2017 Comprehensive Update of the Canadian Cardiovascular Society

Guidelines for the Management of Heart Failure

Justin A. Ezekowitz MBBCh (chair), Eileen O'Meara MD (co-chair), Michael A. McDonald MD, Howard Abrams MD, Michael Chan MBBS, Anique Ducharme MD, Nadia Giannetti MD, Adam Grzeslo MD, Peter G. Hamilton MBBCh, George A. Heckman MD, Jonathan G. Howlett MD, Sheri L. Koshman Pharm D, Serge Lepage MD, Robert S. McKelvie MD, Gordon W. Moe MD, Miroslaw Rajda MD, Elizabeth Swiggum MD, Sean A. Virani MD, and Shelley Zieroth MD.

Secondary Panel Members: Abdul Al-Hesayen MD, Alain Cohen-Solal MD, Michel D'Astous MD, Sabe De MD, Estrellita Estrella-Holder RN, Stephen Fremes MD, Lee Green MD, Haissam Haddad MD, Karen Harkness RN, Adrian F. Hernandez MD, Simon Kouz MD, Marie-Hélène LeBlanc MD, Frederick A. Masoudi MD, Heather J. Ross MD, Andre Roussin MD, Bruce Sussex MBBS.

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Corresponding author:

Justin Ezekowitz MBBCh, MSc
Canadian VIGOUR Centre
2-132 Li Ka Shing Centre for Health Research Innovation, Edmonton (AB), Canada, T6G 2E1
Tel: (780) 407-8719, Email: jae2@ualberta.ca

Abstract:

Since the inception of the Canadian Cardiovascular Society (CCS) Heart Failure (HF) guidelines in 2006, much has changed in the care for patients with heart failure. Over the past decade, the HF Guidelines Committee has published regular updates. However, given the major changes that have occurred in this area, the Guidelines Committee felt that a comprehensive reassessment of the HF management recommendations is presently needed, with a view to producing a full and complete set of updated guidelines. The primary and secondary CCS HF panel members as well as external experts have reviewed clinically relevant literature in order 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 heart failure. Among specific issues covered are risk scores, the differences in management for HF with preserved versus 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 heart failure 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.

Contents

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 heart failure. The 2017 update is a comprehensive set of guidelines incorporating new evidence and identifying areas of uncertainty and challenges facing healthcare providers in HF management. It integrates and updates the last 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 described on 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 committee, and are endorsed by those committees from a HF perspective.

2. Definitions of Heart Failure

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. While 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 (e.g., dilated, congestive), unless a specific definition exists. The term "stable" is not considered to be clinically appropriate given 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 section *7.1.4 Advance HF Management Strategies* as it pertains to selecting advanced mechanical devices, transplant or palliative therapies.

2.1 Ejection fraction terminology

This guideline uses the following terms:

- HF with preserved ejection fraction (HFpEF): LVEF ≥ 50%;
- HF with a mid-range ejection fraction (HFmEF): LVEF 41-49%;
- HF with a reduced ejection fraction (HFrEF): LVEF ≤ 40%.

This recognizes the uncertainty that often occurs in the measurement of left ventricular ejection fraction (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) may vary due to patient or technical factors, as well as therapy or clinical deterioration. The previously stated EF cutpoints 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 may 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 that 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 which can be easily accessed and calculated, and describes 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.

Table 2: Risk Scores

Risk Scores					
Score Name	**Population**	**Endpoint**	**Other Considerations**	**Access**	**Variables**
Seattle Heart Failure Model[7]	HFrEF	Mortality risk at 1, 2 and 5 years with or	Restricted to clinical trial patients with	https://depts.washington.e	Age, gender, NYHA class, weight, EF, SBP, ischemic

		without intervention. Mean life expectancy.	'severe' HF; Lab data entry non-SI units; More than 20 variables to enter.	du/shfm/	etiology, diuretic dose, Na, lymphocyte count, Hgb, cholesterol, uric acid, use of ACEi/ARB/BB/aldosterone blocker/allopurinol/statins, QRS>120msec, 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, gender, NYHA class, diabetes, COPD, timing of diagnosis, EF, smoking, SBP, creatinine, BMI, use of beta-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; Lab data entry in non-SI units.	http://www.3chf.org/site/home.php	Age, NYHA class, AF, valvular heart disease, EF, anemia, diabetes, hypertension, creatinine, use of ACEi/ARB or beta-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. Lab data entry in US units. Use of biomarkers improves accuracy but is optional.	www.BCNBioHFcalculator.cat	Age, gender, NYHA class, Na, eGFR, Hgb, EF, diuretic dose, use of statins, beta-blockers or ACEi/ARB. Optional: hs-cTnT, ST2, Nt-pro-BNP
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 Emergency Department	7 day mortality	Limited to patients presenting to the ER and only short-term mortality; missing current clinically important variables	https://ehmrg.ices.on.ca	Age, arrival by ambulance, triage SBP, triage HR, triage O2 sat, potassium, creatinine, active cancer, metolazone, troponin. Optional: BNP
ELAN[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, # of ED visits in last 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, **B**ar**c**elo**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**L**laboration on **A**cute decompe**N**sated **H**eart **F**ailure; HF,

heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; 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.

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 may allow intervention on contributing risk factors and pharmacotherapy to delay or reverse the progression of adverse LV remodeling. Data on medications, including ACEs, ARBs, and beta-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 natriuretic peptides (NPs) may be useful to identify individuals who are at higher risk for the development of HF and in whom preventative strategies has 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 use of renin-angiotensin-aldosterone system (RAAS) inhibition therapies, fewer HF events and significant reduction in hospitalizations for major cardiovascular events over a follow up on average of 4.2 years. The NT-proBNP Selected **P**reventi**o**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 beta-blockade and RAAS uptitration. Patients in the group randomized to intensified therapy had a 65% relative risk reduction in the primary combined event rate of hospitalization or death due to cardiac disease at 2 years. Therapies used in these two 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 reported 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 prior acute coronary syndromes (ACS) should have these appropriately treated to prevent future HF events.

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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

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

Recommendation 1: We suggest clinical assessment in all patients to identify known or potential risk factors for the development of heart failure (Weak Recommendation, Moderate Quality Evidence).

Recommendation 2: We recommend ACE inhibitors be used in all asymptomatic patients with an EF < 35% (Strong Recommendation, Moderate Quality Evidence).

Recommendation 3: We recommend that an ACE inhibitor 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).

Recommendation 4: We recommend that in ACE-intolerant patients, an ARB may 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).

Recommendation 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).

Recommendation 6: We recommend physical activity to reduce the risk of developing HF in all individuals (Strong Recommendation, Moderate Quality Evidence).

Practical tips:

- Natriuretic peptide (NP) screening of individuals at risk for the development of HF can aide decision making on whom to send for echocardiography. A value of BNP > 50 pg/mL or 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.
- Dyslipidemia should be treated in patients with evidence of vascular disease or diabetes with lipid-lowering drugs, especially statins.
- Smoking cessation, improved cardiorespiratory fitness and weight reduction for overweight or obese individuals are important preventive strategies for HF.
- Patients at high risk for developing HF should receive annual influenza vaccine and periodic pneumococcal pneumonia immunizations.

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 demonstrated 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 mmHg) versus standard (systolic BP < 140 mmHg) blood-pressure control demonstrated 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 for additional information.

Recommendation 7: We recommend that most patients should have their blood pressures controlled to less than 140/90 mmHg; those with diabetes or at high risk for cardiovascular events should be treated to a systolic blood pressure of less than 130 mmHg to reduce the risk of developing heart failure (Strong Recommendation, Moderate Quality Evidence).

Recommendation 8: We recommend that beta-blockers should be considered in all asymptomatic patients with an LVEF lower than 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 (e.g., 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 lower cardiovascular risk. Older trials evaluating 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 HbA1c); 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 is largely extrapolated from the **D**iabetes **C**ontrol and **C**omplications **T**rial (DCCT) study of type 1 diabetics,[39] the **UK P**rospective **D**iabetes **S**tudy (UKPDS) study,[40] the **UK P**rospective **D**iabetes **S**tudy (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 **Va**scular 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 diabetics. Instead, each individual should be assessed for his / her optimal glycemic target for the prevention of macrovascular events or HF.

Recommendation 9: We recommend that diabetes should be treated according to the Diabetes Canada'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 RCTs that tighter glycemic control reduces cardiovascular outcomes. Potential risks of tight glycemic control may outweigh its benefits in certain individuals such as those with long duration of diabetes, frequent episodes of hypoglycemia; those with advanced cardiovascular disease; advanced age, frailty or multiple comorbidities.

Practical tip:

- Each individual patient should be assessed for his/ her "optimal" glycemic control HbA1c 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 may be considered a first-line agent for type 2 diabetes treatment (Weak Recommendation, Moderate Quality Evidence).

Values and preferences: Metformin is the current Diabetes Canada first line treatment for type 2 diabetes.

Practical tip:

- If the eGFR is < 30 mL/min., a temporary discontinuation of metformin and certain other diabetes medications should be considered.

