates for primary prevention ICD therapy (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. These recommendations place great value on the prevention of SCD in patients perceived to be at high risk from observational studies. Primary prevention ICD recommendations in this population place significant weight on individualizing risk assessment whenever possible by clinicians/centres with significant experience in HCM, taking into consideration the potential for device complications.

Practical tip. Emerging risk factors for SCD, including late gadolinium enhancement (LGE) on CMR imaging, specific genetic mutations, and electrocardiographic features might be considered to modify estimates of risk on an individual basis by clinicians/centres with significant experience managing patients with HCM.

7.1.3.3. CRT

Despite optimization of GDMT, LV systolic dysfunction and HF symptoms persist for many patients. Commonly, these patients have conduction delay, typically expressed as an LBBB pattern that is associated with cardiac mechanical dyssynchrony. This compromises ventricular function and is associated with poor prognosis. CRT attempts to synchronize the activation of the ventricles as well as the atrioventricular activation sequence, which leads to short-term and long-term improvements in overall LV function.

The publication of landmark trials and analyses mandated the revision of the earlier recommendations to include patients with mild HF symptoms and to place more emphasis on QRS morphology and duration, and the importance of sinus rhythm in the selection of CRT patients.[183,184] Further systematic reviews and long-term follow-up data from RCTs have confirmed the benefits of CRT and helped refine the selection of ideal candidates for this therapy. The updated recommendations have been harmonized with the comprehensive CCS guidelines on the use of cardiac resynchronization therapy: evidence and patient selection.[198]

Several landmark studies have shown the effectiveness of CRT to improve morbidity and mortality in selected patients with HFrEF. Al-Majed et al. performed a systematic review of RCTs[217] that included 25 studies of 9082 patients with LVEF $\leq$ 40% and compared CRT vs usual care or ICD or RV pacing alone. Pooled data from all studies showed that CRT reduced mortality by 19%. Analysis of outcomes according to NYHA functional class revealed a 17% reduction in mortality and 29% reduction in HF hospitalization among patients

Table 44. Summary of performance indicators for heart failure according to development group

Indicator	CCORT inpatient	CCORT outpatient	Canadian primary care	AHA/ACC inpatient	AHA/ACC outpatient	JCAHO	OPTIMIZE-HF	ACOVE	IMPROVE HF
Therapeutics									
ACEi and/or ARB if LV systolic dysfunction in eligible patients	X	X	X	X	X	X	X	X	X
Use of β-blockers (evidence-based or not) in eligible patients	X	X	X	X	X		X	X	X
Use of statins in eligible patients if underlying CAD, PVD, CVD, or diabetes							X		
Aldosterone antagonists for eligible patients		X					X		X
Anticoagulants for atrial fibrillation	X	X		X	X		X		X
Use of ICDs in eligible patients									X
Use of CRT in eligible patients									X
Avoid first- and second-generation CCBs if LV systolic dysfunction								X	
Avoid type 1 antiarrhythmic agents if LV systolic dysfunction (unless ICD in place)								X	
Investigations									
Outpatient assessment including 1 or more of regular volume assessment, weight, blood pressure, activity level	X		X		X			X	
Appropriate baseline blood/urine tests, ECG, CXR					X			X	
Appropriate biochemical monitoring or renal function and electrolytes			X		X			X	
Assessment of LV function	X	X	X	X	X	X	X	X	X
Measure digoxin levels if toxicity suspected								X	
Education and follow-up									
Heart failure patient education/discharge instructions	X			X	X	X	X	X	X
Outpatient follow-up within 4 weeks		X							
Advice on smoking cessation				X		X	X		

ACEi, angiotensin-converting enzyme inhibitor; ACOVE, Assessing the Care of Vulnerable Elders Project; AHA/ACC, American Heart Association/American College of Cardiology; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CCORT, Canadian Cardiovascular Outcomes Research Team; CRT, cardiac resynchronization therapy; CVD, cerebrovascular disease; CXR, chest x-ray; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; IMPROVE HF, Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; JCAHO, Joint Commission on Accreditation of Healthcare Organizations; LV, left ventricular; OPTIMIZE-HF, Organized Program to Indicate Lifesaving Treatment in Hospitalized Patients with Heart Failure; PVD, peripheral vascular disease.

with NYHA I-II symptoms. Similarly, there was a 20% reduction in mortality and 35% reduction in HF hospitalization among patients with NYHA III-IV symptoms. CRT was associated with a 94.4% implantation success rate, 3.2% risk of mechanical complications, 6.2% risk of lead complications, and peri-implant mortality of 0.3%. Results of other systematic reviews, including individual patient meta-analyses[218-222] have yielded similar findings, suggesting that CRT improves survival and HF hospitalization in a spectrum of HFrEF patients with mild or severe HF symptoms. Finally, since the publication of these reviews, the long-term follow-up of the **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial With **C**ardiac **R**esynchronization **T**herapy (MADIT-CRT) study has been published.[223] In this trial, 1818 patients with NYHA I and II symptoms, LVEF $< 30\%$, and QRS ≥ 130 ms were randomized to CRT defibrillators (CRT-D) vs ICD only and median follow-up was 5.6 years. Among patients with LBBB, there was a 41% relative reduction in mortality, and among patients with right bundle branch block, a 57% relative increase in mortality. This analysis confirms the long-term mortality benefit in patients with mild HF, reduced EF, and LBBB beyond the benefits in morbidity reported in the primary trial.

An important and consistent finding in systematic reviews and in subgroup analyses of RCTs is that the benefits of CRT are greatest for patients with a broader QRS, typically defined as QRS duration > 150 ms, and for patients with a typical LBBB QRS morphology.[223-227] It remains unclear whether patients with a relatively narrow QRS (120-150 ms) or those with non-LBBB derive any benefit from CRT, or whether other clinical factors could help select potentially appropriate candidates among these subgroups. Last, the interaction between QRS duration and morphology and its importance for CRT also warrants further evaluation; it is conceivable that patients with very broad QRS and non-LBBB morphology might derive some magnitude of benefit from CRT.[226] Current recommendations for CRT candidate selection are therefore on the basis of the characteristics of patients included in landmark studies and on the clinical characteristics of patients shown to derive significant benefit from CRT on the basis of the totality of available data (Fig. 5).

7.1.3.3.1. CRT in patients with AF

Most RCTs that evaluated CRT included only patients in sinus rhythm, and relatively few patients with permanent AF were included in prospective randomized studies of CRT efficacy. Achieving atrioventricular synchronization is an important goal for most patients in sinus rhythm who undergo CRT, and it is therefore unclear whether patients with permanent AF who are otherwise candidates derive any meaningful benefit from CRT. To date, the **R**esynchronization for **A**mbulatory Heart **F**ailure **T**rial (RAFT) is the largest RCT to include patients with AF with intact AV nodal conduction. In a substudy of RAFT[228] the effect of CRT in patients with permanent AF was evaluated; 114 patients were randomized to CRT-D and 115 patients were randomized to ICD alone and LVEF (22.9% vs 22.3%) and QRS duration (151.0 ms vs 153.4 ms) were similar between groups. In this study, CRT was not associated with improvements in the combined end point of death or HF hospitalization or cardiovascular death, HF hospitalizations, change in 6-minute walk, or quality of life. A major limitation of this analysis is that only one-third of patients achieved biventricular pacing $> 95\%$, and only 1 patient underwent AV nodal ablation to effect 100% biventricular pacing.

Indeed, observational data strongly suggest that outcomes in AF patients who receive CRT are associated with the degree of biventricular pacing achieved, and that differential effects in survival might be seen when biventricular pacing achieved is $< 98\%$ vs $> 98\%$.[229] A meta-analysis of observational studies of AV node ablation vs pharmacologic rate control in AF and CRT (1256 patients; 644 with AV node ablation, 798 without AV node ablation) suggested that AV nodal ablation is associated with a higher degree of biventricular pacing (100% vs 82%-96%), reduced mortality, and lower rates of CRT nonresponse compared with pharmacologic rate control.[230] Ongoing prospective RCTs, including the multicentre **R**esynchronization/Defibrillation for **A**mbulatory Heart **F**ailure **T**rial in Patients With **Perm**anent **AF** (RAFT-PermAF) should help refine the role of CRT in patients with AF who would otherwise be suitable candidates.

7.1.3.3.2. CRT in patients with RV pacing and reduced EF

The use of CRT in patients with LVSD who require permanent ventricular pacing, or in patients with suspected RV pacing-induced HF has been investigated.[231-233] Although the prognostic significance of RV pacing-induced dyssynchrony vs intrinsic LBBB-related dyssynchrony is uncertain, a subgroup of patients with frequent RV pacing will experience worsening of LV function, particularly in the setting of abnormal LVEF and HF at baseline. The results of these studies suggested that CRT in this clinical situation improves LV function, symptoms, and exercise capacity.[231] To address this issue further, the Biventricular Versus RV Pacing in Patients with LVSD and Atrioventricular Block (BLOCK HF) study randomized 691 patients with LVEF $\leq 50\%$ and heart block to CRT vs RV pacing (with an ICD or pacemaker as indicated).[234] Patients in this study had a mean LVEF of 40%, and $> 80\%$ had NYHA class II or III symptoms. After a mean follow-up of 37 months, CRT was associated with fewer primary outcome events including the composite of death, urgent care visit for intravenous (I.V.) HF therapy, or an increase in LV end systolic volume index $\geq 15\%$ (HR, 0.74; 95% CI, 0.60-0.90). The benefits observed with CRT were driven by reductions in HF events. Notably, pacing percentage in both study groups was $> 97\%$ and serious adverse events occurred in 14% of patients, mainly related to lead complications. Overall, it appears that patients similar to those included in the BLOCK HF study derive significant benefits with CRT compared with RV only pacing with respect to HF events, but the potential for procedural complications needs to be considered carefully for individual patients.

7.1.3.3.3. CRT in patients with narrow QRS

Compared with ICD alone, CRT has not been associated with improvements in mortality or HF hospitalization, and there is a suggestion of increased harm with CRT in some studies.[235-239]

RECOMMENDATION

58. We recommend CRT for patients in sinus rhythm with NYHA class II, III, or ambulatory class IV HF despite optimal medical therapy, a LVEF $\leq$ 35%, and QRS duration $\geq$ 130 ms with left bundle branch block (LBBB) (Strong Recommendation; High-Quality Evidence).
59. We suggest that CRT may be considered for patients in sinus rhythm with NYHA class II, III, or ambulatory class IV HF despite optimal medical therapy, a LVEF $\leq$ 35%, and QRS duration $\geq$ 150 ms with non-LBBB (Weak Recommendation; Low-Quality Evidence).

Practical tip. There is no clear evidence of benefit with CRT among patients with QRS durations < 150 ms because of non-LBBB conduction.

RECOMMENDATION

60. We suggest that CRT may be considered for patients in permanent AF who can expect to achieve close to 100% pacing and are otherwise suitable for this therapy (Weak Recommendation; Low-Quality Evidence).

Practical tip. It is important to ensure that the amount of biventricular pacing approaches 100% where possible. AV junctional ablation might be necessary to achieve sufficient biventricular pacing.

RECOMMENDATION

61. We suggest that CRT might be considered for patients who require chronic right ventricular (RV) pacing in the setting of HF symptoms and reduced LVEF (Weak Recommendation; Moderate-Quality Evidence).
62. We recommend CRT not be used for patients with QRS < 130 ms, irrespective of HF symptoms, LVEF, or the presence or absence of mechanical dyssynchrony shown on current imaging techniques (Strong Recommendation; Moderate-Quality Evidence).
63. We recommend the addition of ICD therapy be considered for patients referred for CRT who meet primary ICD requirements (Strong Recommendation; High-Quality Evidence).

Values and preferences. These recommendations place a value on the benefit of CRT in patient groups included in the landmark RCTs and high-quality systematic reviews, and less value on post hoc subgroup analyses from clinical trials. On the basis of the available evidence, there is insufficient evidence to recommend CRT in patients with NYHA class I status or in hospitalized NYHA class IV patients. Patients with a QRS duration $\geq$ 150 ms are universally more likely to benefit from CRT than patients with less QRS prolongation. CRT pacemaker therapy should also be considered in patients who are not candidates for ICD therapy such as those with a limited life expectancy because of significant comorbidities, and in patients who decline to receive an ICD.

7.1.4. Advanced HF management strategies

Although the term, advanced HF has many definitions, to guide clinicians as to which patients should be considered for advanced HF management (such as but not limited to cardiac transplantation, MCS, or palliative care) the following is a general guide. Cardiac transplantation is well established in Canada and further guidance is available at http://www.ccs.ca/en/cctn-home. Cardiac transplantation assessment is typically done by a multispecialty, multidisciplinary team in a specialized setting, using Canadian and international guidance for appropriate workup and eligibility.

Patients with advanced HF to be considered for advanced HF management strategies include those who, despite optimal treatment, continue to exhibit progressive/persistent NYHA III or IV HF symptoms and accompanied by more than one of the following:

- LVEF < 25% and, if measured, peak exercise oxygen consumption < 14 mL/kg/min (or less than 50% predicted).
- Evidence of progressive end organ dysfunction due to reduced perfusion and not to inadequate ventricular filling pressures.
- Recurrent HF hospitalizations ($\geq$ 2 in 12 months) not due to a clearly reversible cause.
- Need to progressively reduce or eliminate evidence-based HF therapies such as ACEis, MRAs, or β-blockers, because of circulatory-renal limitations such as renal insufficiency or symptomatic hypotension.
- Diuretic refractoriness associated with worsening renal function.
- Requirement for inotropic support for symptomatic relief or to maintain end organ function.
- Worsening right HF (RHF) and secondary pulmonary hypertension.
- Six-minute walk distance < 300 m.
- Increased 1-year mortality (eg, > 20%-25%) predicted by HF risk scores
- Progressive renal or hepatic end organ dysfunction.
- Persistent hyponatremia (serum sodium < 134 mEq/L).
- Cardiac cachexia.
- Inability to perform activities of daily living.

It should be noted that most patients will have a number of the listed criteria and there is no single criterion that determines candidacy for cardiac transplantation, MCS, or palliative care. Patient preferences should be incorporated into the decision process when assessing further choices.

7.1.5. MCS

7.1.5.1. What is mechanical circulatory support?

MCS is a group of technologies that increase forward cardiac output in patients.[240] MCS therapies consist of ventricular assist devices that augment or replace the ventricle. They may be used to assist the right ventricle, left ventricle, or both ventricles.[241] The choice depends on the clinical presentation, and can be divided into 2 categories—temporary circulatory support and long-term devices. Details of the purpose of MCS, the decision process, description of patient profiles, management, and other issues are outlined in sections *7.1.5.2-7.1.5.7* of the Supplementary Material, and in Tables 15-17.

Practical tip (choice of temporary MCS). Vasopressors and positive inotropic agents remain the first lines of treatment, but frequently offer inadequate support; then, the use of percutaneous MCS in severe, refractory cardiogenic shock should be considered early in a patient's clinical course.

Practical tip (choice of temporary MCS). The choice of which MCS device to use is on the basis of many factors, including patient characteristics, the degree of desired hemodynamic support, operator abilities, and institutional resources.

Practical tip (choice of temporary MCS). In general, there is a continuum of increasing hemodynamic support from the intra-aortic balloon pump (IABP) to the Impella 2.5 and CP devices to the TandemHeart and VA-ECMO.

Practical tip (choice of temporary MCS). The choice of which device to use is multifactorial, on the basis of patient characteristics, operator ability, and the degree of hemodynamic support desired.

Practical tip (choice of temporary MCS). These devices are best managed with a care team approach that includes an advanced HF cardiologist.

Practical tip (candidacy for MCS). In general, patients with HF are potentially candidates for MCS if they fulfil the advanced HF criteria mentioned previously.

Practical tip (MCS-performing centres). Cardiac centres that perform MCS should have adequate manpower and resources for support of patients requiring MCS support. These include:

- An identified and adequately trained multidisciplinary MCS team;
- Access to the full array of medical and surgical consultative support, and institutional administrative and financial support; and
- Expertise in MCS implantation, follow-up, and explantation.

RECOMMENDATION

64. We recommend that patients with either acute severe or chronic advanced HF and with an otherwise good life expectancy be referred to a fully equipped cardiac centre for assessment and management by a team with expertise in the treatment of severe HF, including MCS (Strong Recommendation; Moderate-Quality Evidence).
65. We recommend MCS be considered for patients who are listed for cardiac transplantation and who deteriorate or are otherwise not likely to survive until a suitable donor organ is found, including those for whom a long wait is expected (Strong Recommendation; High-Quality Evidence).
66. We recommend that MCS be considered for patients for whom there is a contraindication for cardiac transplantation but might, via MCS, be rendered transplantation-eligible (Strong Recommendation; Low-Quality Evidence).
67. We recommend that patients in cardiogenic shock be considered for temporary MCS to afford an opportunity for evaluation for long-term options (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Extracorporeal circulatory membrane oxygenator or other mechanical circulatory temporary devices should be preferred over the IABP except if the patient is suffering an acute ischemic event, because the increase in cardiac output offered by the IABP is usually minimal.

RECOMMENDATION

68. We recommend permanent MCS be considered for highly selected transplantation-ineligible patients (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences: This recommendation places a high value on the potential variability of patient preference as well as the need to interact with the patient to ensure the choice reflects the patient's values, with less value on the effectiveness of therapy.

69. We recommend that institutions providing MCS therapy develop a policy regarding destination therapy within the conventions, resources, and philosophy of care of their organization (Strong Recommendation; Low-Quality Evidence).
70. We recommend that ambulatory patients with MCS therapy who are discharged from hospital and who have had minimal HF symptoms or ventricular arrhythmias for a period of at least 2 months be considered candidates for operation of a personal motor vehicle for a period not exceeding two-thirds of the known battery charge time (Strong Recommendation; Low-Quality Evidence).

Values and preferences. An objective assessment of the disease severity and prognosis for an individual patient using a validated scoring system is recommended. If the expected mortality is higher than the procedural risk of advanced HF therapies, these patients should be considered for referral, provided they have a good life expectancy otherwise.