Sodium-glucose co-transporter-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 a RCT to show cardiovascular benefit in the treatment of diabetes. An SGLT-2 inhibitor empagliflozin was compared to 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 endpoint occurred less commonly in the patients treated with empagliflozin (10.5%) than in those receiving placebo (hazard ratio [HR], 12.1%; 95% confidence interval [CI], 0.74-0.99). Moreover, empagliflozin had a relative risk reduction for cardiovascular mortality by 38%, all-cause mortality by 32% and HF hospitalization by 35%. SGLT-2 inhibitors have not yet been studied in populations of patients with HF. Of note, only a subgroup of ≈ 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 may affect future recommendations, namely for patients with established HF.

Recommendation 11: We suggest that the use of empagliflozin, a SGLT-2 inhibitor, be considered for patients with type 2 diabetes and established cardiovascular disease 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 may change this recommendation.

Dipeptidyl peptidase-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 (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 a DPP-4 inhibitor saxagliptin or placebo and followed them for a median of 2.1 years. The primary endpoint 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% versus 2.8%; HR, 1.27; P=0.007).

On the other hand, 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 to 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 heart failure (Strong Recommendation, Moderate Quality Evidence).

Recommendation 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 heart failure (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 (e.g., sitagliptin, alogliptin, linagliptin) did not have the same adverse effect of HF hospitalization as saxagliptin; 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 5,238 type 2 diabetic patients, comparing pioglitazone to 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 (hazard ratio 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 a RCT of 4447 people with type 2 diabetes 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 one admission to hospital for HF compared with the placebo group had this outcome (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 from rosiglitazone.

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

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 (e.g., thyroid dysfunction) that might affect its development or progression (Figure 1, Tables 5, 6, 7, and 8). 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.[56]

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 cardiac magnetic resonance (CMR) imaging can be used when other noninvasive tests are inconclusive and might be required for specific cardiomyopathies (see section *7.5.1 Cardiomyopathies* and Figures 1 and 2).

Recommendation 15: We recommend the choice of investigations should first be guided by careful history and physical examinations 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).

Recommendation 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).

Recommendation 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).

Recommendation 18: We recommend that CMR imaging may be used when echocardiographic imaging (including contrast echocardiography) is non-diagnostic, or help to elucidate the etiologies (e.g., myocarditis) (Strong Recommendation, Low Quality Evidence).

Recommendation 19: We recommend that in a patient suspected of a cardiomyopathy, an inquiry should be made regarding family history, concomitant illnesses, prior 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, 7, and 8) (Strong Recommendation, Low Quality Evidence).

Recommendation 20: We recommend that tachycardia-induced cardiomyopathy should be suspected when left ventricular systolic dysfunction, 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 may have heart failure even without a history or current evidence of volume overload.
- An imaging-based assessment (typically with echocardiography) of valvular abnormalities should be done early in the diagnosis of HF.

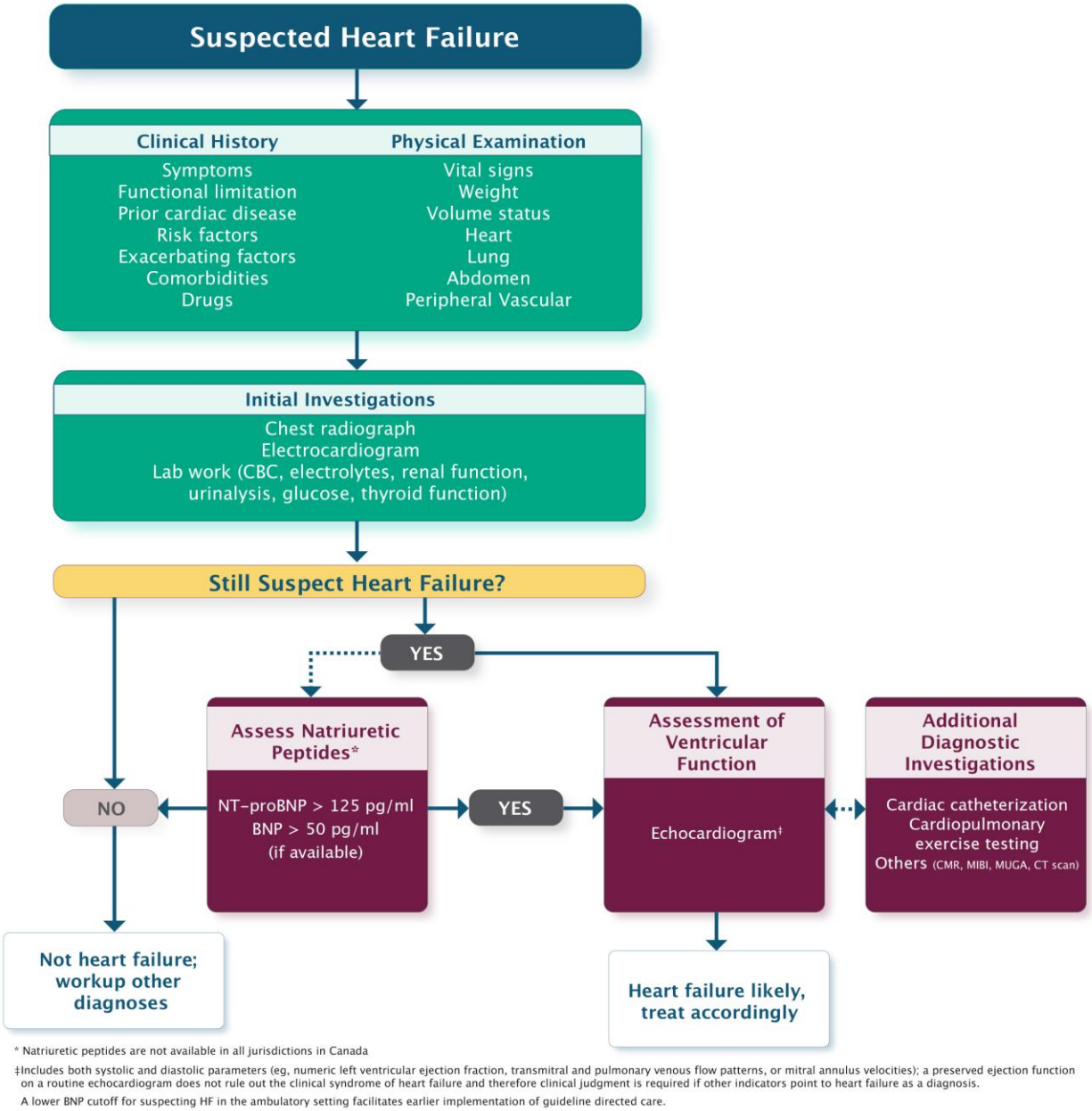

Figure 1: Algorithm for the diagnosis of heart failure in the ambulatory care setting. For patients with heart failure, a history, physical exam and initial investigations should be supplemented with natriuretic peptides and/or imaging tests. BNP, B-type natriuretic peptide; CBC, complete blood count; CMR, cardiac magnetic resonance; CT, computed tomography; MIBI, myocardial perfusion scan; MUGA,multigated acquisition scan; NT-proBNP, N-terminal propeptide B-type natriuretic peptide.

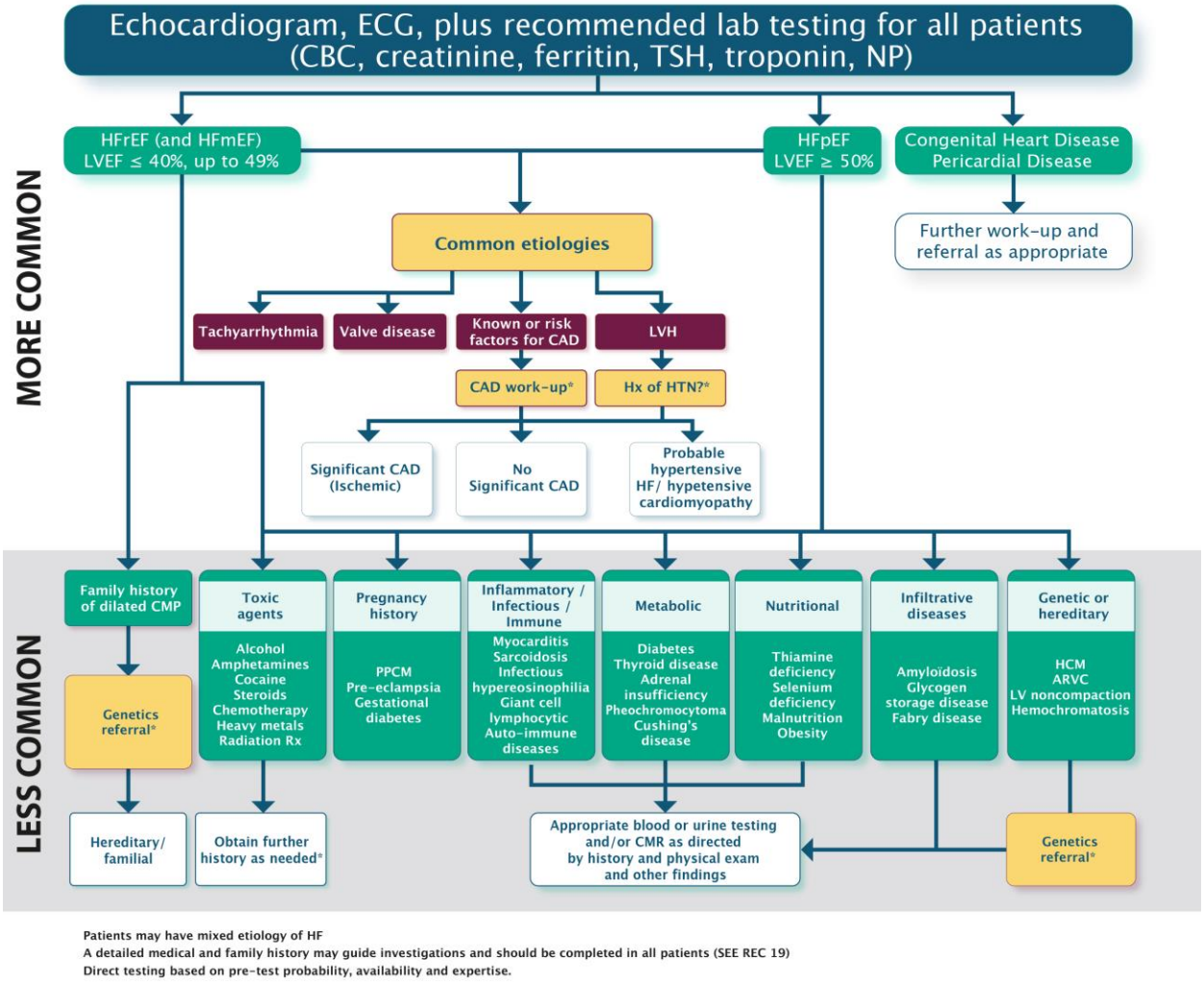

Figure 2: General guidance as to the work-up to identify the most probable etiology for a patient's heart failure. At all stages, a thorough clinical history and physical exam should aid in the selection of additional investigations. A detailed family history is invaluable, especially in patients who are younger or do not have an obvious etiology. Testing should be placed in context of the pre-test probability, availability and expertise of the test. More common etiologies (e.g., 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 (e.g., hemachromatosis in a patient with known coronary artery disease). 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, HF with a mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with a reduced ejection fraction; HTN, hypertension; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NP, natriuretic peptide; PPCM, peripartum cardiomyopathy; TSH, thyroid stimulating hormone.

Table 4: Clinical presentations of heart failure (HF)

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	

*May be a more common presentation in elderly patients

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
Following 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, CT or other measures are appropriate and acceptable in certain circumstances taking into account radiation, cost and information gained.
ACS, acute coronary syndrome; CMRI, cardiac magnetic resonance imaging; CRT, cardiac resynchronization therapy; ECHO, echocardiogram; EF, ejection fraction; HF, heart failure; HFrEF, HF

with reduced EF; ICD, implantable cardioverter defibrillator; LVEF, left ventricular EF; MUGA, radionuclide angiography; RVSP, right ventricular systolic pressure.

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 more than 3 drinks and for men more than 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. May 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 Metamphetamine, antidepressants, corticosteroids, anabolic steroids, phenothiazines		Cocaine may cause thrombosis, coronary spasm, chest pain and myocardial infraction. May also cause myocarditis and aortic dissection	Prior or recent history of cocaine use; urinary metabolites	Calcium channel blockers may be useful in cocaine-induced chest pain or coronary spasm
Chemotherapy[57] 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	Prior history of malignancies with chemotherapy. May need myocardial biopsy.	Standard heart failure treatment may 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 two main target organs are the skin and the respiratory tract. Cobalt itself may 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 may 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	Nonsuppressibilty of serum growth hormone levels following glucose loading	Surgery or pharmacotherapy may improve cardiovascular morbidity
Adrenal insufficiency (Addison's 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's 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 beta-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, beta-blockers and surgery

ACTH, adrenocorticotropic hormone; LVH, left ventricular hypertrophy; T3 and T4, triiodothyronine (**T3**) and thyroxine (**T4**); 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	Edema; high CO heart failure; peripheral	History and physical; decreased serum thiamine	Thiamine replacement

	thiamine (eg 'polished rice'): alcohol	neuritis; midsystolic murmur, third heart sound	level	
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

6. Biomarkers/Natriuretic Peptides

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] Non-cardiac 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 (Figure 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 ≥ 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, angiotensin converting enzyme

inhibitors (ACEis), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs) and CRT.[73,76,77] With beta-blockers, an initial increase in NPs 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 (Figure 3).[79]

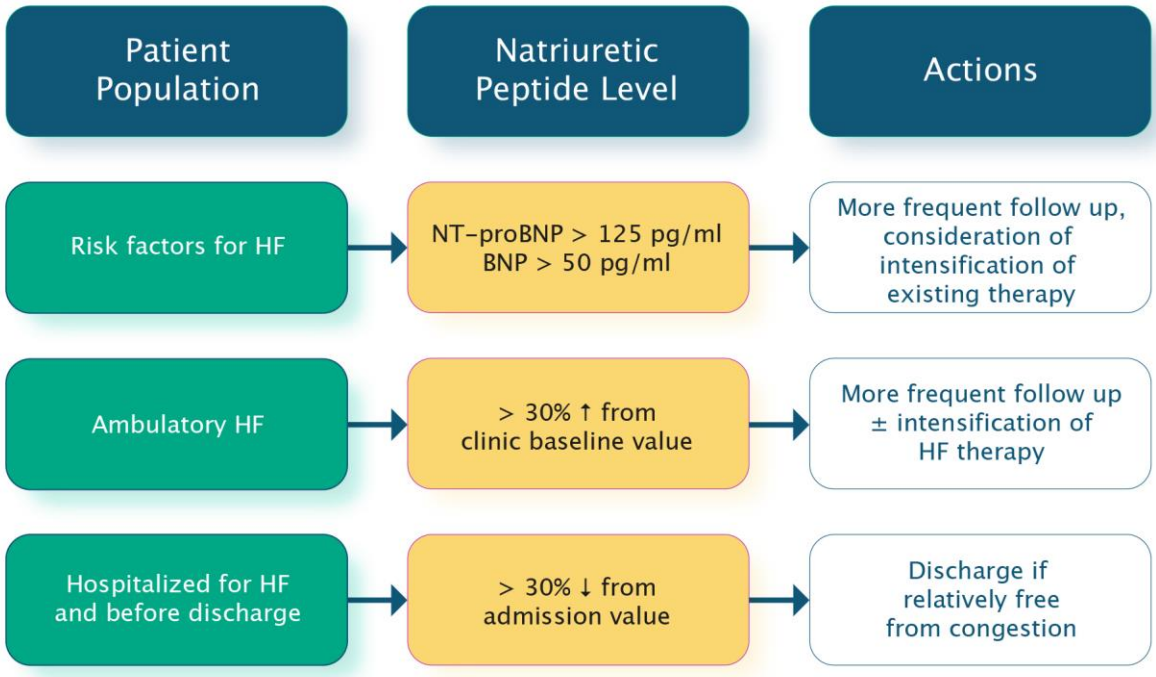

Figure 3: Algorithm for the use of natriuretic peptides in different heart failure (HF)-related clinical scenarios. Clinical evaluation and the risks and benefits of the action suggested should be considered. BNP, B-type natriuretic peptide; NT-proBNP, N-terminal propeptide B-type natriuretic peptide.

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 **T**rial (PEP-CHF) with available measurements of NT-proBNP at baseline, those in the highest quartile (> 1035 pg/mL) had more than 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.[21] These findings might have been influenced by significant regional variations in the trial[85] but nevertheless, they demonstrate the utility of NPs in selecting patients who may respond to a specific treatment.[86]

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 (e.g., emergency department [ED]) versus 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.

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 B-type natriuretic peptide.

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 demonstrates favorable cost-effectiveness. Elevated NP levels are recommended as an additional diagnostic criterion for HFpEF and are associated with increased risk, although the levels may be lower than in HFrEF. Older age and comorbidities may also influence variations in NP levels.

Recommendation 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; 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 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 based on multiple small randomized controlled trials (RCTs), most of which demonstrated benefit, and 3 meta-analyses, which universally demonstrated benefit. An ongoing RCT is likely to affect this recommendation.

Practical tips:

- A change in NP levels by > 30% probably reflects more than daily variation in patients with compensated HF.
- The timing of NP measurements in outpatient settings should be dictated according to clinical status; NP measurments 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, given the prognostic value of these biomarkers in predicting rehospitalization and mortality (Strong Recommendation, Moderate Quality Evidence).

Values and preferences:
This recommendation is based on multiple small RCTs, all of which demonstrated an association with clinical outcomes.

Practical tip:

- A patient with persistently elevated NP levels might need closer follow-up in order to reduce the risk of rehospitalization.
- 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 **V**alsartan in **H**eart **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 a high-sensitivity assay (hs-cTnT; detection limit 0.001 ng/mL) was used.[87] Although 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 both ambulatory and 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 **Re**gistry (ADHERE) registry 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 4,053 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 troponins be measured on admission for acute HF, to rule out acute coronary syndromes 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 both ambulatory and 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.