Practical tip. The timing of discussions should strongly consider the high mortality rate in the year after a first HF hospitalization. A surrogate decision-maker should be identified early and regularly participate in these discussions.

7.1.6. Exercise and rehabilitation

Exercise intolerance is recognized as a hallmark of HF. It is now understood that exercise intolerance in HF has a multifactorial etiology and that parameters such as intracardiac filling pressures and LVEF might not be reliable predictors of exercise capacity. Changes in the periphery and LV function are both important determinants of exercise capacity. Therefore, it is rational that exercise training could potentially benefit patients with HF.

There have been several systematic reviews and meta-analyses that show the benefits of exercise training for patients with HF.[243-245] There has been one large RCT that has shown the benefits of exercise training.[246] In the **H**eart **F**ailure: **A** **C**ontrolled **T**rial **I**nvestigating **O**utcomes of Exercise Trai**n**ing (HF-ACTION) study 2331 medically stable patients with HF were randomized to regular exercise training or usual care. There was a nonsignificant 7% relative reduction in the primary outcome of all-cause mortality or hospitalization. After adjusting for the key covariates of duration of the cardiopulmonary exercise test, LVEF, Beck Depression Inventory II score, and history of AF or flutter along with HF etiology exercise training was found to produce an 11% relative reduction of all-cause mortality or all-cause hospitalization. There was no difference in adverse events between the 2 groups. A systematic review examined the effectiveness of exercise-based rehabilitation in 33 trials with 4740 patients with predominately HFrEF.[243] There was no reduction in all-cause mortality with up to 1 year of follow-up, and a trend to reduction in all-cause mortality in trials with more than 1 year of follow-up (6 trials; 2845 participants; relative risk, 0.88; 95% CI, 0.75-1.02). Exercise training did reduce all-cause hospitalization and HF hospitalizations. Importantly, no safety concerns were raised in any of the studies.[245-248]

Exercise training results in increases of exercise capacity.[249,250] A meta-analysis of studies that directly measured peak volume of oxygen (VO_2) reported an average 17% improvement in peak VO_2.[245] The evidence for quality of life improvements in patients with HF exposed to exercise training is further supported by multiple studies.[245,251] Although there have been a great variety of types of exercise training strategies most have involved moderate to vigorous exercise as was prescribed in the HF-ACTION study.[250]

Although the dose of physical activity that conveys cardiovascular and other health benefits is difficult to categorically quantify, there is support for as little as 15 minutes per day of moderate-intensity physical activity with further dose response thereafter.[252] Piepoli et al.[253] have provided an overview about the practical approaches to exercise training for patients with HF.

The role of exercise training in HFpEF patients is less well established. However, the available data suggest exercise training has benefits that include improvements in exercise capacity and quality of life.[244,254-256] Studies have also shown that exercise training can take place in patients with ICD or CRT therapy. These studies have shown that properly prescribed and monitored exercise training can safely result in improvements in exercise capacity in patients with an ICD and/or CRT therapy (Table 18).[257,258]

RECOMMENDATION

71. We recommend regular exercise to improve exercise capacity, symptoms, and quality of life in all HF patients (Strong Recommendation; Moderate-Quality Evidence).
72. We recommend regular exercise in HF patients with reduced EF to decrease hospital admissions (Strong Recommendation; Moderate-Quality Evidence).

Values and Preferences. These recommendations have placed a high value on regular exercise and not emphasized structured exercise training because it is recognized that not all patients will be able to participate in a structured exercise training program because of patient preferences or availability of resources.

Practical tip. It is important to individualize the exercise training for each patient, with the more deconditioned patients starting at a lower training intensity and with shorter sessions.

7.1.7. Important nonpharmacological and nondevice management options

The basic treatment of HF has included advice on dietary salt and fluid restriction. The evidence to support these concepts is scarce and some evidence suggests the opposite of current clinical practice.[259-262]

Dietary sodium consumption for patients with HF remains controversial. Several cohort studies and 1 RCT suggest that lower dietary sodium intake is associated with better clinical outcomes.[260,262,263] Other studies suggest that the combination of dietary sodium restriction and high-dose diuretics with or without saline infusions can be deleterious, summarized by Gupta et al.[264] An ongoing RCT will provide guidance on this topic (NCT02012179).

Severe fluid restriction is not only difficult to maintain but could also have deleterious effects without additional benefit. Three hospital-based RCTs in this area suggest no additional benefit of the combination of fluid restriction with or without sodium restriction.[265-267] Special consideration for severe water restriction should be considered for hyponatremic patients with hypervolemia and applied sparingly. High-quality data are lacking on this topic, and no high-quality evidence exists in the ambulatory care environment. Thus, for patients admitted to hospital or as outpatients, allowing liberal fluid intake is reasonable.

Alcohol consumption should be limited for all patients with HF, and if it is believed to be responsible and/or contributing to the syndrome it should be avoided altogether because there is a dose-dependent effect and individual susceptibility to the deleterious effects of alcohol.[268]

Because smoking has been linked to the progression of CAD all attempts should be done to promote smoking

cessation, even if HF is not present. Nicotine replacement therapy and/or other smoking cessation therapies are acceptable for most patients with HF. There is limited evidence of the effects of e-cigarettes ("vaping") or medical marijuana for patients with established HF.

RECOMMENDATION

73. We suggest that patients with HF should restrict their dietary salt intake to between 2 g/d and 3 g/d (Weak Recommendation; Low-Quality Evidence).

Practical tip. The optimal quantity of salt in the diet is still a subject of debate. The amount should be adapted to the clinical situation, the severity of symptoms, and baseline consumption without interfering with other nutritional content.

RECOMMENDATION

74. We suggest daily morning weight should be monitored in patients with HF with fluid retention or congestion that is not easily controlled with diuretics, or in patients with significant renal dysfunction (Weak Recommendation; Low-Quality Evidence).

Practical tip. Weight should be closely monitored for unstable or frail patients. Any rapid weight gain (ie, $>$ 1.5 or 2 kg) should prompt a rapid medical visit. Weight loss should also be addressed medically.

RECOMMENDATION

75. We suggest that restriction of daily fluid intake to approximately 2 L/d should be considered for patients with fluid retention or congestion that is not easily controlled with diuretics (Weak Recommendation; Low-Quality Evidence).

Practical tip. The appropriate quantity of fluid intake is a subject of debate. Strict limits should be imposed when there is clear fluid overload or demonstrated sensitivity to fluid intake.

Practical tip. Severely limiting daily fluid intake to $<$ 1.5 L might have adverse consequences on nutrition, renal function, and quality of life without known additional benefit and should be applied selectively.

Practical tip. Special consideration for hyponatremic patients should be applied.

Practical tip. Alcohol intake should be avoided if it is a precipitating or contributing factor.

Practical tip. Patients should quit smoking and a referral for counselling should be offered.

7.2. Cardiovascular comorbidities

7.2.1. Atrial fibrillation

AF and HF share common risk factors and frequently coexist.[270,271] Up to 50% of patients with HF might develop AF; the reported prevalence rates of AF among HF cohorts varies significantly and is largely dependent on the clinical setting (acute vs community), the extent of LV dysfunction, NYHA functional class, and the use of background HF therapies.[272]

The presence of AF is associated with a worse prognosis in terms of overall survival[273,274] as well as risk of stroke.[275] AF might also exacerbate the HF syndrome through a number of mechanisms including: (1) decreased cardiac output secondary to loss of atrial systole; (2) increased myocardial oxygen consumption and decreased coronary perfusion during periods of rapid ventricular response; (3) neurohormonal activation; and (4) the development of tachycardia-induced cardiomyopathy.[276] Further details pertaining to primary prevention, rate and rhythm control, and anticoagulation can be found in sections *7.2.1.1-7.2.1.3* of the Supplementary Material.

RECOMMENDATION

76. We recommend in patients with HF and AF that the ventricular rate be controlled at rest and during exercise (Strong Recommendation; Moderate-Quality Evidence).
77. We recommend β-blockers for rate control particularly in those with HFrEF (Strong Recommendation; Moderate-Quality Evidence).
78. We recommend rate-limiting CCBs be considered for rate control in HFpEF (Weak Recommendation; Low-Quality Evidence).
79. We recommend the use of antiarrhythmic therapy to achieve and maintain sinus rhythm; if rhythm control is indicated, it should be restricted to amiodarone (Strong Recommendation; Moderate-Quality Evidence).
80. We recommend the additional use of digoxin in patients with HFrEF and chronic AF and poor control of ventricular rate and/or persistent symptoms despite optimally tolerated β-blocker therapy, or when β-blockers cannot be used (Strong Recommendation; Low-Quality Evidence).
81. We recommend that restoration and maintenance of sinus rhythm in chronic HF not be performed routinely, but individualized on the basis of patient characteristics and clinical status (Strong Recommendation; High-Quality Evidence).
82. We suggest catheter ablation of AF be considered as a therapeutic strategy to achieve and maintain sinus rhythm if rhythm control is indicated and antiarrhythmic therapy has failed or the patient is unable to tolerate antiarrhythmic therapy (Weak Recommendation; Low-Quality Evidence).

83. We recommend oral anticoagulation for AF in patients with HF unless contraindicated, as per current CCS AF guidelines,[269] and not to coadminister antiplatelet agents unless the latter are strongly indicated for other reasons (Strong Recommendation; High-Quality Evidence).
84. We suggest that non-vitamin K antagonist oral anticoagulants should be the agent of choice for stroke prophylaxis in patients with HF and nonvalvular AF, and that the treatment dose be guided by patient-specific characteristics including age, weight, and renal function (Weak Recommendation; Moderate-Quality Evidence).
85. We suggest the application of evidence-based therapies for HFrEF, per CCS HF guidelines, for primary prevention of AF (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. These recommendations are on the basis of an understanding that the management of patients with HF with AF should be individualized with respect to the need to identify precipitating factors, to assess the risk of therapy such as the development of bradycardia and proarrhythmia with antiarrhythmic agents, and the bleeding risk of systemic anticoagulation.

These recommendations place a high value on the understanding that the use of cardiac glycosides in patients with chronic HF and AF remains controversial with conflicting results from meta-analyses. Digoxin can cause atrial and ventricular arrhythmias particularly in the presence of hypokalemia. Not all glycosides and not all preparations have been studied in terms of efficacy and safety.

These recommendations are consistent with the current CCS AF guidelines.[269]

In patients with HF with AF, for whom a rate control strategy is used, the heart rate treatment target remains unclear. Retrospective analyses of large RCTs suggest that rates $>$ 110-115 bpm might be associated with worse outcomes.[269]

Practical tips. In patients who are symptomatic from AF or whose symptoms of HF are believed to have substantial contribution from arrhythmia, consideration can be given for rhythm control.

Practical tip. Nondihydropyridine CCBs (eg, verapamil and diltiazem) should not be used to control heart rate in patients with HFrEF because they can depress cardiac function and worsen HF.

Practical tip. Dronedarone should not be used in patients with an EF $<$ 35% and/or with recent decompensated HF because of increased risk of mortality. Agents such as sotalol, flecainide, and propafenone should also be avoided.

Practical tip. β-Blockers and nondihydropyridine CCBs should not be routinely combined as part of a rate control strategy in patients with HF because this might be associated with high-degree AV block.

Practical tip. In acutely decompensated patients with AF and HFrEF, digoxin is the first choice for heart rate control and β-blockers may be used in addition when the patient has clinically stabilized; long-term digoxin use is not often required.

Practical tip. Among patients with HF who receive digoxin for rate control, trough serum digoxin levels should not exceed 1.0 ng/mL.

7.2.2. CAD and revascularization

Nearly 60% of patients with chronic HF suffer from CAD, and approximately 15% of AHF cases occur in the setting of an ACS.[278,279] Despite the coexistence of CAD and HF, few clinical trials have been performed that can inform optimal care for patients with these conditions. Several areas exist in which high-grade evidence is lacking, such as coronary revascularization in the setting of HFpEF. Although ample evidence exists to support PCI in patients with HF due to ACS,[280] there is limited evidence to support its use in the setting of chronic HF to reduce adverse clinical outcomes.[281] A detailed discussion of different imaging modalities, an approach to the diagnosis of CAD, and the perioperative management and the approach to revascularization are covered in sections *7.2.2.1-7.2.2.5* of the Supplementary Material, and Figures 6 and 7.

RECOMMENDATION

86. We recommend that noninvasive imaging for patients with HF be considered to determine the presence or absence of CAD (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places value on identification of CAD as the cause of HF, which might have prognostic implications, and require treatments aimed toward secondary vascular prevention.

87. We recommend that coronary angiography be:
    i. Performed in patients with HF with ischemic symptoms and who are likely to be good candidates for revascularization (Strong Recommendation; Moderate-Quality Evidence);
    ii. Considered in patients with systolic HF, LVEF $<$ 35%, at risk of CAD, irrespective of angina, who might be good candidates for revascularization (Strong Recommendation; Low-Quality Evidence);
    iii. Considered in patients with systolic HF and in whom noninvasive coronary perfusion testing yields features consistent with high risk (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. These recommendations place value on the need for coronary angiography to identify CAD amenable to revascularization. Available evidence suggests that coronary revascularization might provide quality of life and prognostic benefits to patients with HF and noninvasive imaging delineating high risk. In particular, patients with systolic HF because of ischemic heart disease might derive clinical benefit from coronary revascularization even in the absence of angina or reversible ischemia.

Practical tip. Several noninvasive methods for detection of CAD are in widespread use, including dobutamine stress echo, perfusion CMR, cardiac positron emission tomography testing, cardiac CT, and nuclear stress imaging. Local factors (availability, price, expertise, practice patterns) will determine the optimal strategy for imaging (Fig. 6).[277]

Practical tip. Noninvasive imaging modalities might provide critical information such as the amount and degree of ischemic or hibernating myocardium, and might be used to determine the likelihood of regional and global improvement in LV systolic function after revascularization.

Practical tip. Patients with HF and reduced LVEF are more likely to experience significant improvement in LVEF after successful coronary revascularization if they have:

- Reversible ischemia or a large segment of viable myocardium (> 30% of the left ventricle) in nuclear stress testing/viability study;
- Reversible ischemia or > 7% hibernating myocardium on positron emission tomography scanning;
- Reversible ischemia or > 20% of the left ventricle shown as viable using dobutamine stress echo;
- Less than 50% wall thickness scarring shown by LGE on CMR imaging.

7.2.2.4. Disease management, referral, and perioperative care

RECOMMENDATION

88. We recommend that the decision to refer patients with HF and ischemic heart disease for coronary revascularization should be made on an individual basis and in consideration of all cardiac and noncardiac factors that affect procedural candidacy (Strong Recommendation; Low-Quality Evidence).
89. We recommend that efforts be made to optimize medical status before coronary revascularization, including optimizing intravascular volume (Strong Recommendation; Low-Quality Evidence).
90. We recommend that performance of coronary revascularization procedures in patients with chronic HF and reduced LVEF be undertaken with a medical-surgical team approach with experience and expertise in high-risk interventions (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation reflects the preference that high-risk revascularization is best preformed in higher volume centres with significant experience, and known, published outcomes.

Practical tip. Assessment for advanced HF therapies, by an appropriate team, should be performed before the revascularization procedure in any patient with advanced HF.

7.2.2.5. Surgical revascularization for patients with CAD and HF

The approach to the decision of coronary revascularization in patients with HF is illustrated in Figure 7. CABG surgery is indicated in adult patients with symptoms of angina, a history of HF in association with LV dysfunction (LVEF < 35%), graftable coronary arteries, and who have an otherwise good life expectancy. This recommendation is on the basis of historical data from earlier landmark clinical trials comparing medical and surgical therapy, which identified a survival benefit with CABG in patients with triple vessel CAD along with ventricular dysfunction.[283-286] Further details of the trials in this area are available in section *7.2.2.5* of the Supplementary Material.

The **S**urgical **T**reatment for **I**schemi**c** **H**eart Failure (STICH) trial sought to address 2 hypotheses: (1) does CABG improve survival in combination with optimal medical therapy for patients with HF and CAD (LVEF < 35%) who are acceptable candidates for cardiac surgery; and (2) does the additional use of SVR of an akinetic/dyskinetic anterior wall provide better outcomes than isolated CABG for eligible individuals.[287] This study evaluated patients with ischemic cardiomyopathy with or without HF symptoms and randomized them into 3 groups, namely, optimal medical therapy and CABG alone, CABG with the SVR procedure, or neither procedure. Details pertaining to the 2 hypotheses are available in the Supplementary Material.

A major concern regarding surgical revascularization in patients with LV dysfunction is a greater rate of operative mortality. A meta-analysis of 26 observational studies (3621 patients) with a preoperative LVEF < 35% showed an operative mortality of 5.4%.[288] The 2 risk calculators for surgical mortality have been recently updated: EuroSCORE II (http://www.euroscore.org/calc.html) and the (Society of Thoracic Surgeons) STS score (http://riskcalc.sts.org/STSWebRiskCalc273/de.aspx).

RECOMMENDATION

91. We recommend consideration of coronary artery bypass surgery for patients with chronic ischemic cardiomyopathy, LVEF < 35%, graftable coronary arteries, and who are otherwise suitable candidates for surgery, irrespective of the presence of angina and HF symptoms to improve mortality, repeat hospitalization rates, and quality of life (Strong Recommendation; Moderate-Quality Evidence).
92. We suggest consideration of PCI for patients with HF and limiting symptoms of cardiac ischemia, and for whom CABG surgery is not considered appropriate (Weak Recommendation; Low-Quality Evidence).
93. We recommend against routine performance of surgical ventricular restoration for patients with HF (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. These recommendations are on the basis of data from RCTs on CABG and surgical ventricular restoration in patients with reduced systolic function and CAD, regardless of the results of viability imaging. The recommendation on PCI is on the basis of clinical need rather than RCT trial data.

Practical tip. In the setting of HF, angina and single territory CAD, PCI might be the treatment of choice. However, PCI has not been shown to improve outcomes for patients with chronic stable HF, irrespective of underlying anatomy.

Practical tip. In contrast to the chronic stable patient with HF, urgent directed culprit vessel angioplasty continues to be the revascularization modality of choice for patients with ACS complicated by HF.