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

Biomarkers*	Pathophysiological pathways/comorbid conditions with prognostic implications	HF populations targeted	Advantages	Potential Benefits	Challenges before implementation
Cardiac hs-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 based on levels could improve outcomes	ST2 may 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

*This list is not exhaustive; multiple biomarkers have been and are being studied.
CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs, high-sensitivity; 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.

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 outlines 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.

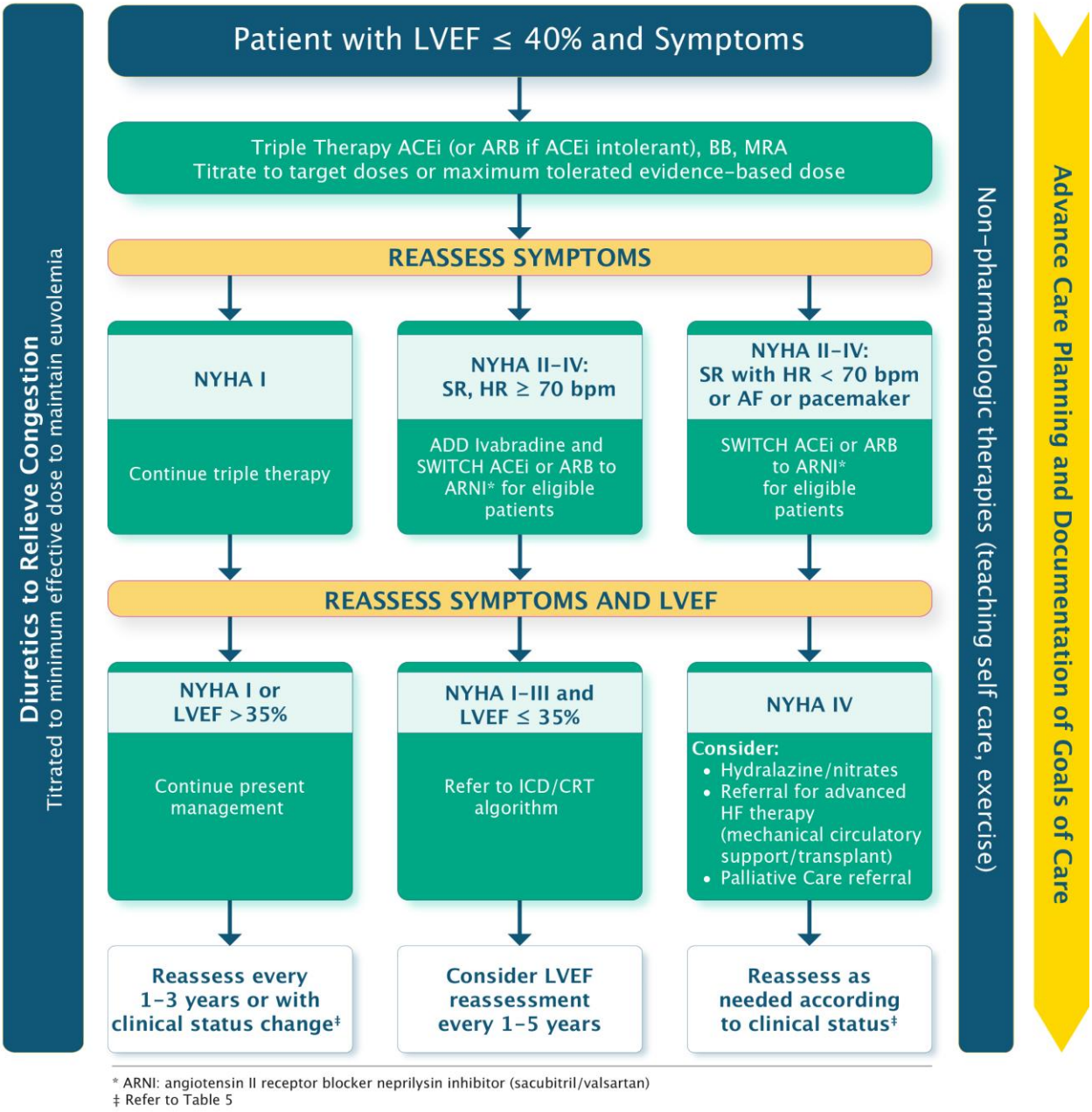

Figure 4: Therapeutic approach to patients with symptoms of heart failure (HF) and a reduced ejection fraction. ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, β-blocker; bpm, beats per minute; 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.

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	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
Beta-blockers		
Carvedilol	3.125mg BID	25mg BID 50mg BID (> 85kg)
Bisoprolol	1.25mg daily	10mg daily
Metoprolol CR/XL*	12.5-25mg daily	200mg daily
MRA		
Spironolactone	12.5mg daily	50 mg daily
Eplerenone	25 mg daily	50 mg daily
ARNI		
Sacubutril/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-QID

* Limited evidence of short acting metoprolol tartrate in HF. Metoprolol CR/XL is not available in Canada.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BID, twice per day; CR/XL, Controlled Release/Extended Release; 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.

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 beta-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 beta-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 two key clinical trials and one 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 beta-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 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 that are ACEi intolerant), a beta-blocker and a MRA unless specific contraindications exist (Strong Recommendation, Moderate Quality Evidence).

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

Recommendation 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).

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 + 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 + LV volumes • NYHA I • Abstinence ETOH	Nutritional deficiency, obesity and obstructive sleep apnea might coexist and require therapy
Chemotherapy-related CM	• Normal EF + 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 + 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+ 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; FC, functional class; GDMT, guideline-directed medical therapy; HR, heart rate; LV, left ventricle; LVEF, left ventricular EF; 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 re-titrate 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)	• 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)	• Contact patient to proceed to health centers 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

∗The above actions are suggested based on 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.
RAAS, renin-angiotensin-aldosterone system.

Practical tips:

General

- If a drug with proven mortality or morbidity benefits does not appear to be tolerated by the patient (e.g., low blood pressure, low heart rate or renal dysfunction), other concomitant drugs, including diuretics, with less proven benefit should be carefully reevaluated to determine whether their dose can be reduced or the drug discontinued.

- HFrEF GDMT should be continued at their usual dose during acute intercurrent illness (e.g., pneumonia, exacerbation of COPD, other systemic infection, etc), unless they are not tolerated (e.g., if significant reactive airways disease is present). GDMT should be restarted before discharge if temporarily withheld.
- In a life-threatening complication, GDMT may be discontinued abruptly, but generally, if there 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 up-titrated to the previous tolerated dose as soon as safely possible.
- If symptomatic hypotension persists with GDMT, consider separating the administration of the dose from the timing of other medications that could also lower blood pressure.

ACEi/ARB

- ACEi intolerance describes a patient that is unable to tolerate ACEi therapy secondary to a bothersome cough (most commonly, 10-20%) or those experiencing angioedema with ACEi therapy (uncommon, < 1%). ARB therapy is a reasonable alternative in both of these cases, however caution should be used in those that develop angioedema while on ACEi therapy as there have been case reports of patients that 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.
- An increase in serum creatinine or eGFR of up to 30% is not unexpected when an ACE inhibitor or ARB is introduced; if the increase stabilizes at 30% or less, there is no immediate need to decrease the drug dose but closer long-term monitoring might be required.
- Blood pressure may fall when an ACE inhibitor or ARB is introduced, especially if introduced at a high dose or in combination with diuretic therapy. Check blood pressure supine and erect to detect whether hypotension is present, requiring slower up-titration.
- Cough occurs in 10-20% of patients on ACEi and does not require discontinuation of the agent unless it is bothersome to the patient.

Beta-blockers

- Objective improvement in cardiac function might not be apparent for 6-12 months after beta-blocker initiation.
- Patients in NYHA class I or II can be safely initiated and titrated with a beta-blocker by non-specialist physicians.
- Patients in NYHA class III or IV should have their beta-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.
- The starting dose of beta-blockers should be low and increased slowly (e.g., double the dose every two to four weeks). Transient fluid retention may occur with initiation or uptitration of beta-blockers and may require assessment of diuretic dosage (e.g., may consider deferring dosage reduction).
- If concomitant reactive airways disease is present, consider using more selective beta-1 blockade (e.g., bisoprolol).

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

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 beta-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 therapy of ACEi and ARB, previously recommended. The combination of an ACEi with 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 (e.g., hypotension, hyperkalemia, and renal dysfunction).[108,114,115] More contemporary treatments with both MRAs and ARNIs, have a stronger evidence base across the spectrum of outcomes (e.g., morbidity and mortality) and therefore further limit the role of combination ACEi and ARB therapy.

Recommendation 28: We recommend an ACE inhibitor, 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 Beta-adrenergic receptor blocker (beta-blocker)

Beta-blockers are part of the first line therapy in the treatment of HFrEF, as 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 beta-blocker (Strong Recommendation, High Quality Evidence).

Recommendation 30: We recommend that beta-blockers be initiated as soon as possible after diagnosis of heart failure, including during the index hospitalization, provided that the patient is hemodynamically stable. Clinicians should not wait until hospital discharge to start a beta-blocker in stabilized patients (Strong Recommendation, High Quality Evidence).

Recommendation 31: We recommend that beta-blockers be initiated in all patients with an LVEF < 40% with prior myocardial infarction (Strong recommendation, Moderate Quality Evidence).

7.1.1.4 MRAs

A single RCT supports the use of eplerenone (target 50 mg daily) compared to 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 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 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 remodeling.[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 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 ≤ 40% (amended to ≤ 35%), had a BNP ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL), or hospitalization for HF in the past year and BNP ≥ 100 pg/mL (or NT-proBNP ≥ 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 (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, beta-blockers and MRAs. This trial also closely reflects contemporary practice with high utilization of ACEi, beta-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, that remain symptomatic despite treatment with appropriate doses of GDMT in order 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 tips:

- Drug tolerability, side effects and laboratory monitoring with use of ARNIs is similar to that of ACEi or ARB noted above.
- 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 blood pressure of < 100 mmHg.
- 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.
- ARNIs should not be used in anyone with a history of angioedema.
- Currently, there is only one ARNI, sacubitril-valsartan, available on the Canadian market. Initial dosing and rate of titration is dependent on pre-existing treatment and co-morbidities 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.

Table 14: Potential sacubitril/valsartan dosing and titration

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

*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.

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

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 beta-blocker therapy might be their rate-lowering effect.[128-130] Despite their benefits beta-blockers, are generally

underused and underdosed.[129-131] Ivabradine is approved for the treatment of heart failure by Health Canada. The latter drug selectively inhibits the depolarizing *if* current in the sinus node. It thus requires sinus rhythm to provide its pharmacological effect. In contrast to beta-blockers, ivabradine does so without lowering blood pressure or myocardial contractility.[132,133]

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 7.5mg twice daily was evaluated in patients with CAD and LVEF < 40% in sinus rhythm with a heart rate > 60 bpm in over 10,000 patients. Although ivabradine did not reduce the primary composite endpoint of cardiovascular death, hospitalization for MI or new-onset or worsening HF, it did reduce the incidence of the secondary endpoint of fatal and non-fatal 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 ≤ 35%, and HF admission within 12 months. Patients were randomized to a target dose of ivabradine 7.5 mg twice daily versus placebo. The primary endpoint was a composite of cardiovascular death or HF admission. Ninety percent of patients were receiving a beta-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 (relative risk reduction, 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 beta-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 bpm, in sinus rhythm and a prior 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 beats per minute with the trial entry criteria of 70 bpm.

Practical tips:

- Every effort should be made to achieve target or maximally tolerated doses of beta-blockers prior to initiation of ivabradine.

- Ivabradine has no effect on blood pressure or myocardial contractility.

7.1.1.7 Hydralazine and isosorbide dinitrate (H-ISDN)

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 beta-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, beta-blocker, MRA) in self-identified black patients with NYHA class III/IV HFrEF.[138] Black patients were specifically evaluated in this trial as 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 / 120 mg) was evaluated versus 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 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).

Recommendation 36: We recommend that H-ISDN be considered in patients with HFrEF unable to tolerate an ACE inhibitor, 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 a H-ISDN recommendation without considering the tolerability and adverse effects. Adverse effects related to H-ISDN are frequent, limit up-titration and result in discontinuation in a significant proportion of patients. Every effort should be made to utilizing ACEi/ARB/ARNI therapy including utilizing low dose and/or re-challenging therapy prior to changing to H-ISDN.

Practical tips:

- Renal dysfunction warranting a trial of H-ISDN includes those that have a significant change in creatinine from baseline with ACEi/ARB/ARNI that persists despite modification of dose, re-challenge and/or removal of other potentially nephrotoxic agents. It may also be considered in those with a serum creatinine > 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 (e.g., potential worsened renal function requiring renal replacement therapy) is thought to outweigh benefits.

- 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.
- Nitrates alone may 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. round 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 beta-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, CV hospitalizations, exercise or the primary endpoint in the 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 tips:

- In patients receiving digoxin, serum potassium and creatinine should be measured with increases in digoxin or diuretic dose, addition or discontinuation of an interacting drug, or during a dehydrating illness, to reduce the risk of digoxin toxicity. Patients with reduced or fluctuating renal function, the elderly, those with low body weight, and women are at increased risk of digoxin toxicity and might require more frequent monitoring including digoxin levels.

- 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 acids (n-3 PUFA)

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 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 endpoints 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 higher than 3 g/day, but this remains controversial.[143,144]

Recommendation 38: We suggest omega-3 polyunsaturated fatty acid (n-3 PUFA) therapy at a dose of 1 g daily be considered for reduction in morbidity and cardiovascular mortality in patients with HFrEF (Weak Recommendation, Moderate Quality Evidence).

Values and preferences: While 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 tips:

- With most data, the dose of n-3 PUFA is 1 g/day. It is unknown whether higher or lower doses would confer clinical benefit and they are therefore not suggested. Doses greater than 3 g/day are associated with excessive bleeding.
- n-3 PUFA therapy may affect measures of anticoagulation. Close monitoring of the international normalized ratio in patients taking warfarin following institution of n-3 PUFA is suggested.
- 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 daily with placebo.[145] There was no difference in the primary endpoint 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 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 daily or placebo, and followed for a median of 3.9 years.[147] There was no difference in the primary endpoints 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 tips:

- Routine statin therapy is unlikely to provide clinical benefit for patients with HF due to non-ischemic causes and in the absence of very high risk of vascular events (such as recent myocardial infarction, diabetes and known vascular disease).
- In those already on 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 two 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 endpoint of all-cause mortality, nonfatal MI or nonfatal stroke in any of the groups. However, there was a reduction in stoke in the warfarin arm compared to the antiplatelet arms, but there was also a higher risk of bleeding in the warfarin group compared to 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 versus 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 non-fatal 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 COMMANDER-HF trial is testing the additional use of rivaroxaban versus 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 to 162 mg be considered only in patients with HFrEF with clear indications for secondary prevention of atherosclerotic cardiovascular events (Strong Recommendation, High Quality Evidence).

Recommendation 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 dual antiplatelet therapy (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.

A retrospective study of 460 patients done in 2015 evaluated the role of warfarin post 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 NOACs 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 of bleeding given the contemporary treatment recommendations with dual antiplatelet therapy (DAPT) post MI, the emerging efficacy of direct oral anticoagulants post PCI and the lack of high quality trial evidence for anticoagulation with warfarin post-MI.

Practical tips:

- Anticoagulation may be considered in those with a LV thrombus.
- If anticoagulation is used, a duration of three months before re-evaluating is reasonable.
- Either warfarin or direct oral anticoagulant could be used for LV thrombus based on 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 (NSAIDS) 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 both non-steroidal anti-inflammatories and cyclooxygenase-**2** (COX-2) inhibitors in patients with HFrEF (Strong Recommendation, High Quality Evidence).

Values and preferences: These agents may cause sodium and water retention, worsen renal function, interact with HF medications (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.

Practical tip:

- High doses of ASA may share the same risks as nonsteroidal anti-inflammatory drugs (NSAIDs) and may aggravate HF, especially in unstable patients.

7.1.1.13 Calcium channel blockers (CCB)

The majority of studies examining 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 **P**rospective **R**andomized **A**mlod**i**pine **S**urvival **E**valuation **2** (PRAISE-2) trials were RCTs that evaluated the effect of amlodipine versus 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 demonstrated a reduction on cardiovascular events in patients with a non-ischemic 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 in patients with HFrEF (Strong Recommendation, Moderate Quality Evidence).

Value and preferences: Several RCTs have demonstrated no benefits on, or worsening of, HF outcomes in patients treated with CCB. 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

The majority of anti-arrhythmic drugs (e.g. amiodarone) have significant concerns related to their safety profile, especially in HFrEF, and while 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 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 which may exacerbate the HF syndrome; (3) control of symptoms; and (4) realization of clinically meaningful cardiovascular endpoints 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 pharmacological and non-pharmacological therapies, should be aggressively pursued.

7.1.2.1 ACE inhibitors and ARBs in HFpEF

There is, however, evidence to support the use of ARBs to reduce HF hospitalizations that draws upon secondary endpoint 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 ≥ 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 demonstrated with ACEis, although the evidence is less robust and limited to data from the **P**erindopril in **E**lderly **P**eople with **C**hronic **H**eart **F**ailure (PEP-CHF) study[172] which included patients 70 years of age or older with an LVEF ≥ 45%. The trial, which had a lower than anticipated event rate and high open-label crossover, did show that perindopril reduced the secondary endpoint 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

Prospective comparison of **ARN**I with **A**RB **G**lobal **O**utcomes in heart failure with preserved ejectioN fraction (PARAGON-HF) trial is comparing sacubitril-valsartan to valsartan on clinical outcomes in patients with HFpEF (NCT 01920711).

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) or placebo. Patients were generally older (age > 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 endpoint of cardiovascular death, aborted cardiac arrest or HF hospitalization between groups. When considering the constituent components of the primary endpoint, only HF hospitalization was decreased in spironolactone treated patients (HR 0.83; 95% CI 0.69-0.99). While 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.