Practical tip. In highly selected cases, patients with advanced HF symptoms in association with large areas of dyskinetic and nonviable myocardium might experience clinical improvement with surgical ventricular reconstruction (SVR) or similar type procedures, when performed by experienced surgeons.

Practical tip. Although mitral valve repair or replacement are both considered acceptable strategies for treatment of severe mitral regurgitation (MR), it should be noted that the additional use of mitral repair has not been shown to improve survival despite technical success. This is also the case for catheter-based treatment of MR.

The Canadian Association of Cardiac Rehabilitation and CCS joint position statement includes routine cardiac rehabilitation for patients with HF who successfully complete CABG surgery.[282]

RECOMMENDATION

94. We recommend that after successful cardiac surgery, all patients be referred to a local cardiac rehabilitation program (Strong Recommendation; High-Quality Evidence).

Values and preferences. These recommendations reflect our support of and conformity with preexisting rehabilitation guidelines statements.

7.2.3. Right heart failure

RHF is defined as the clinical syndrome in which the right ventricle function is impaired secondary to any structural or functional cardiac disorders leading to inadequate blood flow through the pulmonary circulation at a normal central venous pressure.[289] The most common reason for RHF is left-sided HF but occasionally RHF might occur as pure right-sided HF (Table 19).

In HF, RV dysfunction is a strong predictor of mortality.[290,291] In a study of 377 patients with chronic HF who underwent right heart catheterization, 75% of patients had reduced RV function which was an independent risk of death.[292] In another study of 250 consecutive patients with dilated cardiomyopathy it was shown that reduced RV EF $<$ 45% using magnetic resonance imaging (MRI) was an independent predictor of transplantation-free survival and worse prognosis.[293] The underlying pathophysiology of RHF might include venous congestion, RV enlargement, increased pulmonary artery pressure (PAP) and tricuspid or pulmonary valve abnormalities.

The clinical presentation of RHF is variable but typically involves fluid retention (ascites, peripheral edema), decreased systolic reserve or low cardiac output (fatigue, exercise intolerance), atrial or ventricular arrhythmias, and hypotension. Gastrointestinal symptoms like anorexia, bloating, nausea, and constipation are very common in patients with advanced RV failure. There are several medical conditions that mimic or coexist with RHF including liver cirrhosis, nephrotic syndrome, and renal failure with volume overload.

Of all physical signs of RHF, an abnormal jugular venous pressure is almost always present. In more advanced cases pitting edema, ascites, and liver enlargement are present. In the absence of elevated venous pressure, peripheral edema and ascites are unlikely to be due to RHF.

All patients with suspected RHF should undergo transthoracic echocardiography. CMR imaging has become the test of choice for noninvasive assessment of RV size, function, viability, potential etiology, and mass.[294] In selected patients with RHF, right heart catheterization should be considered to help determine etiology of RHF and provide PAP, PCWP, and PVR. PH is defined by a mean PAP of $\geq$ 25 mm Hg and increased PVR of $>$ 3 Wood units with a normal PCWP $<$ 15 mm Hg.[295]

There are very few RCTs that addressed the management of isolated RHF, recognizing that the most common cause of RHF is left heart disease. Generally, diuretics are the mainstay of therapy. Because patients with RHF might have normal or even low LV filling pressures, cautious use of diuretics is the key, because excessive diuresis can result in prerenal azotemia, hypotension, and exacerbation of arrhythmias. As such, it is not uncommon to see combination diuretic therapy to avoid excessive potassium loss or alkalosis.

Studies designed to see if treatment for LHF also ameliorates RHF failed to show benefit because these studies were underpowered or mechanisms of injury and repair might differ.[296-299]

Patients with RHF secondary to congenital heart disease or secondary to PH should be referred early to specialized clinics for investigations and management.[300,301]

Cor pulmonale term is used in cases of RHF associated with pulmonary hypertension as a result of lung disease. Determination of the etiological factor is of utmost importance because several therapies specific to the underlying cause have been developed (Table 20). For these reasons, patients with HF and PH (without LV failure) should be referred to centres with experience and expertise in the management of this disorder. In particular, patients with congenital heart disease might present with RHF due to a wide variety of specific anomalies or surgical residua. When identified, these patients should be referred to an adult congenital heart disease centre.[301]

The diagnosis of cor pulmonale should be considered in all patients with lung disease and symptoms and/or signs of RHF. The tests used for the diagnosis of cor pulmonale include chest x-ray, ECG, echocardiogram (ECHO), CT scan, ventilation/perfusion lung scanning, MRI, pulmonary function test, and right heart catheterization. In some cases lung biopsy might be required to determine the underlying cause for cor pulmonale. The treatment of PH and cor pulmonale is determined by the etiology and specific management of these patients is addressed in disease-specific

guidelines.[302,303] Patients with PH and cor pulmonale should be referred to the centres with appropriate expertise for the confirmation of diagnosis, vasoreactivity testing, and institution of appropriate treatment.

7.2.3.1. Arrhythmogenic right ventricular cardiomyopathy

ARVC is a genetic form of cardiomyopathy characterized by fatty/fibrofatty infiltration of the myocardium affecting mostly the right ventricle but occasionally the left ventricle too.[304] ARVC is an autosomal dominant inherited disease with variable penetrance and expression. Prevalence of ARVC is estimated to be 1:1000-1:5000[305,306] affecting men more frequently than women with a ratio of 1:3.[307]

ARVC should be suspected in a patient with unexplained RV dysfunction, dilation, or RHF, a history of ventricular tachyarrhythmia (particularly of LBBB morphology) or syncope, characteristic ECG changes (eg, epsilon waves), a family history suggestive of syncope or sudden death, and in young people or athletes with a history of syncope or cardiac arrest during exercise or sports activities.

In 2010, the 1994 European Society of Cardiology/International Society and Federation of Cardiology joint task force criteria for ARVC were revised by introducing quantitative measures into the criteria.[308] Current task force criteria for ARVC diagnosis include diagnostic criteria on the basis of 6 categories: typical ECG findings (eg, epsilon waves), ventricular arrhythmias (left bundle block morphology), morphological and functional changes in the right ventricle, histopathology, family history, and genetic findings. On the basis of these criteria, 3 levels for the ARVC diagnoses were established. Major and minor criteria for ARVC are listed in Table 21.[308]

Echocardiography and CMR imaging are the most commonly used tests for the diagnosis of ARVC.[309] Strain echocardiography is one of the newest modalities and it appears to be very effective in the assessment of RV function.[310] CMR imaging if available is a preferred test to echocardiography for ARVC.[311] It can provide very accurate information on LV and RV function and the presence of intramyocardial fat and fibrosis via LGE. In some patients myocardial biopsy might be useful but diagnostic sensitivity is very low because of the patchy distribution of the disease.

Genetic testing can be useful in patients with a diagnosis of ARVC however, an existing known gene mutation is present in only approximately 50% of cases. Therefore, negative gene testing does not rule out ARVC.

The primary goal of treatment of ARVC is to identify high-risk patients to reduce the risk of sudden arrhythmic death. The secondary goal of treatment is to manage symptoms of ventricular arrhythmias and RHF. To date, there have been no RCTs to determine the efficacy of pharmacological and device therapies on the prevention of sudden death. Patients with ARVC and RV or LV failure should be treated with standard medical therapy. Antiarrhythmic medications have been used frequently to decrease frequency of ICD discharges.[312] β-blockers have shown effectiveness in reducing adrenergically stimulated arrhythmias.[313]

ARVC patients at high risk for sudden death on the basis of a clinical profile with one or more risk factors for sudden death should be considered for ICD as a primary prevention.[314] For secondary prevention of sudden death in the ARVC population, ICDs are indicated.[315] Cardiac transplantation is an option for eligible patients with advanced ARVC and intractable HF or ventricular tachyarrhythmia.

Exercise has been linked to the increased risk of ventricular tachycardia secondary to the elevated levels of catecholamines during physical activity in the setting of ARVC.[316] Patients with suspected or confirmed ARVC should avoid vigorous physical activity like competitive sports, or regular activities associated with symptoms.[317,318]

All patients with ARVC should be referred to experienced centres with electrophysiology services and genetic counselling.

7.2.3.2. Constrictive pericarditis

Constrictive pericarditis is an uncommon disease of pericardium resulting from chronic inflammation and fibrosis leading to impaired diastolic filling of the ventricles with or without reduced systolic function. In developing countries, the most common reason for the constrictive pericarditis is tuberculosis.[319]

Constrictive pericarditis should be suspected in patients with unexplained RHF in whom there is a history of pericardial disease or predisposing pericardial injury. The most commonly reported symptoms are peripheral edema and exertional dyspnea. Almost all patients have abnormal jugular venous pressure. It is elevated with very prominent, deep y-descent and frequently there is an increase in the jugular venous pressure with inspiration (Kussmaul sign). Pulsus paradoxus is frequently present as are an enlarged liver and ascites.

The diagnosis of constrictive pericarditis is frequently delayed because clinical presentation is often atypical and might mimic other causes of the RHF.[320] Chest x-ray is very helpful in diagnosis of constrictive pericarditis because in 27% of cases, calcification can be seen in the pericardium.[321] In cases in which diagnosis of constrictive pericarditis is suspected, a special "constriction protocol" should be requested when ordering an ECHO.[322] It should include a focus on the motion of the ventricular septum, variation in the mitral inflow velocity, variation in the hepatic vein profile, and tissue Doppler assessment of mitral annular velocities with simultaneous recording of respiration and tissue strain.[323-325] A CT scan is helpful in the assessment of pericardial thickness and calcifications. CMR imaging can provide anatomical details, hemodynamic information, and an assessment of pericardial inflammation. When noninvasive evaluation is indeterminate, cardiac catheterization with hemodynamic assessment is the test of choice.[326]

Management includes treatment to relieve symptoms of RHF, control secondary arrhythmia, and provide timely surgical consultation for pericardiectomy. Transient constrictive pericarditis post cardiac surgery can resolve spontaneously or after a short course of anti-inflammatory medications or corticosteroids.[327]

All patients with constrictive pericarditis should be referred to experienced centres with advanced cardiac imaging, catheterization, and surgical availability for assessment and treatment. All symptomatic patients with chronic constrictive pericarditis should be considered for pericardiotomy.

Current surgical mortality rates average 6%-12%,[328,329] but can be elevated further if there is coexisting myocardial damage, extensive pericardial calcification ('outer porcelain heart'), or previous mediastinal radiation.

RECOMMENDATION

95. We recommend RHF should be considered in patients with unexplained symptoms of exercise intolerance or hypotension in combination with evidence of elevated jugular venous pressure, peripheral edema, hepatomegaly, or any combination of these findings. Echocardiography should be performed to assess cardiac structure and function, and inferior vena cava dispensability. In cases of refractory RHF, or when the diagnosis is not clear, hemodynamic assessment with complete right heart catheterization should be considered (Strong Recommendation; Low-Quality Evidence).
96. We recommend that patients with RHF secondary to or in association with left HF (LHF) should be managed as per LHF guidelines (Strong Recommendation; High-Quality Evidence).
97. We recommend judicious diuretic therapy for patients with symptomatic RHF, with a goal of euvolemia if feasible and tolerated (Strong Recommendation; Low-Quality Evidence).

Practical tip. Cor pulmonale is RHF caused by pulmonary arterial hypertension (PH), which is usually a consequence of lung disease. Cor pulmonale should be suspected in patients with PH or lung disease who also have signs and/or symptoms of RHF.

RECOMMENDATION

98. We recommend patients with PH undergo evaluation in centres with experience and expertise in the management of this disorder (Strong Recommendation; Low-Quality Evidence).
99. We recommend that right heart catheterization be considered in selected patients with right-sided HF to determine the true pulmonary artery systolic pressure, pulmonary vascular resistance (PVR), transpulmonary gradient, and pulmonary capillary wedge pressure (PCWP), and to exclude left-sided HF as the underlying cause (Strong Recommendation; Low-Quality Evidence).
100. We recommend cardiologist referral for patients with any right-sided obstructive cardiac lesion and moderate or severe right-sided regurgitant lesion for assessment of etiology, associated diseases, and treatment plan (Strong Recommendation; Low-Quality Evidence).
101. We recommend that symptomatic patients with severe right-sided obstructive or severe regurgitant lesions be evaluated and considered for surgical or percutaneous intervention at a centre with expertise and experience in the management of these conditions (Strong Recommendation; Low-Quality Evidence).
102. We recommend that patients with severe (peak gradient > 80 mm Hg) or symptomatic moderate (peak gradient 50-79 mm Hg) pulmonary valvular stenosis should be referred or considered for balloon valvuloplasty or surgical intervention (Strong Recommendation; Low-Quality Evidence).
103. We recommend bioprosthetic rather than metallic prosthesis for replacement of right-sided valvular lesions (Strong Recommendation; Low-Quality Evidence).
104. We recommend diagnosis of arrhythmogenic RV cardiomyopathy (ARVC) be made according to the European Society of Cardiology/International Society and Federation of Cardiology criteria (revised in 2010) (https://www.escardio.org/Working-groups/Working-Group-on-Myocardial-and-Pericardial-Diseases/Publications/Paper-of-the-Month/Diagnosis-of-arrhythmogenic-right-ventricular-cardiomyopathy-dysplasia) to establish a diagnosis (Strong Recommendation; Low-Quality Evidence).
105. We recommend individuals with ARVC avoid strenuous or high-intensity sports activities (Strong Recommendation; Moderate-Quality Evidence).
106. We recommend an ICD be offered to all eligible patients with ARVC who have had a cardiac arrest or a history of sustained ventricular tachycardia (Strong Recommendation; Low-Quality Evidence).
107. We recommend an ICD be considered for the prevention of SCD in eligible patients with ARVC in whom the risk of SCD is judged to be high (Strong Recommendation; Low-Quality Evidence).
108. We recommend all patients with ARVC be referred to a centre with experience and expertise in the management of this condition (Strong Recommendation; Low-Quality Evidence).
109. We recommend genetic counselling be considered for families with ARVC for the purpose of screening and/or genetic testing (Strong Recommendation; Low-Quality Evidence).
110. We recommend CT scan or CMR imaging be performed in all patients with suspected constrictive pericarditis to assess for pericardial thickening (Strong Recommendation; Low-Quality Evidence).
111. We recommend that echocardiography with Doppler assessment of ventricular filling, as well as a right- and left-sided (simultaneous) cardiac catheterization (with manoeuvres if necessary) be performed in all cases of constrictive pericarditis to confirm the presence of a constrictive physiology (Strong Recommendation; Low-Quality Evidence).
112. We recommend surgical referral for pericardiectomy be considered for patients with constrictive pericarditis and persistent advanced symptoms despite medical therapy (Strong Recommendation; Moderate-Quality Evidence).
113. We recommend that patients with symptomatic constrictive pericarditis be offered referral to a centre with expertise in the management of this condition (Strong Recommendation; Low-Quality Evidence).

Practical tip. Atrial septal defect might be difficult to diagnose and should be suspected in the setting of unexplained RHF or RV enlargement. Bubble study or transesophageal echocardiography might be required for diagnosis.

Practical tip. Patients with RHF might not have increased left atrial filling pressures and might be more sensitive to change in reduction of cardiac preload and renal dysfunction. This might manifest as light-headedness or elevation of serum creatinine level. Careful monitoring of volume status is necessary.

Practical tip. Patients with RHF might require increased doses of diuretics, which might lead to increased likelihood of hypokalemia. Judicious use of potassium-sparing diuretics might be useful in the maintenance of potassium homeostasis.

Practical tip. Carefully selected patients with advanced HF and severe pulmonary hypertension during optimal therapy might be considered for therapy with sildenafil for improvement of symptoms and exercise tolerance.

Practical tip. Ventilation/perfusion lung scanning should be used as a screening test for chronic thromboembolic pulmonary hypertension but CT pulmonary angiography or conventional pulmonary angiography will be required for the confirmation of chronic thromboembolic pulmonary hypertension diagnosis.

Practical tip. Pulmonary function testing with diffusion of carbon monoxide should be performed to determine underlying obstructive or interstitial lung disease.

Practical tip. Lung biopsy might be considered for diagnosis in cases in which the diagnosis is in doubt and will refine treatment.

Practical tip. Evaluation for lung and heart-lung transplantation should be considered for end-stage cor pulmonale.

Practical tip. Patients with trivial (mean gradient $<$ 25 mm Hg) or mild (gradient $<$ 50 mm Hg) pulmonary stenosis require no intervention or exercise limitation, but should have periodic follow-up (approximately every 5 years).

Practical tip. Patients with right-sided valvular stenosis might have underlying carcinoid syndrome or ingestion of appetite suppressants.

Practical tip. ARVC should be suspected in individuals with unexplained dilation or dysfunction of the right ventricle in whom there is a history of ventricular arrhythmia, syncope, or HF, or in whom characteristic ECG changes or a positive family history of ARVC is noted.

Practical tip. Up to 40% of patients with ARVC might have a normal ECG on initial presentation, although almost all patients will develop pathological ECG changes within 6 years.

Practical tip. Interpretation of CMR imaging for ARVC should be performed at experienced centres. An abnormal scan in isolation is not diagnostic for ARVC.

Practical tip. Endomyocardial biopsy (EMB) of the RV free wall for ARVC should be performed with extreme caution and at an experienced centre because of the high risk of myocardial perforation and cardiac tamponade.

Practical tip. Antiarrhythmic drugs or catheter ablation should not be used in the place of ICD therapy for patients with ARVC, but might be considered in patients who refuse or who are not candidates for device therapy.

Practical tip. Transthoracic echocardiography is insensitive for detecting pericardial thickening but is a useful first test for examining constrictive physiology; transesophageal echocardiography might further improve the sensitivity over the transthoracic approach.

Practical tip. When extensive calcification of the pericardium is present, CT imaging might be more effective than CMR imaging for measuring pericardial thickness.

Practical tip. Provocation testing in the cardiac catheterization laboratory, such as rapid volume loading (eg, I.V. infusion of 1 L of normal saline over 6-8 minutes) and simultaneous LV and RV measurement during respiration, might unmask hemodynamic signs of constriction in patients with early or occult forms of constrictive pericarditis.

Practical tip. The diagnosis of pericardial constriction might be difficult and is made on clinical grounds with supporting information from diagnostic testing. Despite extensive workup, information from EMB or even at open thoracotomy might be required to assist in the diagnosis.

7.3. Noncardiovascular comorbidities

Although treatments that improve survival, exercise capacity, and reduce hospitalizations have been established for HFrEF, the increased complexity of patients and their comorbidities often confound treatment. The latter issues have proven even more challenging for the HFpEF population. Comorbid conditions become risk factors for future deterioration and might contribute to clinical deterioration, complicate management, and are often associated with poor prognosis.

7.3.1. Anemia and iron deficiency

Anemia is often defined according to knowledge of normal, age- and sex-specific values of Hb, or hematocrit. The World Health Organization (WHO) defines anemia as a Hb level $<$ 130 g/dL for men and 120 g/dL for women[330]; other definitions also exist.

Anemia has a prevalence ranging from 10% to 68%[331,332]; a wide range attributable to the various definitions used and populations studied. Factors associated with anemia in chronic HF include older age, diabetes, chronic kidney disease (CKD), more advanced HF, recent HF hospitalizations, signs of HF, higher levels of neurohormones and inflammatory markers, exercise intolerance, and reduced quality of life.[333-337]

The prevalence of anemia is similar whether EF is reduced or preserved.[334,338] Although anemia in HF was once thought to be almost solely attributable to CKD; anemia and CKD are now both established independent predictors of mortality and hospitalizations for HF.[339,340] Even small reductions in Hb levels are associated with worse outcomes and even mild anemia is associated with worsening of symptoms, increased NYHA class, and impairment in functional capacity and quality of life. Anemia is associated with higher costs of hospitalization for patients with HF.[341,342] A decline in Hb over time is also associated with mortality and morbidity.[335] Therefore, there has been continued interest for more than a decade in finding appropriate treatments for anemia in patients with HF, although the underlying pathophysiology is complex and remains only partly understood. The main mechanisms include CKD, inflammation, hemodilution, absolute or relative iron deficiency (ID), rarer nutritional deficiencies (vitamin B12, folic acid, thiamine), gastrointestinal blood loss, and a few therapeutic agents with a generally low effect on Hb levels (eg, ACEis) (Table 22). In HFrEF, increased myocardial remodelling, inflammation, and volume

overload have been described as the hallmarks of patients with anemia and HF.[333]

In the CHARM studies, the effect of anemia on the primary outcome of cardiovascular death or HF hospitalization was slightly less in HFpEF than in HFrEF.[334] However, observational and population-based studies suggest that the effect of anemia on prognosis appears similar for HFpEF and HFrEF.[343,344]

As for any other group of patients, reversible causes of anemia should be sought and treated. Beyond this first step, treatment options for patients with HF include evaluation of the contribution of volume overload, of concomitant medications (eg, antiplatelet agents, anticoagulants, and especially their combination); identification of ID and treatment with oral or intravenous (I.V.) iron supplements; and optimization of HF therapy.

RECOMMENDATION

114. We recommend that anemia be investigated and reversible causes treated (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. Multiple clinical trials and population studies have shown the prognostic effect of anemia. Reversible causes of anemia are common and should be treated.

Practical tip. Anemia in patients with HFrEF is associated with more advanced HF, active ventricular remodelling processes, inflammation, renal dysfunction, and volume overload. Optimization of therapies directed at HF pathophysiology and volume control should therefore improve anemia.

7.3.1.1. Iron deficiency

Iron is necessary for optimal hematopoiesis but also plays a central role in oxygen transport (Hb), storage (myoglobin), cardiac and skeletal muscle metabolism; synthesis, and degradation of proteins, lipids, ribonucleic acids, and for mitochondrial function. ID, either absolute or functional, has emerged as another independent predictor of outcomes[332,345] and a major contributor to exercise intolerance in HF, even in the absence of anemia.[346] ID might be detected before anemia appears, thus providing an earlier opportunity in view of improving outcomes. In a cohort of 1506 patients with chronic HF, ID, defined as a ferritin level < 100 μg/L or ferritin 100-299 μg/L if the transferrin saturation was $< 20\%$, had a prevalence of 50%.[345] It is estimated that 60% of patients with HF with anemia and 40% of those without anemia have ID.[347] This definition might underestimate the prevalence of ID.

Functional ID is seen when there is a deficit in the mobilization of iron from tissues while iron stores are normal, which is frequent in chronic diseases with inflammation.[348,349] Hepcidin, soluble transferrin receptor and reticulocyte Hb have been proposed as more sensitive indices to evaluate ID.[347,350,351]

A meta-analysis by Avni and colleagues[352] had reported improvements in quality of life, 6-minute walk distance, and all-cause hospitalization with iron replacement therapy. Qian and colleagues[353] reported on the effects of I.V. iron therapy on clinical outcomes in HF, in a second meta-analysis, including a total of 907 patients from 5 clinical trials. There were no increases in adverse events with I.V. iron therapy, using iron sucrose or ferric carboxymaltose (FCM) in these studies. Most patients included in that meta-analysis came from 2 larger trials, Ferric **C**arboxymalt**o**se Evaluatio**n** on Per**f**ormance in Patients With **I**ron Deficiency In Co**m**bination With Chronic **H**eart **F**ailure (CONFIRM-HF) ($n = 301$)[354] and **F**erric Carboxymaltose **A**ssessment in Patients With **I**ron Deficiency and Chronic **H**eart **F**ailure (FAIR HF) ($n = 459$).[355] The CONFIRM-HF trial[354] included 301 patients (251 completed the trial) with moderate HF symptoms (NYHA class II-III), LVEF $\leq 45\%$, elevated BNP or NT-proBNP, and ID. I.V. iron was given as a FCM solution equivalent to 500 or 1000 mg of iron. At week 24, the primary end point of change in the 6-minute walk distance improved more in the FCM group (difference, 33 ± 11 m; $P = 0.002$). The benefit was maintained up to 52 weeks. Fatigue, NYHA class, and quality of life scores also improved on through week 52, and FCM was associated with a reduction in the risk of hospitalization due to worsening HF. The **Eff**ect of **F**erric Carboxymaltose on **E**xercise **C**apaci**t**y in Patients With Iron Deficiency and Chronic **H**eart **F**ailure (EFFECT-HF) study ($n = 173$) also recently reported benefits of I.V. FCM on peak VO_2 compared with standard of care in patients with HF, EF $\leq 45\%$, and ID.[353,356,357]

In patients with HF with anemia and ID in whom iron repletion is being contemplated, iron supplementation should be considered to improve functional capacity.[358] Oral iron has no known efficacy in this context, and therefore I.V. iron should be given considering the recently presented results from the **I**ron **R**epletion Effects **on** **O**xygen **U**p**t**ake in **H**eart **F**ailure (IRONOUT HF) study. In that study ($n = 225$), high-dose oral iron minimally repleted iron stores and did not improve peak VO_2 in patients with ID and HFrEF.[359] It is essential that the causes of absolute ID (such as iron loss) have also been investigated and treated by other means when possible (eg, endoscopy for gastric ulcer, colon cancer, etc). In such cases, concomitant I.V. iron therapy can reduce the time needed to correct anemia, as well as the need for transfusions.

Further evidence is warranted regarding the effect of I.V. iron repletion on major cardiovascular events (namely death), especially for nonanemic patients with HF and those with HFpEF. Cost-effectiveness also requires further validation with various I.V. iron formulations.

RECOMMENDATION

115. We recommend that I.V. iron therapy be considered for patients with HFrEF and ID, in view of improving exercise tolerance, quality of life, and reducing HF hospitalizations (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. The CONFIRM-HF trial, 3 meta-analyses, and the recent EFFECT-HF trial have improved the quality of evidence regarding benefits of I.V. iron therapy on the previously discussed outcome

measures but there is yet no evidence regarding benefits on mortality. Because of the rapid rate of iron repletion using the I.V. route and the available evidence, this treatment should be considered rather than oral iron repletion. Ongoing hospitalization can provide a good opportunity to facilitate I.V. iron administration.

Practical tip. ID can be difficult to diagnose in patients with HF and diagnosis should ideally be done in a clinically stable state. The most widely accepted definition is a serum ferritin < 100 mg/L or ferritin between 100 and 299 mg/L and transferrin saturation < 20%. New biomarkers, such as soluble transferrin receptor, hepcidin, and reticulocyte Hb might improve the sensitivity and specificity for the diagnosis of ID; but their clinical utility has yet to be shown.

7.3.1.2. Erythropoiesis-stimulating agents

ESAs have been studied as a potentially promising class of agents to increase Hb in HF, considering not only CKD but multiple proposed pleiotropic properties of such agents. The 2 largest trials on ESAs in HF were the **St**udy of **A**ne**mi**a i**n** **He**art **F**ailure **T**rial (STAMINA-HeFT)[360] and the **R**eduction of **E**vents with **D**arbepoetin Alfa in **H**eart **F**ailure (RED-HF) trial.[361] These 2 trials, and a meta-analysis[362] failed to show benefits on mortality, cardiovascular events, and hospitalizations. In RED-HF, a significant increase in thromboembolic events was reported in patients with Hb levels > 130 g/dL.[361] On the basis of the results of those studies, it is unlikely that another morbidity or mortality study will be undertaken with results that will support the use of ESAs in HF.

Although ESA administration is common practice in advanced CKD, the debate continues on target Hb and the effect on quality of life, which is likely higher for those with lower Hb levels.[363] Patients with advanced CKD (eGFR < 30 mL/min/1.73 m^2) should be managed in concert with nephrologists, especially when hemodialysis is contemplated. In those cases, as well as in some hemato-oncologic conditions, ESA therapy might be an option.

RECOMMENDATION

116. We recommend erythropoiesis-stimulating agents (ESAs) not be routinely used to treat anemia in HF (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation against the use of ESAs for the treatment of anemia in HFrEF at large was derived from robust data from RCTs.

Practical tip. Patients with severe CKD or hemato-oncologic conditions might benefit from an ESA and should be referred to a specialist with expertise in such treatments, for proper initiation and follow-up.

7.3.2. Diabetes (treatment)

7.3.2.1. Glycemic control in patients with diabetes and HF

With the available evidence, an intensive glycemic control strategy cannot be recommended for all patients with diabetes. Instead, each individual should be assessed for his or her optimal glycemic target for the prevention of macrovascular events.

7.3.2.2. Pharmacological therapy for type 2 diabetes in patients with HF

Metformin. Metformin is still considered first-line pharmacological therapy for type 2 diabetes.

RECOMMENDATION

117. We suggest that metformin be considered a first-line agent for type 2 diabetes treatment (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. Metformin is the current Canadian Diabetes Association first-line treatment for type 2 diabetes.

SGLT-2 inhibitors. Ongoing trials of SGLT-2 inhibitors will inform the use of the class of agents in patients with established HF. Few patients in the EMPA-REG OUTCOME trial had HF at baseline (approximately 10%), however, patients with HF had results similar to those in the overall trial.[27] There are ongoing trials of SGLT-2 inhibitors specifically enrolling patients with HF that might inform future recommendations.

DPP-4 inhibitors. There are no high-quality HF-specific studies from which to provide guidance for patients with established HF.

GLP-1 agonists. Several small trials have tested the additional use of a GLP-1 agonist in patients with HF. None have shown any additional benefit in patients with HF, with or without diabetes.[364,365]

Thiazolidinediones. Two such thiazolidinedione drugs (pioglitazone and rosiglitazone) have each been shown to increase the risk of HF events and should be avoided in patients with HF, as summarized in section *4.3.1. Glycemic Control in Diabetes to Prevent HF*.

RECOMMENDATION

118. We recommend that thiazolidinediones should not be used in patients with HF (Strong Recommendation; High-Quality Evidence).

Values and preferences: Pioglitazone as well as rosiglitazone have been shown in studies to increase the risk for HF.

7.3.3. Cardiorenal syndrome

Cardiac and renal dysfunction often occurs in concert with hemodynamic, neurohormonal, vascular, and hematologic

consequences. Previously, renal dysfunction was thought to represent merely comorbidity in patients with advanced HF. It is increasingly recognized that cardiac and renal interaction is complex. Cardiorenal syndrome (CRS) refers to interactions in which renal dysfunction and HF interact and mutually reinforce each other.[370] Mechanistic hypotheses are discussed elsewhere.[370,371] Elevated intra-abdominal pressure as well as central venous pressure are linked to rising serum creatinine levels. Elevated renal vein hydrostatic pressure is an important mechanism in volume-expanded patients.[372,373]

When managing these patients the Acute Dialysis Quality Initiative (ADQI) definition of CRS should be followed (Table 23).[371,374]

RECOMMENDATION

119. We recommend that patients with CRS should be managed by a multispecialty team that has expertise in this area (Strong Recommendation; Low-Quality Evidence).
120. We suggest that for patients with persistent volume overload despite optimal medical therapy and increases in loop diuretics, cautious additional use of a second diuretic (a thiazide/low-dose metolazone) may be considered as long as it is possible to closely monitor morning weight, renal function, and serum potassium (Weak Recommendation; Moderate-Quality Evidence).
121. We suggest that patients with CRS who develop diuretic resistance should be tried on stepped pharmacologic therapy (Weak Recommendation; Low-Quality Evidence).

Values and preferences. These recommendations place a high value on the understanding that diuretics have not been shown to improve survival but are frequently required to relieve congestion.

Practical tip. Serum potassium should be maintained at 4-5.5 mmol/L. Serum magnesium levels should be checked if there is persistent or resistant hypokalemia or the patient develops muscle cramps or ventricular arrhythmia, but has no additional proven benefit to test or replace magnesium in routine HF care.

A meta-analysis of observational studies confirms that patients with HF with moderate to severe renal dysfunction have more than a twofold increase in relative mortality risk.[366] The presence of HF in a hemodialysis population portends a poor prognosis with mean survival of < 36 months.[367]

Creatinine clearance calculated using Cockcroft and Gault,[368] **C**hronic **K**idney **D**isease **Epi**demiology Collaboration (CKD-EPI), or the Modification of Diet in Renal Disease formula[369] is used to estimate the glomerular filtration rate (GFR). Standardized and validated criteria might be useful to estimate acute changes in renal function at the bedside for patients with AHF when renal injury is a possibility. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines should be used for the classification, and evaluation of CKD (Table 24).[369] It is important to recognize that markers used in the assessment of HF including BNP and NT-proBNP might need to be interpreted with caution in the presence of acute renal failure or end-stage renal disease.

RECOMMENDATION

122. We recommend that HF patients with stable, chronic mild-to-moderate renal insufficiency (GFR > 30) should receive standard therapy with an ACEi or ARB and an MRA (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Because the isolated measurement of serum creatinine might not accurately reflect the degree of renal function we recommend using the eGFR when evaluating renal function. The standard definition of chronic renal insufficiency should be used when evaluating renal function.

Practical tip. No large, randomized, outcome trials on the use of diuretics have been conducted in patients with renal insufficiency.

Practical tip. Monitoring of electrolytes and creatinine in patients with CRS should be more frequent especially with acute illness, dehydration, and when increasing the doses of cardiac drugs, including diuretics.

Practical tip. Changes in GFR after commencing therapy are not necessarily associated with worsening outcome.

Practical tip. As a general rule, the serum creatinine level can rise or eGFR level can decrease by as much as 30% from baseline before it becomes necessary to stop or reduce the dose of the ACEi, ARB, or MRA.

RECOMMENDATION

123. We recommend that in all cases, potential reversible causes for declining renal function must be excluded and referral to a nephrologist should be considered (Strong Recommendation; Moderate-Quality Evidence).
124. We recommend that digoxin should be avoided in patients with acute renal injury and in patients with chronic, severe renal insufficiency (GFR < 30). In mild-to-moderate, stable renal insufficiency, digoxin should be used judiciously, at a low dose. As renal function declines, digoxin usage should be reassessed to avoid development of digoxin toxicity (Strong Recommendation; Low-Quality Evidence).

7.3.3.1. Role of hemodialysis

Hemodynamic stress, metabolic changes, and electrolyte shifts often occur in patients receiving hemodialysis and might be poorly tolerated. Dialysis should be considered in patients with HF with signs and symptoms of complications of renal failure.[375] Early consultation with a nephrologist is recommended for patients with acute kidney injury and in situations in which dialysis is being considered.

Before initiating dialysis, clinicians should be aware of the poor prognosis of patients with HF and end-stage renal disease (see section *8. Community Management of HF*). When initiated, clinicians and patients might have difficulty accepting the need to discontinue or continue dialysis. Common complications associated with dialysis include dehydration and electrolyte imbalance, which might lead to angina, hypotension, or arrhythmias if left untreated. A reduction in medical therapy might be necessary for effective hemodialysis to occur, and there should be caution when reintroducing these at a later time.

Medications specific to HF should be continued for patients treated with hemodialysis when possible. An RCT of carvedilol in 114 hemodialysis patients with a low LVEF and HF symptoms showed a significant reduction in mortality or hospitalization over 2 years and improvement in NYHA and LV remodelling.[376] Cohort data suggest that ACEis are associated with a reduction in all-cause mortality.[377] A single RCT of 397 high-risk patients without HF receiving hemodialysis showed a trend toward a lower event rate with the use of fosinopril.[378] Similarly, ARBs have been tested in an open-label trial in hemodialysis patients[379] and were not reported to reduce clinical events. One randomized trial of 332 patients with HF receiving an ACEi and hemodialysis showed a significant all-cause mortality reduction over 3 years with the ARB telmisartan but with significantly more hypotension and dropouts in the treatment arm.[380] These results do not alter previous recommendations on combination therapy with an ACEi and an ARB. Aldosterone blockade has been evaluated in 3 small cohorts for safety[381-383] and 1 small RCT of 16 patients with HF without significant benefits.[384] There are limited safety data and no efficacy data favouring digoxin for patients with HF receiving hemodialysis.