Numerous pre-specified 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 endpoint compared to those receiving 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 demonstrated a 15% relative risk reduction in the primary endpoint favouring spironolactone in patients enrolled in the Americas versus those enrolled in Russia or Georgia.[85]

7.1.2.3 Beta-blockers in HFpEF

While beta-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 endpoint of all-cause mortality and cardiovascular hospitalization (HR 0.81; CI 0.63-1.04; p-value for sub-group interaction=0.043) among those study participants with an LVEF ≥ 35% who received nebivolol compared with placebo. However, given the small effect size of nebivolol in the main SENIORS trial, this analysis lacks power to definitively rule out significant interaction between outcomes of interest and EF. High dropout rates in the main trial, small sample size and low event rate in the non-reduced 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 daily) 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 non-significant trend toward a lower rate of daily activity for patients who received long-acting nitrates.

Recommendation 46: We suggest candesartan be considered to reduce heart failure hospitalizations in patients with HFpEF (Weak Recommendation, Moderate Quality Evidence).

Recommendation 47: We recommend systolic/diastolic hypertension be controlled according to current CHEP hypertension guidelines (2017) to prevent and treat HFpEF (Strong Recommendation, High Quality Evidence).

Recommendation 48: We recommend loop diuretics be used to control symptoms of congestion and peripheral edema (Strong Recommendation, Moderate Quality Evidence).

Recommendation 49: We suggest that in individuals with HFpEF, serum potassium < 5.0 mmol/L, and an estimated glomerular filtration rate (eGFR) > 30 mL/min, a 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 based on the post-hoc geographic subgroup analyses of the TOPCAT trial conducted within North and South America mentioned above.

Practical tips:

- 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.
- There is insufficient quality of data to provide strong recommendations regarding statin therapy in HFpEF, so the decision to treat should be customized and based on existing guidelines for primary and secondary prevention of cardiovascular disease.
- After an MRA or ARB is initiated and with a change in dose, serum potassium and creatinine should be 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, the majority of patients had CAD with previous MI or non-ischemic 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 receive at least as much benefit as patients not meeting these clinical criteria.

Recommendation 50: We recommend an implantable cardioverter-defibrillator 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)

Based on the available evidence, ICD therapy for primary prevention improves survival in patients with NYHA II-III ischemic and non-ischemic 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 cut-off was 35%, although the **M**ulticenter **A**utomatic **De**fibrillator **I**mplantation **T**rial II (MADIT II[190]), used < 30%. While 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 three months.

When considering the risk of sudden death and potential benefit from an ICD, the contribution of systolic dysfunction per se versus 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%).

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 relative risk reduction) than those with NYHA class II symptoms.[189]

Results based on 12 RCTs (8516 patients) and 76 observational studies (96,951 patients), showed that ICD therapy was associated with a 1.2% implant mortality and a total 3.5% annual likelihood of complications including device malfunction, lead problems or infections. There was a 4% to 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 based largely on 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 demonstrated 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 to ICD versus 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 < 68 years of age. DANISH also included a very high proportion of patients treated with CRT (58%) which may 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; an updated meta-analysis of primary prevention ICDs in nonischemic cardiomyopathy that included the DANISH trial found a significant 23% risk reduction in all-cause mortality favoring ICD use.[196] In balance, the weight of evidence appears to favor the use of ICDs for primary prevention in nonischemic HF; however, recent data highlights 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 following titration and optimization of medical therapy. It is reasonable to evaluate response to therapy and LV function

at least 3 months following 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 implantable cardioverter-defibrillator therapy in patients with:

i. Ischemic cardiomyopathy, NYHA class II-III, EF ≤ 35%, measured at least 1 month post MI, and at least 3 months post coronary revascularization procedure (Strong Recommendation, High Quality Evidence);
ii. Ischemic cardiomyopathy, NYHA class I, and an EF ≤ 30% at least 1 month post MI, and at least 3 months post coronary revascularization procedure (Strong Recommendation, High Quality Evidence);
iii. Nonischemic cardiomyopathy, NYHA class II-III, EF ≤ 35%, measured at least 3 months after titration and optimization of GDMT (Strong Recommendation, High Quality Evidence).

Recommendation 52: We recommend against implantable cardioverter-defibrillator 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 transplant or mechanical circulatory support (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 or revascularization.[191] The **C**oronary **A**rtery **B**ypass **G**raft (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 demonstrating 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 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).

Recommendation 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 (http://dx.doi.org/10.1016/j.cjca.2016.09.009) (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

While a detailed review of specific cardiomyopathies is beyond the scope of this document, prevention of SCD in patients with an established diagnosis of hypertrophic cardiomyopathy (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: prior 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 ≥ 30 mm, nonsustained ventricular tachycardia (≥ 3 beats at ≥ 120 beats per minute) on Holter monitoring, and blunted BP response to exercise.[211] While 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 versus 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 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 late gadolinium enhancement (LGE) on CMR imaging, for example) may 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. While there are no 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 HCM who survive a cardiac arrest should be offered an implantable cardioverter defibrillator (Strong Recommendation, Moderate Quality Evidence).

Recommendation 56: We recommend patients with HCM who have sustained ventricular tachycardia should be considered for an implantable cardioverter-defibrillator (Strong Recommendation, Moderate Quality Evidence).

Recommendation 57: We suggest an estimate of risk for SCD in patients with HCM should be determined based on validated risk scores and/or the presence of one or more high risk clinical factors to select appropriate candidates for primary prevention implantable cardioverter-defibrillator 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 implantable cardioverter-defibrillator recommendations in this population place significant weight on individualizing risk assessment whenever possible by clinicians/centers with significant experience in HCM, taking into consideration the potential for device complications.

Practical tip:

- Emerging risk factors for SCD, including late gadolinium enhancement on cardiac MRI, specific genetic mutations and electrocardiographic features may be considered to modify estimate of risk on an individual basis by clinicians/centers 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 demonstrated 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 ≤ 40% and compared CRT versus 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 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% implant 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-D versus 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 based

on the characteristics of patients included in landmark studies and on the clinical characteristics of patients shown to derive significant benefit from CRT based on the totality of available data (Figure 5).

7.1.3.3.1 CRT in patients with AF

The majority of 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 sub-study 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 endpoint 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 one patient underwent AV nodal ablation to effect 100% biventricular pacing.

Indeed, observational data strongly suggests that outcomes in AF patients who receive CRT are associated with the degree of biventricular pacing achieved, and that differential effects in survival may be seen when biventricular pacing achieved is < 98% vs. > 98%.[229] A meta-analysis of observational studies of AV node ablation versus 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 non-response compared with pharmacologic rate control.[230] Ongoing prospective RCTs, including the multicenter **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 versus 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 ≤ 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 HF therapy, or an increase in LV end systolic volume index ≥ 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 ≤ 35%, and QRS duration ≥ 130 ms with LBBB (Strong Recommendation, High Quality Evidence).

Recommendation 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 ≤ 35%, and QRS duration ≥ 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 may be considered for patients requiring chronic RV pacing in the setting of heart failure symptoms and reduced LVEF (Weak Recommendation, Moderate Quality Evidence).

Recommendation 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 demonstrated on current imaging techniques (Strong Recommendation, Moderate Quality Evidence).

Recommendation 63: We recommend the addition of implantable cardioverter-defibrillator (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. Based on 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 ≥ 150 ms are universally more likely to benefit from CRT than patients with less QRS prolongation. The 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.