RECOMMENDATION

125. We recommend starting or continuing the use of ACEis/ARBs, and β-blockers in patients with HF and receiving chronic dialysis (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. The use of MRAs in hemodialysis patients with HF has been shown to reduce mortality.

7.3.3.2. Role of renal transplantation

Renal transplantation is an option for selected candidates with HF according to internationally accepted guidelines.[385] Three cohort studies have highlighted the importance of the cardiorenal interaction in patients who have undergone renal transplantation and subsequently had improvement in symptoms, LV function, and remodelling.[386,387] Postoperative adverse cardiac events were low (< 5%) in these patient cohorts.

7.3.3.3. Role of ultrafiltration

Diuretic therapy is the mainstay for relief of volume overload for AHF.[388] However, evidence-based data are sparse and diuretics have adverse effects such as activation of the neurohormonal cascade, electrolyte depletion, and renal injury.[389,390] Venovenous UF has been evaluated as an alternative therapy in this setting. Potential advantages of UF include greater control over the rate and volume of fluid removal, greater net loss of sodium, and less neurohormonal activation.[391]

In the multicentre randomized controlled **R**elief for **A**cutely Fluid-Overloaded **Pa**ti**e**nts With **D**ecompensated **C**ongestive **H**eart **F**ailure (RAPID-CHF) trial the feasibility, safety, and efficacy of early UF vs usual care in the management of AHF was assessed.[392] Early UF resulted in a trend toward greater weight loss and fluid removal at 24 hours. UF was well tolerated and the median volume of ultrafiltrate removed during a single 8-hour course of UF was 3213 mL. Dyspnea and HF symptoms were improved in the UF group at 48 hours.

In the **U**ltrafiltratio**n** versus Intravenous Diuretics for Patients Hospita**l**ized f**o**r **A**cute **D**ecompensated Congestive Heart Failure (UNLOAD) trial, early UF was compared with standard I.V. diuretic therapy in patients with AHF.[393] UF produced greater weight loss and net fluid loss over 48 hours but no difference in dyspnea scores, creatinine level, or length of stay. There was an associated decrease in HF rehospitalization at 90 days but other important clinical outcomes were not affected. The studies on UF were not powered to address major clinical outcomes, and no long-term evaluation (> 90 days) of the effect on HF or all-cause hospitalizations has been performed.

In a randomized trial **Car**idorenal **Res**cue **S**tudy in Acute Decompensated **H**eart **F**ailure (CARRESS-HF) of UF in decompensated HF with CRS, stepped pharmacologic therapy using I.V. diuretics and other medications in an organized fashion was reported to be superior to UF for the preservation of renal function, with similar weight loss. A higher percentage of patients in the UF group had a serious adverse event.[394]

The potential risks associated with UF include hypotension, bleeding, hemolysis, catheter-related complications, allergic reactions, air emboli, and worsening renal function. Currently, patients receiving UF require systemic anticoagulation, placing an additional risk of systemic bleeding. Estimates regarding the safety of UF, on the basis of the published literature, are from small RCTs and cannot be readily extrapolated to a broader population and in centres without experience and expertise in UF.

RECOMMENDATION

126. We do not recommend the routine use of ultrafiltration (UF) for the management of intractable edema in decompensated HF (Weak Recommendation; Low-Quality Evidence).

Practical tip. Although the routine use of UF for volume and symptom control in HF is not supported by trial evidence, it could be tried in refractory cases for patients in whom stepped pharmacologic therapy has failed. All forms of UF should be avoided unless it is used, as a last resort for

symptom control in a centre well versed in its use with the understanding that it could further compromise renal function and that the benefits are short-lived.

7.3.4. Sleep apnea

7.3.4.1. Sleep disordered breathing in HF

The subject of sleep apnea, generally referred as sleep disordered breathing (SDB) in patients with HF has recently been extensively reviewed.[395] There are 2 types of SDB, namely obstructive sleep apnea (OSA) and central sleep apnea (CSA), which operate through different pathophysiological mechanisms, although they can interact with each other.[396] OSA results from collapse of the pharynx. Struggling to breathe causes generation of negative intrathoracic pressure, leading to loading of the ventricles. CSA results from either a reduction in central respiratory drive or instability in feedback control of the central respiratory centre. It might be a consequence of HF, but when present, increases the risk of arrhythmias and worsen prognosis.[396]

About 40% of patients with HF have CSA and 11% have OSA.[396-398] A significant number patients with HF with SDB remain undiagnosed, possibly because of a lack of awareness and limited availability of sleep laboratories. Although nocturnal polysomnography in a sleep laboratory is the preferred diagnostic method,[399] home-based unattended sleep studies have been used as screening tools.[396] Patients with HF should be asked screening questions, such as on snoring and falling asleep during the day.

7.3.4.2. Treatment of SDB

There have been several RCTs of CPAP therapy in patients with HF and OSA or CSA. For OSA, small studies consistently showed that CPAP reversed obstructive apnea and improved oxygenation at night.[396] There are also small RCTs of CPAP in CSA, when applied for at least 1-3 months, reduced the apnea-hypopnea index and improved EF and functional class.[396] One study reported a reduction in combined mortality and heart transplantation rate in HF with CSA, but not in patients without CSA,[400] which in part prompted the conduct of the **Can**adian Continuous **P**ositive **A**irway **P**ressure for Patients With Central Sleep Apnea and Heart Failure (CANPAP) trial.[401] This study was terminated early because of a lower than expected event rate. Despite a reported 50% reduction in the apnea-hypopnea index and 6-minute walking distance, the transplantation-free survival and rates of HF-related hospitalizations were identical in both groups. Thus, data to date suggest that although CPAP alleviated CSA and improved cardiac function, its effectiveness in improving clinical outcomes remains unclear.

The adaptive servo-ventilator has been designed for the treatment of CSA and provides a baseline degree of ventilatory support, in which the patient's ventilation is servo-controlled to maintain the ventilation at 90% of the long-term average.[402] Short-term RCTs have shown abolition of CSA but an inconsistent effect on EF.[395] In the recently published Adaptive **Ser**vo **Ven**tilation in Patients With **H**eart **F**ailure (SERVE-HF) trial,[403] 1325 patients with an LVEF $\leq$ 45%, apnea-hypopnea index $\geq$ 15 events per hour, and a predominance of central events were randomized to receive medical treatment with adaptive servo-ventilation or medical treatment alone. The primary end point of death, cardiovascular interventions, and HF hospitalization, was not altered. However, all-cause mortality and cardiovascular mortality were significantly higher in the adaptive servo-ventilation group than in the control group. The ongoing Effect of **Ad**aptive Servo **Vent**ilation on Survival and Hospital Admissions in **H**eart **F**ailure (ADVENT-HF) trial (NCT01128816) might provide more insight into the role of servo-ventilation in HF.

RECOMMENDATION

127. We suggest that patients with HFrEF and CSA not be treated with adaptive servo-ventilator treatment (Weak Recommendation; Moderate-Quality Evidence).
128. We suggest that physicians treating patients with HF encourage greater involvement in their programs of experienced sleep physicians and sleep laboratories with demonstrated capacity to discriminate between OSA and CSA using contemporary diagnostic standards (Weak Recommendation; Moderate-Quality Evidence).
129. We recommend continuous positive airway pressure (CPAP) for symptom relief for patients with HF with OSA either who are limited by daytime hypersomnolence (Strong Recommendation; Moderate-Quality Evidence) or whose OSA initiates arrhythmias including AF (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. SDB treatment is complex and ongoing trials, including the ADVENT-HF trial will improve the knowledge of how best to treat patients with HF. This recommendation takes into account the value of treating OSA and the cost of diagnosis and treatment for OSA and/or CSA.

Practical tip. Because the prevalence of coexisting OSA and CSA in patients managed by HF programs remains $>$ 50% despite contemporary medical and device therapy and because most patients with HF with sleep apnea do not complain of daytime sleepiness, their evaluation should include inquiry from sleep partners into witnessed apneas, airway obstruction, and oscillating breathing patterns during sleep.

Practical tip. Consider OSA in patients with HF who present with paroxysmal or recurrent AF, hypertension refractory to optimal HF therapy, high body mass index, and unanticipated pulmonary hypertension or RV dysfunction.

Practical tip. Consider the coexistence of sleep-related breathing disorders in patients with HF when malignant ventricular arrhythmias are detected, particularly at night.

7.4. Acute heart failure

7.4.1. Diagnosis, evaluations, and investigation

The diagnosis of AHF is on the basis of a constellation of symptoms (eg, orthopnea and shortness of breath on exertion)

and signs (eg, edema and respiratory crackles) and supported by targeted investigations.[404,405] Physical examination evaluates systemic perfusion and presence of congestion.[182,405-407] Laboratory testing, ECG, chest x-ray, and ECHO are all important to obtain relatively efficiently.[406]

Clinicians should consider potential etiology and precipitating factors (Table 3). In many cases (75%-80%), a precipitant can be found (Table 25).[408,409] Failure to uncover the responsible precipitating factor might lead to intractable HF. Noncompliance with diet or medication intake, infections, arrhythmias, pulmonary embolism, and ACS are frequent situations that might cause AHF.

It is essential to perform an ECG in AHF, although it might sometimes be normal. It assists in identifying rhythm abnormalities (AF, flutter, or bradycardia and ventricular tachycardia), ACS,[410] RV, LV, or atrial hypertrophy or strain, and myopericarditis. Cardiac arrhythmias should be evaluated using a 12-lead ECG and continuous ECG monitoring. A chest x-ray should also be performed in all patients with suspected AHF within the first 1-2 hours of arrival to assess cardiac size and shape, pulmonary congestion, and other pulmonary conditions (Fig. 8).

The utility of NPs to exclude ("rule out") or confirm ("rule in") the diagnosis in the appropriate clinical scenario is well established and discussed in section *6. Biomarkers/NPs*.[57,406,411,412] Several clinical scoring systems have been derived and validated and combine commonly used clinical features with NP values to improve diagnosis and decision-making (Table 26).[413,414] One such clinical scoring system) was developed from the **Pro**BNP **I**nvestigation of **D**yspnea in the **E**mergency Department (PRIDE) study.[413]

RECOMMENDATION

130. We suggest the use of a validated diagnostic scoring system for patients in whom the diagnosis of AHF is being considered (Weak Recommendation; Low-Quality Evidence).
131. We recommend the diagnosis of AHF be established within < 2 hours of the initial contact in the ED (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a relatively high value on evaluating the constellation of clinical findings in a patient with suspected AHF and less value on an individual physical examination finding, presenting symptom, or investigation.

Practical tip. A precipitating cause for AHF should be sought.

Practical tip. An ECG, blood tests, and a chest x-ray should be performed within 2 hours of initial presentation.

Practical tip. Initial blood tests should include: complete blood count, creatinine, blood urea nitrogen, glucose, sodium, potassium, and troponin.

Practical tip. A transthoracic ECHO should be performed within 72 hours of presentation. For patients with a previous ECHO, another is not required unless there has been a significant change in clinical status requiring investigation, a lack of clinical response to appropriate therapy, and/or it is > 12 months since the previous ECHO.

7.4.2. Initial and ongoing treatment

Oxygen should be used cautiously in normoxic patients because of concerns of increasing systemic vascular resistance and reducing cardiac output.[415,416] There is a paucity of evidence to support the use of I.V. morphine to treat dyspnea, and data suggest there might be adverse effects, even after accounting for the severity of illness, comorbid conditions, and cointerventions (Fig. 9).[417-419]

RECOMMENDATION

132. We recommend supplemental oxygen be considered for patients who are hypoxemic; titrated to an oxygen saturation > 90% (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places higher value on the physiologic studies showing potential harm with the use of excess oxygen in normoxic patients and less value on long-term clinical usage of supplemental oxygen without supportive data.

133. We recommend that morphine not be used routinely in patients with AHF (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places higher value on large epidemiological studies with appropriate methods showing harm with the use of morphine in patients with AHF.

BiPAP or CPAP should be considered for patients with a high respiratory rate (eg, > 25 breaths per minute) and persistent systemic arterial hypoxemia despite high-flow oxygen administration.[420,421] However, routine use of noninvasive ventilation (NIV) is not advisable. In the **Three** Interventions in **C**ardiogenic **P**ulmonary **O**edema (3CPO) trial,[417] patients with acute pulmonary edema were randomized to standard oxygen therapy, CPAP, or NIV, and followed to the primary end point of 7-day mortality. There was no difference between the 3 arms on 7-day mortality rate and 30-day mortality rates, intubation rates, or admission to an intensive care unit. Therefore NIV should be used only in patients with acute respiratory distress unresponsive to medical therapy. NIV carries the risk of worsening RHF, hypercapnia, aspiration, and pneumothorax. Endotracheal intubation might be used if less invasive modes of oxygen delivery fail or if the patient is in cardiogenic shock.

RECOMMENDATION

134. We recommend that CPAP or bilevel positive airway pressure (BiPAP) not be used routinely in/for patients with AHF (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places high weight on RCT data with a demonstrated lack of efficacy and with safety concerns in routine use. Treatment with BiPAP/CPAP might be appropriate for patients with persistent hypoxia (peripheral O_2 saturation < 90%), high respiratory rate (> 25 breaths per minute), and pulmonary edema despite other appropriate therapies.

Oral and I.V. diuretics remain the mainstay of early therapy directed toward AHF (Table 27).[422] Diuretics generally lead to excretion of sodium and water, leading to a decrease in extracellular fluid volume, total body water, and sodium. A reduction in cardiac filling pressures, peripheral congestion, and pulmonary edema usually follow.[423] I.V. loop diuretics might cause an early decrease in right atrial pressure and PCWP. When using high I.V. doses reflex vasoconstriction might occur. In AHF, by normalizing loading conditions, these high doses might reduce neurohormonal activation in the short-term.[424]

Diuretic therapy may be initiated in the ambulance,[425] HF clinic, or in-hospital. Combining loop diuretics with thiazides[426,427] or spironolactone[428] has been proposed and appears effective, with fewer side effects than a higher dose of a loop diuretic. In patients with severe edema, oral loop diuretics might not be adequately absorbed and might be of little use.[406] Using stepped pharmacologic diuretic therapy is a useful approach and has been used as the control arm in the CARRESS-HF trial (Fig. 10).[394]

The **D**iuretic **O**ptimization **S**trategies **E**valuation (DOSE) trial enrolled 308 patients with AHF and tested 2 I.V. strategies (high- vs low-dose furosemide; continuous infusion vs bolus intermittent dose) for the primary end point of global symptom assessment and creatinine at 72 hours.[422] There was no difference between the continuous infusion and bolus dosing in either symptoms or renal function. There was greater early symptom improvement with high- compared with low-dose diuretics without a difference in renal function. A number of secondary end points favoured high-dose: a greater diuresis, more weight loss, and a lower NT-proBNP resultant level. A systematic review of 9 additional small trials showed similar findings (Fig. 11).[429] Thus, there is no advantage in the routine use of continuous diuretic infusions and a higher dose of diuretics could be considered for many patients, with careful observation of renal function and electrolytes. Diuretic responsiveness is another consideration and metrics for the re-evaluation of a patient's individual response have been reported.[425,431] For example, weight loss (or urine output) per diuretic dose unit have been retrospectively evaluated to identify patients with a poor response to diuretics (over 1 day losing < 0.4 kg per 40 mg furosemide) as those at higher risk for short- and long-term morbidity.[430]

RECOMMENDATION

135. We recommend that I.V. diuretics be given as first-line therapy for patients with pulmonary or peripheral congestion (Strong Recommendation; Low-Quality Evidence).
136. We recommend that for patients requiring I.V. diuretic therapy, furosemide may be dosed intermittently (eg, twice daily) or as a continuous infusion (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. When acute congestion is cleared, the lowest dose that is compatible with stable signs and symptoms should be used.

Practical tip. Target 0.5-1.0 kg of weight loss per 24-hour period while a patient with volume overload is actively diuresing. Patients who are losing < 0.5 kg per day despite at least 40 mg of I.V. furosemide will need a reassessment of fluid status and might be diuretic resistant.

Practical tip. When transitioned from I.V. to oral diuretic therapy, the stability of symptoms, weight, and hemodynamics should be observed for approximately 24 hours before hospital discharge.

Practical tip. To transition a patient to oral diuretics, be aware that the oral version of furosemide has approximately 50% bioavailability compared with I.V. furosemide.

Vasodilators have not been shown to convincingly reduce mortality or reduce rehospitalization rates.[432] I.V. isosorbide dinitrate (in conjunction with low-dose furosemide) was tested against low-dose nitrates with high-dose diuretics.[433] This prehospital trial of 110 patients showed that the strategy of high-dose nitroglycerin (compared with high-dose I.V. diuretics) reduced mechanical ventilation rates, and improved oxygen saturation. The **V**asodilatation in the **M**anagement of **A**cute **C**HF (VMAC) trial compared nesiritide, nitroglycerin, or placebo combined with standard therapy for 3 hours, followed by nesiritide or nitroglycerin combined with standard treatment for 24 hours in AHF.[434] The primary end points of changes in PCWP and patient self-evaluation of dyspnea at 3 hours were improved with nesiritide vs placebo. However, nitroglycerin improved early, short-term dyspnea assessment compared with placebo. The **A**cute **S**tudy of **C**linical **E**ffectiveness of **N**esiritide in **D**ecompensated **H**eart **F**ailure (ASCEND-HF) trial tested nesiritide vs placebo in 7141 patients with AHF enrolled within 24 hours of first I.V. medication.[435] Nesiritide did not reduce mortality, rehospitalization, or the composite of these end points at 30 days. Dyspnea was modestly improved at 6 and 24 hours. The use of nitroprusside in AHF has not been supported by adequately powered RCTs. However, observational studies support its use in advanced HF by clinicians with experience and expertise in managing low-output acute or sub-AHF.[436] I.V. serelaxin, a vasodilator, was tested in the **Pre**liminary Study of **Relax**in for the Treatment of **A**cute **H**eart **F**ailure? (PRE-RELAX) trial of 234 patients and had a modest improvement in dyspnea compared with placebo. The **Relax**in for the Treatment of Acute **H**eart **F**ailure (RELAX-AHF) trial tested serelaxin vs placebo in 1161 patients with AHF with a SBP > 125 mm Hg and enrolled within 16 hours of attending the ED. Serelaxin reduced dyspnea measured using a visual analogue scale over 5 days but not using a Likert scale over 24 hours. There was no reduction in the secondary end points of cardiovascular death, hospitalization for heart or renal failure, or days alive out of hospital up to 60 days, but a reduction in mortality at 180 days was seen. There are ongoing trials of serelaxin. There was no clinically meaningful improvement in outcomes with early upfront use of ularitide or TRV-027.[437,438]

RECOMMENDATION

137. We recommend the following I.V. vasodilators for relief of dyspnea in hemodynamically stable patients (systolic blood pressure [SBP] > 100 mm Hg):

i. Nitroglycerin (Weak Recommendation; Moderate-Quality Evidence);
ii. Nesiritide (Weak Recommendation; High-Quality Evidence); or
iii. Nitroprusside (Weak Recommendation; Very Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the relief of the symptom of dyspnea and less value on the lack of efficacy of vasodilators or diuretics to reduce hospitalization or mortality.