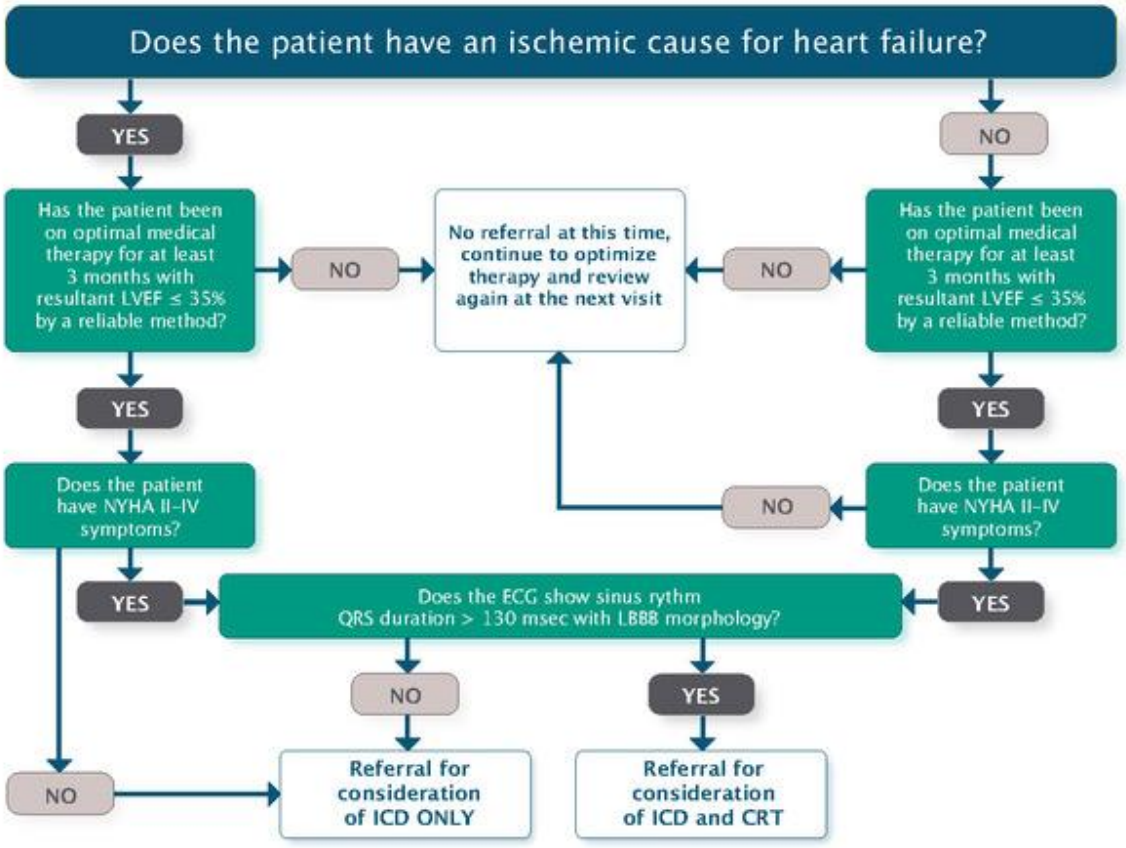

Figure 5: Referral pathway for device therapy in patients with heart failure (HF). The referral pathway for devices should be guided by many factors as outlined in the figure, as well as patient preferences, goals and comorbidity. CRT, cardiac resynchronization therapy; ECG, electrocardiogram; ICD, implantable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

7.1.4 Advanced HF management strategies

While 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 transplant, MCS, or palliative care) the following is a general guide. Cardiac transplant is well established in Canada and further guidance is available at http://www.ccs.ca/en/cctn-home.

Cardiac transplant assessment is typically done by a multispecialty, multidisciplinary team in a specialized setting, using Canadian and international guidance for appropriate work-up 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 (≥ 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 beta-blockers, due to 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 heart failure and secondary pulmonary hypertension.
- Six-minute walk distance less than 300 m.
- Increased 1-year mortality (e.g., > 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 transplant, MCS, or palliative care. Patient preferences should be incorporated into the decision process when assessing further choices.

7.1.5 Mechanical circulatory support

7.1.5.1 What is mechanical circulatory support?

Mechanical circulatory support (MCS) is a group of technologies that increase forward cardiac output in patients.[240] MCS therapies consist of ventricular assist devices (VADs) that augment or replace the ventricle. They may be used to assist the right ventricle (RVAD), LV (LVAD), or both ventricles (BiVAD).[241] The choice depends on the clinical presentation. Those can be divided into 2 categories, the temporary circulatory support and the 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*, and in Tables 15, 16, and 17.

7.1.5.2 What is the purpose of MCS?

Because NYHA class IV was too wide-ranging to allow physicians to discriminate between the preoperative clinical statuses of patients who need MCS, The **Inter**agency Registry for **M**echanically **A**ssisted **C**irculatory **S**upport (INTERMACS) group has created seven INTERMACS categorizations according to the clinical presentations of patients with advanced

HF.[242] These ranged from profile 7 (advanced NYHA class-III symptoms) to profile 1 (critical cardiogenic shock). In general, MCS should be considered for patients with advanced HF or rapidly progressing HF who do not respond to standard therapy.[243] Since such patients may suddenly and unpredictably become too sick for even MCS, referral for MCS should be made early.[244] In the inotrope arm of the Chronic Mechanical Circulatory Support for Inotrope-Dependent Heart Failure Patients Who Are Not Transplant Candidates (INTrEPID trial) the survival was 22% at 6 months and 11% at 1 year.[245]

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

INTERMACS profile descriptions	**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, may 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 few days.
Profile 3: stable but inotrope dependent Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction "Dependent stability"	Definitive intervention elective over a period of weeks to 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 may be some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.	Definitive intervention elective over period of weeks to 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 may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patient may 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 Patient without evidence of fluid overload is comfortable at rest, and with activities of daily living 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	Transplantation or circulatory support

who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	may not currently be indicated.

ADL, activities of daily living; INTERMACS, **Inte**ragency **R**egistry for **M**echanically **A**ssisted **C**irculatory **S**upport; NYHA, New York Heart Association.

7.1.5.3 MCS may be offered as either short- or long-term therapy

Short-Term. These devices[246] are generally utilized for acute clinical presentations to allow time (a few hours to a few days) to determine if transition to transplantation, a long-term device, or explantation is appropriate.[247] Examples include extracorporeal membrane oxygenation (ECMO),[248-254] surgically implanted pumps,[246,255] and percutaneous[256-259] or surgically[260] implanted devices. 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.[247] MCS devices such as durable LVADs involve surgical implantation for which several patients are considered too sick. Besides, critically ill patients in cardiogenic shock who receive a durable LVAD have high perioperative mortality and complications rate.[261] The choice of which MCS device to use is based on many factors, including patient characteristics, the degree of desired hemodynamic support, operator abilities, and institutional resources. Although it provides the smallest hemodynamic support, the intra-aortic balloon counterpulsation (intraaortic balloon pump [IABP]) remains widely used; it is the most easy to insert in emergent circumstances. However, several studies have shown that percutaneous MCS, including the Impella® devices, TandemHeart™, and veno-arterial (VA) ECMO, provides greater hemodynamic support compared with IABP.[247] In general, there is a continuum of increasing hemodynamic support from the IABP to the Impella 2.5 and CP devices to the TandemHeart and VA ECMO.[247] This increased hemodynamic support is, in general terms, at the expense of more invasive vascular access and greater complication rates (bleeding and leg ischemia). There is a paucity of data comparing one device to another. A Randomized Clinical Trial to Evaluate the Safety and Efficacy of a Percutaneous Left Ventricular Assist Device Versus Intra-Aortic Balloon Pumping for Treatment of Cardiogenic Shock Caused by Myocardial Infarction (ISAR-Shock) studied 26 patients, in which the Impella 2.5 LP device increased cardiac index greater than the IABP (0.49 ± 0.46 L/min/m2 compared with a change of 0.11 ± 0.31 L/min/m2; P<.01).[258] The choice of which device to use is multifactorial, based on patient characteristics, operator ability, and the degree of hemodynamic support desired; these devices are best managed with a care team approach that includes an advanced HF cardiologist.[262]

Long-Term. These devices are used for longer term support, are more reliable, provide better cardiac support, and are associated with fewer complications.[240,241,263] First-generation VADs consisted of an inflow cannula from the ventricle to a chamber, which when filled would then empty into an outflow cannula affixed to the ascending aorta.[264] Clinical trials utilizing newer, second generation CF-LVADs, including the Jarvik 2000®, MicroMed DeBakey®, and HeartMate II™ (Thoratec) pumps and HeartWare® ventricular assist device (HVAD) introduced important changes in the field of MCS. Second- and third-generation VADs still require percutaneous drive lines but are nonpulsatile in nature, have fewer moving parts, and demonstrate significantly improved ease of implantation, use, and follow-up as well as durability up to over 15 years.[265] At present, only LV support is feasible for long-term support. Most

recently, the Food and Drug Administration approved the HVAD, a newer, third-generation LVAD. This miniaturized centrifugal pump uses a hybrid magnetic suspension with one moving part and no mechanical bearings. The HVAD is implanted into the intrapericardial space, abolishing the previous pump pocket, which was a problematic region for infection. A multicenter evaluation of this device revealed actuarial survival rates of 90%, 84%, and 79% at 6, 12, and 24 months, respectively.[266] Similarly, the HeartMate III® LVAD, unlike its axial flow predecessor, is a third-generation centrifugal flow pump. Unique in its three-dimensional, magnetically levitated rotor, it is capable of sharp alterations in speed allowing for an induced pulsatile flow.[267] Whether this would translate into clinical benefits is unknown at the present time.

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, transplant, 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 non-invasive monitoring
Type of Support	May be one 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.

7.1.5.4 MCS may be offered as 1 of 5 strategies

MCS can be used in 5 different situations: (1) bridge to decision is used primarily with short-term devices; (2) bridge to recovery provides support until recovery when the device is explanted; (3) bridge to transplantation (BTT) is most common and supports the patient until transplantation; and (4) bridge to candidacy (BTC) are potentially eligible for transplant, and receive MCS until they become eligible.[265] If they remain ineligible, a decision is made to terminate MCS or to continue as destination therapy (DT); (5) DT is long-term MCS for patients who are ineligible for transplant but otherwise have a good life expectancy.