Practical tip. In situations in which I.V. nitroglycerin is not appropriate or available, repeated sublingual nitroglycerin, a nitroglycerin patch, or oral isosorbide dinitrate might be useful for dyspnea relief in patients with a SBP $>$ 100 mm Hg.

Inotropic agents have not been shown to improve patient outcomes.[406,439-441] The **O**utcomes of a **P**rospective **T**rial of **I**ntravenous **M**ilrinone for **E**xacerbations of **C**hronic **H**eart **F**ailure (OPTIME-CHF) trial randomized 951 patients admitted for HF to a 48-hour infusion of milrinone or placebo.[440] New-onset atrial arrhythmias, worsening HF, and symptomatic hypotension requiring intervention occurred more frequently in the milrinone group. A nonsignificant increase in the number of deaths in-hospital and after 60 days was seen in the milrinone group. A post hoc analysis showed a higher incidence of death or rehospitalization in patients with underlying ischemic HF etiology.[441] Trials using levosimendan have not shown additional benefit compared with placebo[442]; omecamtiv mecarbil is undergoing further testing in a RCT.[443] Low-dose dopamine has been studied in the context of AHF[444,445] and does not improve clinical symptoms, renal function, or reduce clinical events.

RECOMMENDATION

138. We recommend that hemodynamically stable patients not routinely receive inotropes like dobutamine, dopamine, levosimendan, or milrinone (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation for inotropes places a high value on the potential harm shown when systematically studied in clinical trials and less value on potential short-term hemodynamic effects of inotropes.

Practical tip. I.V. vasoconstrictor agents (eg, phenylephrine, norepinephrine) should generally be avoided for AHF management except for hypotensive patients with SBP $<$ 90 mm Hg, associated signs or symptoms, end-organ damage, and a significant change from baseline.

Practical tip. In patients with low SBP ($<$ 90 mm Hg), low cardiac output and either euvolemia or hypervolemia, inotropes may be used for stabilization.

An ACEi (or ARB) should not be started as de novo therapy in the acute setting (eg, the first 8-12 hours) unless an elevated SBP is present, but should be initiated after the acute event (eg, $>$ 24 hours), and be continued particularly if the patient is already being treated with chronic ACEi or ARB therapy. There are no data on initiating an ARNI in this situation.

Continuation of a β-blocker upon admission for AHF is considered safe on the basis of the limited data available, including patients receiving inotropes.[446,447] In an RCT of 169 patients with AHF, patients either discontinued β-blockade for 3 days or continued the medication unchanged. The trial showed that continuing the β-blocker was noninferior for the primary end point of dyspnea and well-being and was associated with a higher rate of β-blocker prescription at 3 months.[447]

RECOMMENDATION

139. We recommend continuation of chronic β-blocker therapy in a patient with AHF, unless the patient is symptomatic from hypotension or bradycardia (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. A major reduction in dose or abrupt β-blocker withdrawal should be avoided in the case of worsening HF. If the patient is hypotensive, consider reducing the dose of other medications before reducing the β-blocker dosage. Temporary discontinuation might occasionally be necessary in patients with shock. Whenever possible, reinstitution of treatment should be attempted before hospital discharge.

Vasopressin receptor antagonists (eg, tolvaptan) can rapidly and effectively reduce body weight and restore serum sodium in patients with significant symptomatic hyponatremia with hypervolemia and congestion.[448,449] The use of a vasopressin antagonist has not yet been associated with mortality or rehospitalization reduction.[450] A subgroup of 11% and 3% of the patients in the **E**fficacy of **V**asopressin Antagonism in **H**eart Failu**re** Outcome **S**tudy With **T**olvaptan (EVEREST) trial had a serum sodium $<$ 135 mmol/L and $<$ 130 mmol/L respectively, and in post hoc analysis, the latter patients had an association with fewer clinical events when treated with tolvaptan.[451]

RECOMMENDATION

140. We suggest that tolvaptan be considered for patients with volume overload, hyponatremia ($<$ 130 mmol/L), and symptoms of hyponatremia for the short-term correction of hyponatremia and associated symptoms (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places higher value on the correction of symptoms and complications related to hyponatremia and less value on the efficacy of vasopressin antagonists to reduce HF-related hospitalizations or mortality.

7.4.3. Initial and ongoing monitoring and disposition decisions

The extent of monitoring will depend on the disease severity and the response to therapy.[406] Vital signs (including

BP, heart rate, O_2 saturation, and daily weight) should be measured on a regular basis until stabilization. Laboratory tests should be repeated regularly (eg, daily in the first 2-3 days): electrolytes, creatinine, and complete blood count, if abnormal. Electrolyte abnormalities, especially hypokalemia, which has been linked to ventricular arrhythmias,[452] should be prevented or corrected promptly. There is limited evidence to support measurement or replacement of magnesium in patients with AHF. Significant renal impairment might require more frequent laboratory testing.

Decisions to admit a patient from the ED to hospital are complex and require integration of the patient's clinical stability and preferences and health system features including the availability of appropriate outpatient follow-up. In Canada, 60%-80% of patients in the ED are admitted with AHF.[446] Whereas there are HF risk models to determine overall mortality risk, there are few instruments to guide clinicians which patients need admission to hospital, continued observation, or discharge home with close follow-up.[453] One instrument developed from prospectively collected data on 1033 patients with AHF created a nomogram for predicting 5- and 30-day clinical events.[454] Using different risk of future event thresholds, the nomogram identified a group of patients potentially eligible for safe ED discharge. Two other Canadian studies have developed prognostic risk scores that are as yet tested in RCTs. Table 28 highlights key considerations for these decisions; also see Table 29.

Clinical deterioration despite initial therapy requires closer supervision, such as transfer to an intensive care unit.[455] Patients in cardiogenic shock or those who have difficulty voiding should have a urinary catheter to monitor urinary output; however, recording of "ins/outs" (also known as fluid balance) is not necessary in all clinically stable patients and can require significant resources to obtain accurately.[406] The decision to insert an arterial line depends on the need for either continuous analysis of BP because of hemodynamic instability or the requirement for repeated arterial blood gas analyses.[406] The use of a central I.V. line depends on the need for delivery of fluids and drugs or for monitoring central venous pressure and oxygen saturation. However, in the critically ill, right atrial pressure does not correlate well with left-sided filling pressures.[456] The insertion of a pulmonary artery catheter is not usually necessary for making a diagnosis or ongoing management of AHF.[457-459] It might, however, be useful to distinguish between cardiogenic and noncardiogenic shock, to guide therapy in the presence of severe diffuse pulmonary disease, or in hemodynamically unstable patients who do not respond in a predictable fashion to therapy.[460]

RECOMMENDATION

141. We recommend that a pulmonary artery catheter not be used routinely in patients with AHF (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Tailored hemodynamic therapy with a pulmonary artery catheter under experienced supervision might be clinically useful in highly selected cases, such as ongoing HF accompanied by CRS, poor response to therapy or systemic hypotension, or as evaluation for advanced therapies (MCS or heart transplantation).

7.5. Special circumstances

7.5.1. Cardiomyopathies

7.5.1.1. HCM

HCM is a disease of the myocardium characterized by pathological and disproportionate hypertrophy of the left ventricle and, sometimes, the right ventricle. It is most often an inherited condition with an autosomal dominant pattern with variable penetrance. The onset of HCM can occur in early as well as late adulthood,[461] with a risk of sudden death, often at a young age. Most patients with HCM are asymptomatic.[462] Symptoms and signs might include chest pain, dyspnea, palpitations, or syncope. Symptoms can arise as a consequence of LV outflow tract obstruction (with secondary MR), tachyarrhythmia (especially ventricular tachycardia and AF), and myocardial ischemia; chest pain is common, even in the absence of CAD[463] and impaired diastolic function or systolic dysfunction. In a small percentage of cases, the disease progresses to a burnt-out phase, with the development of severe systolic dysfunction that resembles dilated cardiomyopathy (Table 30).[463,464]

HCM should be suspected in any individual who presents with unexplained ventricular hypertrophy, heart murmurs (from dynamic outflow obstruction), abnormal ECG patterns (pseudoinfarction, giant negative T waves), unexplained syncope (particularly in young athletes), or a positive family history. A number of hereditary syndromes (including Friedreich ataxia,[465] and LEOPARD syndrome[466]) have also been linked to HCM. Approximately 30% of the cases are diagnosed de novo in elderly patients.[467]

Transthoracic echocardiography (with or without contrast) is the imaging modality of choice, and might include a provocative test for dynamic LV outflow tract obstruction. CMR imaging may be used if initial imaging results are nondiagnostic and might provide other structural details.[468] Tissue Doppler imaging might aid in early diagnosis.[469] Localized hypertrophy of the interventricular septum is the most common pattern of hypertrophy, but other patterns are also possible. Dynamic LV outflow obstruction occurs in approximately 30%-50% of cases and might be latent.[470] Differentiation must be made from other pathologies that mimic HCM in appearance, including concentric hypertrophy due to systemic hypertension, physiological hypertrophy seen in trained athletes, and discrete/disproportionate upper septal hypertrophy in elderly patients.

Practical tip. All first-degree relatives of patients with HCM should be screened for the disease with an ECG and echocardiography.

Practical tip. HF symptoms in patients with HCM might be due to diastolic dysfunction (most common), outflow tract obstruction (less common), rhythm disturbance, or concomitant valvular or ischemic heart disease (Table 30).

7.5.1.2. Restrictive cardiomyopathy and constriction

Restrictive cardiomyopathy (RCM) as the etiology of HF can be difficult to recognize and is the least common category among the cardiomyopathies.[471,472] It is characterized by myocardium with markedly stiff ventricular walls, restrictive

ventricular filling, and reduced diastolic volume of either or both ventricles, and normal or near-normal systolic function.[472,473] Myocardial fibrosis, infiltration, or endomyocardial scarring is responsible for the diastolic dysfunction.[473] Consequently, RCM shares similar functional characteristics with constrictive pericarditis, and differentiation between the two might be difficult but imperative because surgery might potentially cure the latter.[471] Amyloidosis is a frequent cause, but many other situations might also result in RCM. Rare hereditary forms of RCM have been described, such as troponin I gene mutations or in association with skeletal muscle disease (Table 31).[473,474] Prognosis of patients varies substantially, but it is generally one of inevitable downward symptomatic progression with a high mortality.[475]

7.5.1.2.1. Specific imaging and diagnostic tests for restrictive cardiomyopathies and constriction

There are a number of selected tests that will aid either the diagnosis, prognosis, or a selection of appropriate therapy for patients with a suspected RCM or constriction. These are presented and discussed in the following sections. Not all laboratory or imaging tests are readily available in all regions, and therefore, expertise should be sought where necessary.

7.5.1.2.2. Physical examination and ECG

Patients usually exhibit typical symptoms and signs of HF, including Kussmaul sign that might be disproportionate to the degree of systolic or valvular dysfunction. Hepatomegaly, ascites and, in more advanced cases, anasarca, might be present. Notably, the apex beat is usually palpable in RCM, but not in constrictive pericarditis.[473] The ECG is frequently abnormal with decreased voltage intraventricular conduction delay, or poor R wave progression mimicking MI.[476] Sinus node disease is frequent, and typical characteristics of the sick sinus syndrome are encountered.[477] Arrhythmias, mostly AF, are frequent and might be caused by amyloid deposition.[478]

7.5.1.2.3. Laboratory findings

Specific morphological features (especially musculoskeletal) in the setting of renal disease and a family history of metabolic abnormalities suggest the presence of an infiltrative disorder, such as Fabry disease. Fabry disease is a rare X-linked disorder that can present with neuropathy, renal failure, and HF in affected men and hemizygous women. Genetic testing can determine the exact gene defect, but elevated urinary globotriaosylceramide, and reduced plasma α-galactosidase activity are diagnostic.[479] These disorders usually require tissue diagnosis, either from cardiac tissue or other affected organs, such as the kidneys.

Abnormalities in serum protein electrophoresis suggest amyloidosis, whereas a high plasma level of ferritin, in combination with increased transferrin saturation, suggests hemochromatosis. Ventricular arrhythmias might be a forerunner for sudden death, and a signal-averaged ECG has been suggested to help in identifying patients at risk.[480]

An abdominal fat aspirate is safe and might assist in the diagnosis of amyloidosis. If the result of an abdominal fat aspirate is negative, EMB might help if cardiac amyloidosis is suspected, and kidney biopsy might also be useful if the eGFR is low, suggesting renal involvement. Immunohistochemical staining should be performed because it helps to differentiate between systemic senile, familial, and primary forms of amyloidosis, and clarifies prognosis and management, which differ in the various forms.[481,482] Unsuspected hereditary amyloidosis might be present in nearly 10% of patients thought to have the primary amyloid light-chain form.[483] The absence of concomitant symptoms and signs of systemic illness, nonspecific laboratory findings, and negative EMB strongly suggest idiopathic RCM.

7.5.1.2.4. Imaging

Echocardiography might be normal early on, but small ventricular chambers with increased wall thickness, large atria, and thickening of valvular apparatus and interatrial septum are often seen. LV systolic function is usually normal, but might be reduced in advanced disease. Pericardial effusion is common, but rarely results in tamponade.[484] The sparkling appearance of the thickened walls, presumably related to amyloid deposition, was previously believed to be typical on echocardiography, but is less reliable compared with recent technology.[485] Doppler echocardiography is useful for the diagnosis, prognosis, and should be evaluated carefully in centres with experience and expertise.[486,487]

CMR can precisely image functional, morphological changes,[488] fibrosis,[489] and inflammation[490] and might provide early insight into the disease process and etiology. CMR is useful in amyloidosis,[491] with subendocardial contrast enhancement associated with nonsuppressible signal of remote myocardium. CMR might increase the sensitivity of myocardial biopsy,[492] and might help to direct treatment.[493] CMR might be helpful in distinguishing between active myocardial disease and clinical remission in systemic lupus erythematosus,[494] documenting the presence of cardiac fibrosis in Churg-Strauss syndrome, a rare form of systemic vasculitis,[495] and detecting early indications of iron overload in thalassemia patients.[496]

Scintigraphy with technetium-99m pyrophosphate, as well as with other agents that bind to calcium, is frequently positive, with extensive amyloid infiltration. Scanning with specialized agents might also identify sympathetic denervation in patients with cardiac amyloidosis.[497]

7.5.1.2.5. Hemodynamic findings

The characteristic hemodynamic feature of RCM as well as constrictive pericarditis on cardiac catheterization is a rapid early decrease in ventricular pressure at the beginning of diastole, with a rapid increase to a plateau in early diastole (this latter finding might be absent in RCM)—the 'dip and plateau' or 'square root' sign. Systemic as well as pulmonary venous pressures are elevated (frequently > 50 mm Hg in RCM, although lower in constrictive pericarditis), and patients with RCM typically have LV filling pressure that exceeds RV filling pressure by more than 5 mm Hg (this difference can be revealed by exercise, fluid challenge, or the Valsalva manoeuvre). In constrictive pericarditis, filling pressures are similar in both ventricles, and the plateau of the RV diastolic pressure is usually at least one-third of the peak RV systolic pressure, but is frequently lower in RCM. In the setting of rapid early diastolic ventricular filling, an increase in RV peak systolic pressure during inspiration might occur with a reduction of LV peak systolic pressure.

Differentiating between RCM and constrictive pericarditis might be difficult and thus multiple modalities in centres experienced with these techniques is important. EMB and CT might also be useful for differential diagnosis; however, in rare cases, open biopsy might be required.[471]

Practical tip. Radionuclide ventriculography, CMR and/or echocardiography can be used to noninvasively determine RV EF and other measures of RV function.

7.5.2. Ethnicity

On the basis of a Statistics Canada 2006 census,[498] the visible minority population surpassed 5 million, reaching 16.2% of the population. In Ontario, more than 1.5 million people are of Chinese, South Asian, black, or Aboriginal descent. To understand and manage a person's illness it is necessary to appreciate the effects of the person's culture and social environment. This is perhaps most relevant in the health care management of minority groups. Morale is crucial to the patients' adaptation and their maintenance of involvement in their management; miscommunications as a result of ethnocultural differences might have a detrimental effect on their adaptation to their illness. Furthermore, health care providers might contribute to the ethnic care disparities through clinical uncertainty and stereotyping of health behaviours related to minority patients.[499] However, the use ethnicity as a way to differentiate patients might be debatable and differential medical treatment on the basis of the colour of one's skin has been associated with detrimental outcomes for ethnic minorities.[500] A significant contributor is the paucity of research to clearly identify the sources of these differences in outcomes in ethnic groups and to distinguish among biological, environmental, or social causes of disease differences.[501] Evaluation of disease differences in subsegments of the population is needed to understand the mechanisms of pathophysiology and to optimally target therapeutic responses. Thus, effective research that would contribute to a reduction in health care disparities requires collection of data on health status in ethnic populations and assessment of differences in disease patterns. It also requires clinical trials to include adequate numbers of diverse populations to probe for differences in pathophysiology including environmental or social factors contributing to disease and responses to treatment. Where differences are observed among population segments, clinical trials focused in these population groups are warranted.[501,502]

7.5.2.1. General considerations

There have been very few published population-based epidemiological studies or large-scale randomized controlled studies of HF in countries outside North America, Europe, and Australia,[503] regions from which most of the minority groups that reside in the Western countries emigrated. For example, it is generally believed that rheumatic heart disease and congenital heart disease remain important causes of HF in sub-Saharan Africa and certain parts of Asia and South America. Hypertension is thought to be an important cause of HF in Asia, and in the African and African American population, whereas Chagas disease is an important etiology in subjects from South America.[504] Although it is useful to remember region-specific etiologies of HF particularly when managing recent immigrants from the regions where the minority groups were resident, it should be remembered that because these regions also constantly undergo epidemiological and economic transitions the epidemiology of HF is likely to be increasing similar to that of the Western world. The INTERHEART study has shown that the effect of conventional and potentially preventable risk factors on the risk of MIs are consistent across different geographical regions and different ethnic groups.[505] This implies that simple measures that can prevent MI and likely the subsequent development of HF are equally applicable to different ethnic populations in different geographic locations. The recently published **Ca**rdiovascular **He**alth in **A**mbulatory Care **R**esearch **T**eam (CANHEART) Immigrant study[506] shows that most immigrant groups in Canada have lower rates of major cardiovascular events than long-term residents of similar age; striking variations in the event rates exist between immigrants from different ethnic background. East Asian immigrants, predominantly of Chinese descent, had the lowest burden of risk factors and events overall, although the event rate increased with greater duration in Canada. There are also high-risk groups such as South Asian immigrants, who had a high burden of traditional risk factors and frequent cardiovascular events. In general, patients in the Asia Pacific region have historically less CAD as etiology, onset at younger age, fewer uses of devices, more diabetes, and more uses of parenteral agents during acute episodes.[507]

There is little evidence to indicate that criteria used to diagnose HF differ between ethnic populations. For example, a recent study from the United States has shown that the diagnostic performance of the biomarker N-terminal BNP is similar in African American and non-African American individuals.[508] Evidence that different ethnic groups have the same mortality benefit from current standard therapy is scant because very few large RCTs have included regions outside Europe and the United States. There have been smaller trials that confirmed the effectiveness of ACEis and β-blockers in patients from Africa and Asia.[504,509] Because of the fundamental nature of the derangements in HF, it is likely that the current treatment approach such as blockade of neurohormonal activation and the judicious use of devices will be similarly effective, although one cannot rule out the possibility that the degree of response to treatment might vary among ethnic groups. Details that pertain to specific minority populations are available in section *7.5.2.2* of the Supplementary Material. Recommendations and practical tips on the management of patients with HF from the 4 largest ethnic minority groups in Canada are shown in Table 32.

7.5.3. Pregnancy

HF during pregnancy has a number of potential etiologies including PPCM. Preconception counselling is recommended in women with inheritable and/or a known history of HF or PPCM. Maternal risk assessment and frequency of expert follow-up should be scheduled as recommended by the modified WHO risk classification.[510,511] High-risk patients should be referred to a multidisciplinary team with expertise in the management of HF and high-risk pregnancy.[512-514]

7.5.3.1. Diagnosis and management

Hemodynamic changes in normal pregnancy can precipitate HF in patients who are susceptible or have another underlying etiology (Table 33). Decompensation can occur at any time; however it is more common in the late stages of pregnancy and peripartum. Physical examination for HF-related physical signs can be challenging in pregnancy. It is important for clinicians to recognize cardiovascular symptoms and signs that are not normally present in pregnancy (Table 34). Echocardiography remains the preferred imaging modality for HF during pregnancy. Women with AHF during pregnancy should be managed according to the guidelines for AHF and should be referred to a tertiary care centre with expertise in advanced HF management, including MCS and cardiac transplantation.[515,516]

7.5.3.2. Medical therapy of HF in pregnancy

HF in pregnancy should be treated according to the CCS HF guidelines for acute and chronic HF. However, many standard therapies of HF are considered fetotoxic and should not be used during pregnancy including ACEis, ARBs, and MRAs.[517,518] There are no data on the use of ARNIs and thus they are not recommended during pregnancy. When β blockade is used, β1-selective drugs (eg, metoprolol) should be preferred. Atenolol should not be used.[519] Diuretics can be used if pulmonary congestion is present. Medications that might be used for pregnant women with HF are shown in Table 35. An additional comprehensive list of medications is available at www.motherrisk.org.[515,516]

7.5.3.3. PPCM

PPCM is a diagnosis of exclusion typically defined as HF with an LVEF of < 45% within 1 month before delivery to 5 months postpartum. Pathophysiologic mechanisms are not clearly defined but might include genetic predisposition,[520] oxidative stress, and immune mechanisms,[521,522] as well as viral infections[521] and prolactin.[523] Risk factors for the developments of PPCM include multiparity and multiple fetal gestation, advanced maternal age, family history, ethnicity, hypertension, preeclampsia, smoking, diabetes, and prolonged tocolytic therapy.[524]

In addition to standard diagnostic tests for HF and pregnancy, there is now data to support the use of biomarkers for diagnosis as well as prognosis in PPCM.[525,526] There have been several case reports and a small RCT to evaluate bromocriptine[527] with inconclusive results and uncertain safety.[528-530]

Despite advances in HF treatment mortality as well as morbidity related to PPCM remains high. In case series, LV systolic function returns to normal in 23%-72% of patients.[524,531-533] Less is known about the risk of subsequent pregnancy; however, the 2 largest studies of PPCM suggest relapse occurs in almost one-third of the cases.[534,535] Thus most would agree that individualized counselling should occur in individuals with PPCM and they should be advised against future pregnancy particularly if recovery of LVEF has not occurred.[524,536]

RECOMMENDATION

142. We recommend that pregnant women (or those in the peripartum period) with AHF should be managed according to the CCS guidelines for AHF and should be referred to a tertiary centre with expertise in advanced HF management, including MCS and cardiac transplantation (Strong Recommendation; Low-Quality Evidence).
143. We recommend that NPs be used for diagnostic and prognostic purposes in peripartum cardiomyopathy (PPCM) (Strong Recommendation; Low-Quality Evidence).
144. We recommend that bromocriptine not be used routinely for PPCM (Strong Recommendation; Low-Quality Evidence).

Values and preferences. Adequately powered and appropriately designed RCTs have not been completed. The safety of bromocriptine is not well established.

145. We recommend that echocardiography be performed in women with worsening or suspected new-onset HF during pregnancy (Strong Recommendation; Low-Quality Evidence).
146. We recommend prepregnancy counselling in all women with a known history of HF or PPCM (Strong Recommendation; Low-Quality Evidence).
147. We recommend preconception genetic counselling in women with inheritable cardiac diseases that can affect cardiac function, including inheritable cardiomyopathies (Strong Recommendation; Low-Quality Evidence).
148. We recommend maternal risk assessment and frequency of expert follow-up should be determined using the modified WHO risk classification (Strong Recommendation; Low-Quality Evidence).
149. We recommend that decisions regarding timing and mode of delivery should be on the basis of obstetrical factors (Strong Recommendation; Low-Quality Evidence).

Values and preferences. Cesarean deliveries are not routinely necessary and might additional risk to patients with HF. Delivery before term for cardiac decompensation is rarely required.

Practical tip. Vaginal delivery is preferred in women with stable cardiac conditions.

RECOMMENDATION

150. We recommend that patients with PPCM who do not recover normal LV function should be advised against future pregnancies because of the high risk of worsening HF and death (Strong Recommendation; Moderate-Quality Evidence).
151. We recommend that patients with PPCM who recover normal LV function should be advised regarding the potential for recurrent LV dysfunction in subsequent pregnancies (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. The risk of thromboembolism associated with PPCM is increased because of the hypercoagulable state of pregnancy, and is highest during the first 6 weeks postpartum.

RECOMMENDATION

152. We recommend that several commonly used cardiac medications should be avoided because of teratogenic effects during pregnancy and with caution during lactation (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Women with HF during pregnancy should be closely followed and monitored at the time of delivery and the early postpartum period.

Practical tip. Echocardiography is the preferred imaging modality for HF during pregnancy. Postpartum imaging can include CMR imaging for more accurate detection of changes in cardiac function and higher sensitivity for the detection of thrombus.

7.5.4. Cardio-oncology and HF

Cancer therapy might result in subclinical and clinical LV dysfunction. The CCS recently published guidelines for evaluation and management of cardiovascular complications of cancer therapy.[55] Specific recommendations, from that document, related to the development and treatment of LV dysfunction are presented in this document for ease of review; the content has not been modified. Readers are directed to the CCS guidelines for evaluation and management of cardiovascular complications of cancer therapy for a discussion of the evidence underpinning these recommendations. Our current understanding of agents associated with LV dysfunction, their mechanism, and time course for toxicity as well as patient- and treatment-related risk factors are summarized in Table 36. A comprehensive table of cancer treatments associated with all forms of cardiotoxicity are published elsewhere.[55] Additional information is also presented in section *7.5.4* of the Supplementary Material.

RECOMMENDATION

153. (CCS 2016 Cardio-oncology Recommendation 2): We recommend that patients who receive potentially cardiotoxic cancer therapy undergo evaluation of LVEF before initiation of cancer treatments known to cause impairment in LV function (Weak Recommendation; Moderate-Quality Evidence).
154. (CCS 2016 Cardio-oncology Recommendation 5): We suggest that serial use of cardiac biomarkers (eg, BNP, troponin) be considered for early detection of cardiotoxicity in cancer patients who receive cardiotoxic therapies implicated in the development of LV dysfunction (Weak Recommendation; Moderate-Quality Evidence).
155. (CCS 2016 Cardio-oncology Recommendation 6): We suggest that in patients deemed to be at high risk for cancer treatment-related LV dysfunction, an ACEi or ARB, and/or β-blocker, and/or statin be considered to reduce the risk of cardiotoxicity (Weak Recommendation; Moderate-Quality Evidence).
156. (CCS 2016 Cardio-oncology Recommendation 10): We recommend that in cancer patients who develop clinical HF or an asymptomatic decline in LVEF (eg, > 10% decrease in LVEF from baseline or LVEF < 53%) during or after treatment, investigations, and management, follow current CCS guidelines. Other causes of LV dysfunction should be excluded (Strong Recommendation; High-Quality Evidence).
157. (CCS 2016 Cardio-oncology Recommendation 12): We suggest that patients at high risk of cancer therapy-related CVD or patients who develop cardiovascular complications during cancer therapy (eg, > 10% decrease in LVEF from baseline or LVEF < 53%) be referred to a cardio-oncology clinic or practitioner skilled in the management of this patient population, for optimization of cardiac function and consideration of primary or secondary prevention strategies (Weak Recommendation; Low-Quality Evidence).

7.5.5. Myocarditis

Myocarditis, which often presents as HF, is an inflammatory process affecting the myocardium as a result of external antigen triggers such as viruses, bacteria, parasites, drugs, and others, or internal triggers such as autoimmune reaction to self-antigens. The WHO definition of myocarditis is on the basis of established histological, immunological, and immunohistochemical criteria.[537,538]

The incidence of myocarditis is not well established because many patients with clinically suspected myocarditis do not undergo EMB or CMR. In patients with unexplained nonischemic cardiomyopathy, biopsy proven myocarditis was shown in 9%-16% of cases.[539,540] The prognosis for patients with myocarditis is usually favourable. One prospective study suggested that approximately one-third of patients who present with acute myocarditis do not develop HF, one-third develop ventricular dysfunction with subsequent recovery, and approximately one-third are left with significant ventricular dysfunction—a small subgroup of subjects progressively deteriorate and require significant support (MCS or cardiac transplantation).[541,542]

Clinical presentations of patients with myocarditis ranges from asymptomatic patients with abnormal ECG or ECHO findings to patients with atypical symptoms of fatigue, palpitations, chest pain at rest, and patients with arrhythmias, HF, cardiogenic shock, or sudden death. A high index of clinical suspicion along with biomarkers and noninvasive investigations like ECHO and CMR are necessary to make a diagnosis.

Markers of myocardial necrosis (troponin I or T) can assist in the diagnosis of myocarditis but a low or normal troponin level does not rule out myocarditis. The sensitivity of an elevated troponin I level in biopsy proven myocarditis in the Multicentre Myocarditis Treatment trial was 34% and

specificity was 82%.[543] The ECG findings might include arrhythmias (ventricular or supraventricular), AV block, pattern of acute injury or pericarditis, nonspecific repolarization abnormalities or, rarely, might be normal. Echocardiographic findings might include segmental or global LV dysfunction, RV dysfunction, or pericardial effusion.[544]

CMR is the most important noninvasive investigation in the diagnostic workup of myocarditis. CMR allows for accurate and quantitative assessment of LV morphology, volumes, as well as global and regional ventricular function. More importantly however, CMR can be used to detect inflammation, by allowing visualization of myocardial hyperemia (early gadolinium enhancement), intracellular and interstitial edema (water-sensitive CMR), and necrosis/fibrosis (LGE) imaging. The combined protocol (Lake Louise criteria) has high specificity of up to 91% and a sensitivity of 67%. LGE imaging alone, however, also has a variable sensitivity of 44%-100%[545] and is also not specific for acute vs chronic/healed myocarditis.[546]

In a study of 104 patients with subacute myocarditis, the extracellular volume with LGE imaging showed improvement in the diagnostic accuracy of CMR compared with standard Lake Louise criteria.[545] Myocardial mapping as a novel CMR approach might further improve diagnostic accuracy[547,548]; further clinical research is ongoing.

The yield of EMB to provide clinically relevant information using Dallas criteria (histological criteria) is relatively low. Using immunohistochemical criteria and viral polymerase chain reaction in addition to histological criteria increases the diagnostic value of EMB.[549,550] EMB should be considered if the results of biopsy are likely to result in a change of patient management. Giant-cell myocarditis is an example in which biopsy results provide information on prognosis and the need for immunosuppressive treatment. Other situations in which EMB provides unique information are disorders associated with sarcoidosis, hypereosinophilia, infiltrative cardiomyopathies, and others.

EMB is indicated for patients who present with an unexplained new onset of HF (< 2 weeks) and hemodynamic compromise. In this scenario, EMB might help establish diagnosis but has known safety considerations and diagnostic yield issues. EMB is also indicated in patients with new-onset HF associated with ventricular arrhythmias, high-degree AV blocks, and in patients who failed to respond to medical therapy. Ventricular arrhythmias and high-degree AV blocks are frequently associated with giant-cell myocarditis or sarcoidosis.[551]

Irrespective of clinical presentation, patients with myocarditis and HF should be treated with standard medical therapy for HF. The routine use of immunosuppression in myocarditis is not recommended. There are several small RCTs investigating the use of steroids alone or in combination with cyclosporine or azathioprine vs placebo in patients with myocarditis. In the largest study, 111 patients with biopsy proven myocarditis and reduced LV function (EF < 35%) were randomized to conventional therapy vs prednisone and either azathioprine or cyclosporine. At 12 months there was no survival benefit and no significant difference in LV function improvement.[539] In a study of 85 patients with biopsy proven virus-negative myocarditis, patients were assigned to placebo or prednisone in combination with azathioprine. At 6 months 88% of patients in the prednisone/azathioprine group showed significant improvement in echocardiographic parameters.[552] There are no large, randomized, placebo-controlled studies investigating antiviral therapy in patients with myocarditis. A high dose of I.V. immunoglobulin was evaluated in a small number of patients with myocarditis and the treatment was ineffective.[553-555]

Patients with known or suspected myocarditis should be referred to a centre where expertise in the diagnostic assessment and treatment of myocarditis is available. The urgency of referral is dependent on the clinical course. Reports of small case series suggest that aggressive medical support, including a ventricular assist device, along with medical therapy, has allowed for eventual ventricular function recovery and device explantation without the need for transplantation.[556,557]

The intensity of follow-up for patients with myocarditis is dictated by the extent of cardiac dysfunction, the severity of the clinical presentation and the response to therapy. Follow-up consists of ongoing clinical assessment and might include echocardiographic assessment of cardiac function or CMR evaluation of ongoing inflammation. Emerging evidence suggests that CMR follow-up might be useful for predicting outcomes.[558] Persistent inflammation at 4-week follow-up indicates a worse prognosis in patients with no further inflammation. Patients with a positive clinical response to therapy, including improvement in or normalization of cardiac dysfunction, should also undergo clinical follow-up within approximately 3-6 months to confirm clinical stability. Patients with a continued or worsening course, which will be dictated by the clinical severity of symptoms and LV dysfunction, require ongoing expert follow-up.

RECOMMENDATION

158. We recommend that myocarditis should be suspected in the following clinical scenarios:
    i. Cardiogenic shock due to LV systolic dysfunction (global or regional), in patients in whom etiology is not apparent.
    ii. Acute or subacute development of LV systolic dysfunction (global or regional), in patients in whom etiology is not apparent.
    iii. Evidence of myocardial damage not attributable to epicardial CAD or another cause (Strong Recommendation; Low-Quality Evidence).
159. We recommend referral to a centre with experience and expertise in the assessment and management of myocarditis should be considered for patients with suspected myocarditis (Strong Recommendation; Low-Quality Evidence).
160. We recommend that urgent referral for evaluation/consideration for cardiac transplantation or MCS be considered for patients with myocarditis associated with HF, progressive clinical deterioration, or end-organ dysfunction despite standard HF therapy (Strong Recommendation; Low-Quality Evidence).
161. We recommend that all patients with suspected myocarditis have CMR where available and in the

absence of contraindications (Strong Recommendation; High-Quality Evidence).

162. We suggest EMB be considered for patients who present with: (1) new-onset (< 2-week duration) HF of undetermined etiology with hemodynamic compromise; (2) HF and high-grade heart block; (3) HF with recurrent ventricular arrhythmias; or (4) HF unresponsive to medical therapy (Weak Recommendation; Low-Quality Evidence).
163. We recommend best medical therapy, including supportive care for the treatment of myocarditis (Strong Recommendation; Low-Quality Evidence).
164. We recommend against routine use of general or specific immunological therapies directed toward myocarditis, because this has not been shown to alter outcomes, and might lead to side effects or complications (Strong Recommendation; Moderate-Quality Evidence).
165. We suggest that treatment with immunosuppressive therapy should be considered in subgroups of patients with myocarditis due to specific underlying etiologies such as giant-cell myocarditis, sarcoidosis, myocarditis due to systemic autoimmune disease, or biopsy proven myocarditis with undetectable viral infection using polymerase chain reaction (Weak Recommendation; Low-Quality Evidence).
166. We recommend that antiviral therapy should not routinely be used in patients with myocarditis (Strong Recommendation; Low-Quality Evidence).
167. We recommend that expert clinical follow-up is required until myocarditis is determined to be resolved or until a chronic management plan is in place (Strong Recommendation; Low-Quality Evidence).

Practical tip. Clinical signs and symptoms of myocarditis might be highly variable.

Practical tip. Other potential causes of cardiac dysfunction must be ruled out before a diagnosis of myocarditis can be made; additional tests might include cardiac catheterization or CMR, with or without RV biopsy.

Practical tip. Biomarker and 12-lead ECG findings in patients with myocarditis might mimic those of acute MI or acute pericarditis.

Practical tip. Patients with suspected myocarditis should have troponin I or T and BNP or NT-proBNP measured.

Practical tip. Treatment with immunosuppressive agents should be implemented by centres/physicians with considerable experience in managing these cases.

Practical tip. Patients with persistence of HF symptoms or ventricular dysfunction should be followed in a multidisciplinary HF/function clinic, and referred to specialized centres when appropriate.

Practical tip. Precise diagnostic criteria for acute myocarditis have not been prospectively validated; however, the criteria consider 4 major elements in determining the potential for the presence of acute myocarditis. They are:

- Symptoms and clinical findings consistent with acute or recent myocardial damage.
- Evidence of myocardial injury in the absence of a demonstrable epicardial coronary cause.
- Evidence of hyperemia, edema, or irreversible injury on CMR images.
- Presence of inflammatory cell infiltrate or positive viral genome signal on examination of EMB specimens.

Practical tip. Evaluation of EMB samples should be performed by an experienced cardiac pathology laboratory. Evaluation of EMB for myocarditis should include the use of histopathological markers of inflammation and necrosis, immunohistochemical markers, and assessment for viral particles.

8. Community Management of HF

The management of HF should be delivered within an integrated system of care on the basis of chronic disease management and prevention principles.[559] This system must meet and anticipate the evolving goals and complexity of aging patients throughout their entire journey with HF, and provide access to specialized services, community supports, and end of life care according to patient needs and preferences.

8.1. Patient-level considerations

Clinical complexity, cognitive impairment, and frailty. Aging patients with HF often develop additional medical and psychiatric comorbidities, geriatric syndromes, and associated symptoms. Cognitive impairment, which is more common among patients with HF, is associated with impaired self-care capacity and greater risks of functional decline, rehospitalization, and mortality.[321,564-567] Similarly, frailty affects up to 50% of older patients with HF, in whom it is associated with nonspecific clinical features, acute care utilization, poor quality of life, worse outcomes from concomitant conditions, and mortality.[568]

Recommendations regarding HF therapy apply to older patients and should not be restricted on the basis of age alone.[180,182,569-576] Frail patients are vulnerable to side effects due to the polypharmacy inherent to the treatment of HF and other comorbidities. To avoid side effects such as falls, care must be taken when optimizing medications toward target doses.[564,577] Orthostatic hypotension is frequent among frail older patients, but if recognized, can be managed to allow for greater use of evidence-based HF therapies.[564,578,579]

Frailty has important ramifications on the organization of HF care. It is central to defining patient goals and thus to decision-making related to ACP, surgical treatments, implantable device therapy, medication deprescribing, or other treatments not compatible with these goals.[580,581] Frailty is more common with age, but can occur in persons who are relatively young chronologically. There is currently no agreement on a single standard frailty measure.[580] Instruments that address key underlying factors related to frailty might be more clinically useful than performance measures, including the Edmonton Frail Scale,[582] the Clinical Frailty Scale,[583] and scales embedded with the interRAI instruments broadly implemented across multiple care sectors in Canada.[580,584]

An international multidisciplinary working group established, through consensus, **A**cknowledge, **R**outinely Profile, **I**dentify, **S**upport, and **E**valuate **H**eart **F**ailure (ARISE-HF),[567] a framework to optimize health outcomes for patients with HF. The framework includes acknowledging the

importance of multimorbidity, profiling multimorbidity using standardized protocols, and identifying individual patient-centred goals.

RECOMMENDATION

168. We recommend that patients with known or suspected HF should be assessed for multimorbidity, frailty, cognitive impairment, dementia, and depression, all of which might affect treatment, adherence to therapy, follow-up, or prognosis (Strong Recommendation; High-Quality Evidence).

Practical tip. Depression in older patients with HF should be suspected when chronic physical complaints persist despite optimal HF therapy.[560]

Practical tip. Measuring orthostatic vital signs might identify individuals at risk of falls.

Practical tip. Manage fall risk related to orthostatic hypotension:

- Minimize use of diuretics and other vasodilators by optimizing first-line HF therapy;
- Consider a medication review with a pharmacist; and
- Promote physical activity, which might reduce the risk of orthostatic hypotension.

Practical tip. Screening, prevention, and management of delirium is a standard of care for all acutely ill older patients, including those with HF.[561]

Practical tip. Cognitive impairment, even when mild, might interfere with HF self-care.

Practical tip. Patients older than the age of 65 years with HF should be screened for cognitive impairment.[562,563]

Practical tip. If cognitive impairment is identified, a capable substitute decision-maker should be designated.

Practical tip. HF therapies in frail or older patients should be similar to those in younger patients.

Practical tip. In frail older patients, HF medications may be introduced at lower doses and titrated more slowly.

Practical tip. Clinicians should be alert for drug-drug, drug-disease interactions, and therapeutic competition, in cases when the care of one comorbidity is exacerbated by the care of another.[577]

Practical tip. For patients prescribed many medications or those with cognitive impairment, consider adherence aids, such as "blister packs," to reduce medication errors.

Although the course of HF in individual patients can be unpredictable, a high symptom burden and high mortality rates should be anticipated, and ACP discussions should be initiated early in the course of illness.[564,585-589] These discussions should focus on the values and goals of the individual patient—what they find valuable and important in their lives and what they hope for in the future (eg, attending an important upcoming family event). This is an ongoing conversation to pursue after important clinical events, when considering invasive therapies, or when requested by the patient. Many local, provincial, or federal organizations have excellent tools for helping patients and families in decision-making (www.myspeakupplan.ca).

Patients with HF suffer from a substantial burden of physical and psychiatric symptoms (Table 37).[590,591] Palliative care is the promotion of physical and psychosocial health, regardless of diagnosis or prognosis (Table 38).[592] Thus, the delivery of palliative care interventions should be triggered by patient needs and not arbitrarily on the basis of a score on a particular instrument. Several HF-specific and generic quality of life tools have been validated to assess the symptoms of patients with HF, and several are freely available online (Table 39).[584,593-604] Informal caregivers of patients with advanced HF should be evaluated for coping and degree of caregiver burden. Although several tools exist, there is no clear evidence to recommend one tool over another. Management options for symptoms of advanced HF are outlined in Table 40.[585-589,605-614]

RECOMMENDATION

169. We recommend that clinicians caring for patients with HF should initiate and facilitate regular, ongoing, and repeated discussions with patients and family regarding advance care planning (Strong Recommendation; Very Low-Quality Evidence).
170. We recommend that the provision of palliative care to patients with HF should be on the basis of a thorough assessment of needs and symptoms, rather than on individual estimates of remaining life expectancy (Strong Recommendation; Very Low-Quality Evidence).
171. We recommend that the presence of persistent advanced HF symptoms despite optimal therapy be confirmed, ideally by an interdisciplinary team with expertise in HF management, to ensure appropriate HF management strategies have been considered and optimized, in the context of patient goals and comorbidities (Strong Recommendation; Very Low-Quality Evidence).

Practical tip. The timing of advance care planning (ACP) discussions should take into consideration the high mortality rate in the year after a first HF hospitalization.

Practical tip. The substitute decision-maker should be involved in ACP discussions.

Practical tip. Engage patients and families in open and honest discussion about the prognosis of HF, including possible modes of death (sudden, progressive HF, or from a comorbidity).

Practical tip. Care preferences and goals of care should be regularly discussed with patients and documented, with emphasis shifting from quantity to quality of life.

Practical tip. As HF symptoms advance, ACP should be reviewed, and the possible deactivation of implantable defibrillators or cessation of invasive therapies such as MCS or hemodialysis discussed, particularly when these no longer align with goals of care.

Practical tip. Symptoms and psychosocial burden (eg, depression, fear, anxiety, social isolation, home supports, and need for respite care) should be regularly evaluated, and a palliative care referral considered.

Practical tip. Informal caregivers of patients with advanced HF should be evaluated for coping and degree of caregiver burden.

8.2. Clinical practice considerations

Multidisciplinary HF management programs have been shown to lead to better symptom control, less acute care utilization, and lower mortality including among older frail persons with multimorbidity.[622-623] Similarly, multidisciplinary palliative care programs for adults with advanced chronic illness can improve patient and caregiver outcomes, reduce health service utilization, and increase the chances of dying at home.[624-627]

RECOMMENDATION

172. We recommend that a HF specialist or clinic should have the capacity to accept referrals, transition of care, or arrange for transfer to a tertiary care centre within the recommended CCS benchmarks (Strong Recommendation; Very Low-Quality Evidence).
173. We recommend that specialized outpatient HF clinics or disease management programs provide access to an interprofessional team ideally including a physician, a nurse, and a pharmacist with experience and expertise in HF (Strong Recommendation; High-Quality Evidence).
174. We recommend that all patients with recurrent HF hospitalizations, irrespective of age, multimorbidity, or frailty, should be referred to a HF disease management program (Strong Recommendation; High-Quality Evidence).

Practical tip. Patients with HF should have regular follow-up assessments, with their intensity and frequency tailored according to individual risk and stability (Table 41).

Practical tip. Follow-up assessments should include symptoms, function, quality of life, physical examination, medication reconciliation and review, and a review of updated laboratory results and diagnostic test results (Fig. 12). Emerging needs, such as disability, other health concerns (Table 42), caregiver burden, and advance care plans should be reviewed as well.

Practical tip. Follow-up methods might include telemonitoring, structured telephone support, or home visits, all of which have variable evidence to support this and should be localized.[615,616]

Practical tip. HF management includes coaching patients and informal caregivers on self-care skills, through experiential learning, practice, and support.[617,618]

Practical tip. Self-care includes knowledge, skills, and confidence about HF treatments, exercise, dietary measures, symptom-, and weight-monitoring. It also includes an action plan to address exacerbations early and determine if actions were helpful to circumvent further deterioration. This plan should facilitate rapid access, either in person, by phone, or other modes of communication or technology, to HF clinic staff for assistance.[619]

Practical tip. Home-based HF management, which can include hospital-at-home care, might be beneficial for highly selected patients.[620,621]

8.3. Systems-level considerations

Integration is a system-wide process of combining social and health services to meet the needs of the patients with chronic disease through alignment of financial and administrative modalities, with the clinical practices of multidisciplinary care teams.[628-630] Care coordination is integral to the Chronic Disease Management model, which has been recommended as the preferred model for care delivery for CVD by the Canadian Heart Health Strategy Action Plan.[631] Patient assessments throughout their journey with HF should continuously be linked with updated management plans, through seamless communication between the patient, primary to tertiary care, palliative care, and with community care resources.[632] Clinical trials of community-based integrated systems of care for frail seniors have shown better care quality, coordination, and continuity, better health outcomes, and equal or reduced overall costs.[632-636] Further, integration of multidisciplinary palliative care services in the care of patients with advancing HF can reduce symptom burden and health system utilization.[637-639] Features of an integrated care model for patients with HF are described in Table 43.[640]

Proper execution of care transitions from hospital to the community is particularly important, because patients with HF have high rates of readmission. Older patients with multimorbidity, frailty, and previous HF hospitalizations are at increased risk for readmission.[641] Important elements of successful transitional care programs have been identified and should be considered on the basis of local resources, which are outlined in section *8.3* of the Supplementary Material.[642-648]

RECOMMENDATION

175. We recommend that care for patients with HF be organized within an integrated system of health care delivery in which patient information and care plans are accessible to collaborating practitioners across the continuum of care (Strong Recommendation; Moderate-Quality Evidence).

9. Quality Assurance/Improvement

9.1. Quality assurance: what is it?

The Institute of Medicine defines quality of care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[649] In addition to whether care for a particular condition achieves desired health outcomes, other considerations in gauging quality of care include accessibility, the quality of the patient experience when receiving care, and how the processes of care delivery are structured in a manner to constrain health care costs.[650-652]

Quality assurance is a process whereby a health care organization can ensure that the care it delivers for a particular illness meets accepted quality standards.[640,649,650] Inherent characteristics of this process include:

- Existence of evidence-based clinical guidelines for the illness of interest, and from which quality of care

performance indicators can be derived. These indicators can refer to structures, processes, or outcomes of care.[653,654]

- Development and maintenance of a health information database representative of the patients/illness served by the health care organization. The database can be audited and benchmarked against the performance indicators to assess the quality of care.
- Development of mechanisms to address care deficiencies identified in the database audit and improve the quality of care.
- Repeated database audits to assess the effectiveness of measures taken to improve care delivery, and to ensure the ongoing delivery of quality care.
- Placement of a system aimed to monitor patient safety and provide processes to address safety-related issues that become apparent.

A review of the large body of literature regarding quality assurance and safety is beyond the scope of this section. Instead, we address issues specific to quality care in the HF population with additional details in sections *9.2-9.7* of the Supplementary Material, and in Table 44.

RECOMMENDATION

176. We recommend that health care systems should provide for quality assurance in the process as well as content of care provision (Strong Recommendation; High-Quality Evidence).
177. We recommend that quality assurance programs should include the following elements to allow for assessment of patient, provider, and health care institutional outcomes (Strong Recommendation; Moderate-Quality Evidence):
    i. Measurement of evidence-based key performance indicators to assess system performance and outcomes.
    ii. Robust measurement of important clinical and system of care outcomes.
    iii. Intervention supports such as clinical tools to facilitate best practices.
    iv. Performance feedback and education to HF care professionals and administrators.

Practical tip. Selection of performance indicators with outcome data from randomized clinical trials, such as those listed in the CCS Quality Indicators E- Library-Heart Failure (http://ccs.ca/images/Health_Policy/Quality-Project/Indicator_HF_V2.pdf), is preferred.

Practical tip. Institutional quality improvement strategies that include the following features have been shown to improve outcomes:

- Reliance on a set of multimodal rather than single interventions
- Administrative and change management support
- Provision of quality assurance personnel support
- Emphasis on persistent/sustainable rather than temporary interventions
- Resource support, during and after the period of practice change
- Administrative as well as physician champions

Practical tip. It is unclear if any single intervention is superior to another. Use of multiple simultaneous interventions provides a larger effect size.

Practical tip. Examples of interventions with the highest quality of evidence for outcome improvement at a system level include:

- Use of therapies proven to improve clinical outcomes in randomized clinical trials
- Interdisciplinary and longitudinal approach to chronic disease care including with repeated visits, case management, home visits, and multimodal communication methods
- Comprehensive hospital and postacute care in combination
- Timely and accurate communication between health care providers

Practical tip. Examples of ***isolated*** interventions with limited evidence for improved process measure outcome improvement at a system level include:

- Practice audits with multifaceted feedback
- Reminder or decision support tools
- Health care provider education
- Patient/family education
- Pay for performance programs
- Telemedicine/telemonitoring programs

Practical tip. Broader regional, provincial, and national frameworks are required to promote and facilitate quality assurance initiatives at all levels of HF care.

10. Gaps in Evidence and Ongoing Trials

The CCS HF guidelines panel identified several gaps in evidence that, when filled, will aid in the diagnosis, prognosis, treatment, or organization of care for patients with HF. These are not exhaustive and many research avenues should be pursued by the Canadian and global research community.

1. What is the effect of using a validated risk score in clinical practice?
2. Which current or novel therapies should be targeted for patients who present with HFmEF or HFpEF, and which biomarkers should guide these choices?
3. What is the role of sacubitril/valsartan and other new therapies in *de novo* patients with HF?
4. What are the implications of withdrawing therapy with limited or no efficacy in the current era of other therapies (eg, digoxin, statins, multivitamins)?
5. Which of the current or novel diabetes-related therapies should be used in patients with or without diabetes and HF?
6. What role does dietary micro- or macronutrients have on clinical outcomes for patients with HF?
7. What is the role of antiplatelet agents (eg, aspirin) or oral anticoagulants in patients with sinus rhythm and HFrEF?
8. Does genetic variability play a role in response to current therapy (pharmacogenomics), and can this be personalized?

9. Should all patients with HFrEF without a known etiology undergo genetic testing?
10. What is the role of destination therapy LV assist devices in the context of changing medical and device therapy?
11. Should patients with a nonischemic etiology of HF receive CRT alone rather than CRT-D?
12. What is the role of bromocriptine, other HF-related therapies, and genetic testing in patients with PPCM?
13. What role does home-based monitoring including eHealth, telehome monitoring, mHealth, and implantable devices have on clinically relevant outcomes?
14. What is the role of existing and novel therapies in patients with severe renal dysfunction?
15. Are there subgroup populations who would benefit from UF?
16. Can cellular therapies improve long-term clinical outcomes in HFrEF and if yes, which form should they take and who should be the ideal candidates?

Conclusions

The provision of optimal care to patients with HF presents many challenges to the patient, their family or caregivers, the physician, other health care providers, and the health care system. An accurate and timely diagnosis is critical to initiate treatment that will relieve symptoms, improve quality of life, reduce hospitalizations, and prolong survival. These guidelines should provide an evidence-based road map to translate knowledge into practice and allow health care practitioners to make the best clinical judgements and decisions with their patients.

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Supplementary Material

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