Provision of MCS to patients with advanced HF improves function in nearly every major organ, provided irreversible injury has not occurred.[268,269] Less than 5% of patients have the device removed without transition to transplantation.[270-273] Additionally, studies have shown MCS for patients with selected contraindications for transplantation may result in reversal of these conditions and transplantation is no longer contraindicated.[264,265] Studies have suggested MCS may be superior to inotrope infusion in inotrope-dependent patients awaiting transplantation and where wait times for transplantation may be very long.[243,274]

The use of DT is increasing because of unsuccessful attempts at BTC or direct to DT.[264,275,276] To date, only 2 randomized studies have reported on the use of MCS in transplantation-ineligible patients. In the multicentre Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH trial),[275] the 1-year survival rates were 52% in the MCS group and 25% in the medical group (P = 0.002); at 2 years, rates were 23% and 8% (P = 0.09), respectively, with improved quality of life.[277] Unfortunately, at 2 years, survival in the VAD group was < 10%, with most mortality arising from multiple organ failure, stroke, infection, or device failure. The continuous-flow VAD has led to a significant improvement in outcomes.[263,278-281] In 2009, the results of a randomized trial of 200 HF transplant ineligible patients compared the pulsatile HeartMate-XVE[282,283] to the continuous flow HeartMate II device.[263] The primary endpoint of freedom from disabling stroke or reoperation for repair or replacement of the device at 2 years was lower in the HeartMate II group (46% vs. 11%, P < 0.001). Adverse event rates were also significantly reduced with the HeartMate II. Cost analysis of the HeartMate-XVE, compared with medical therapy, demonstrated a cost per life-year saved of US$50,000-US$100,000, which compares to renal replacement therapy.[284] Most studies have excluded patients who represented very high operative risk or those with other comorbidities that adversely affect long-term outcomes.

Recently, INTERMACS[265] published the seventh annual report, which offers an analysis of over 15,000 patients who received durable MCS at 158 contributing hospitals. The authors note that continuous flow (CF) devices have continued to produce acceptable outcomes, with an actuarial survival rate of 80% at 1 year and 70% at 2 years. They found the following risk factors for increased mortality: older age, female gender, elevated body mass index, history of stroke, renal dysfunction, right heart dysfunction, surgical complexity, implantation for DT, and INTERMACS profile level 1 or 2 status.

With the objective of assessing whether earlier implantation would improve outcome, the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management (ROADMAP) trial has been designed.[285] This prospective, nonrandomized, multicenter observational study of 200 patients compared the impact of the CF HeartMate-II LVAD to optimal medical management in non-inotrope-dependent, ambulatory patients with moderately advanced "stable" HF (INTERMACS profiles 4-7). The primary composite endpoint was survival on original therapy with improvement in 6MWD ≥ 75 m at 12 months. More LVAD patients met the primary endpoint (39% LVAD vs. 21% OMM; OR 2.4 [95% CI 1.2 to 4.8]). Adverse events were higher in LVAD patients, at 1.89 events/patient-year (EPPY), primarily driven by bleeding (1.22 EPPY), than with medical therapy, at 0.83 EPPY. [ROADMAP]; NCT01452802)

7.1.5.5 Who should provide MCS therapy?

There are few data regarding short- or long-term outcomes of MCS therapy outside those with a large volume of experience in the treatment of advanced HF. A recent analysis showed that a volume threshold of > 20 LVADs/year was associated with favorable mortality rates of < 10%,[286] which is more than the annual volume of most Canadian centers.

7.1.5.6 What are the problems associated with MCS?

In most high-volume MCS centers, early survival of MCS surgery approaches 90%, depending upon patient selection. Complications following institution of MCS may be divided into those occurring early (< 30 days) and late (> 30 days). The early complications are as follows. Postoperative bleeding is the most common problem (up to 50%-60%) and is frequently implicated in early death.[287,288] Vascular injury can occur due to insertion either percutaneously or via surgical cutdown and increases with the duration of support.[289] RV failure following the institution of left- sided MCS is of particular concern, as the mortality dramatically rises.[265,290,291] Patients are as prone to the usual array of postoperative infections as are any other cardiac surgical patient.[292]

The late complications following MCS surgery are as follows.[293] Thromboembolism, pump thrombosis or stroke,[294-297] and bleeding, with continuous-flow devices, is seen in 10% of cases, are difficult to treat and are associated with increased mortality.[298-304] Bleeding complications are more common with continuous-flow devices, due to platelet dysfunction, acquired Von Willebrand syndrome[305-308] and development of arteriovenous malformations, primarily in the gut.[303,309] Hemolysis is common but usually minor. Infection is a common complication, mostly of the percutaneous cable.[292,293,310-313] In general, with newer devices, rates of malfunction will be 10% per year of follow-up.[289] MCS patients are prone, through a number of mechanisms, to the generation of allosensitization,[314-316] whether this is leading to incompatibility or more episodes of rejection of transplanted hearts remains unknown.[317,318] Valvular problems may occur,[319] involving mostly the aortic valve that may fuse and develop aortic stenosis or insufficiency.[320-324] Despite these complications, reports suggest 2-year survival with MCS approaches 70%, which compares favorably to patients with moderately severe HF without MCS.[265,276]

7.1.5.7 Special considerations in patients with continuous-flow devices

Several physiologic changes occur in the circulation that will affect the manner in which patients are examined and followed.

Measurement of systemic pressure requires a blood pressure cuff and Doppler probe, which will provide a mean blood pressure.[289] VADs are afterload dependent and thus it is important that mean blood pressure is < 90 mm Hg and preferably < 85 mm Hg. This might be even more crucial for the third generation devices.[298]

A survey of high-volume MCS centers with an estimated combined patient-year exposure to MCS of > 200 years found there were no reported cases of a sudden loss of consciousness.[325] Thus, driving short distances may be safe and feasible for stable ambulatory patients, provided device battery charge is adequate. Consequently, under certain conditions, patients with a VAD can drive a personal vehicle without any perceived increase in motor vehicle accidents. CCS Position Statement Update on Assessment of the Cardiac Patient for Fitness to Drive.[326] http://www.onlinecjc.ca/article/S0828-282X%2811%2901426-7/abstract

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 post-pericardiotomy? (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 which limit operational or long term survival present?
Cardiac transplant 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 pre-operative planning and decision making?

VAD, ventricular assist device.

Practical tips:

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.
- The choice of which MCS device to use is based on many factors, including patient characteristics, the degree of desired hemodynamic support, operator abilities, and institutional resources.
- In general, there is a continuum of increasing hemodynamic support from the IABP to the Impella 2.5 and CP devices to the TandemHeart and veno-arterial (VA) -ECMO.
- The choice of which device to use is multifactorial, based on patient characteristics, operator ability, and the degree of hemodynamic support desired.
- These devices are best managed with a care team approach that includes an advanced heart failure cardiologist.

Candidacy for MCS

In general, patients with HF are potentially candidates for MCS if they fulfill the Advanced HF criteria above.

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;
- 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).

Recommendation 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).

Recommendation 66: We recommend that MCS be considered for patients for whom there is a contraindication for cardiac transplantation but may, via MCS, be rendered transplant eligible (Strong Recommendation, Low Quality Evidence).

Recommendation 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 (ECMO) or other mechanical circulatory temporary devices should be preferred over IntraAortic Balloon Pump (IABP) except if the patient is suffering an acute ischemic event, as the increase in cardiac output offered by IABP is usually minimal.

Recommendation 68: We recommend permanent MCS be considered for highly selected transplant 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

Recommendation 69: We recommend that institutions providing MCS therapy develop a policy regarding DT within the conventions, resources, and philosophy of care of their organization (Strong Recommendation, Low Quality Evidence).

Recommendation 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 by a validated scoring system is recommended. If the expected mortality is higher than 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 following 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 demonstrating the benefits of exercise training for patients with HF.[327-329] There has been one large RCT that has demonstrated the benefits of exercise training.[330] 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 two groups. A systematic review examined the effectiveness of exercise-based rehabilitation in 33 trials with 4740 patients with predominately HFrEF.[327] There was no reduction in all-cause mortality with up to one year of follow up, and a trend to reduction in all-cause mortality in trials with more than one year of follow up (6 trials; 2845 participants; relative risk (RR) 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.[329-332]

Exercise training results in increases of exercise capacity.[333,334] A meta-analysis reporting on results of studies that measured peak volume of oxygen (VO_2)directly found an average 17% improvement in peak VO_2.[329] The evidence for quality of life improvements in patients with HF exposed to exercise training is further supported by multiple studies.[327,335] 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.[334]

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.[336] Piepoli et al,[337] 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.[328,338-340] Studies have also demonstrated that exercise training can take place in patients with ICD or CRT therapy. These studies have demonstrated 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).[341,342]

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: o Moderate intensity: RPE scale 3-5, or 65%-85% HR_{max}, or 50%-75% peak VO_2 o Moderate intensity aerobic interval might be incorporated in selected patients o Intervals of 15-30 minutes with an RPE scale of 3-5 o 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, **R**ated **P**erceived **E**xertion; VO_2, volume of oxygen.

Recommendation 71: We recommend regular exercise to improve exercise capacity, symptoms and quality of life in all heart failure patients (Strong Recommendation; Moderate Quality of Evidence).

Recommendation 72: We recommend regular exercise in heart failure patients with reduced ejection fraction to decrease hospital admissions (Strong Recommendation; Moderate Quality of Evidence).

Value 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 non-pharmacological and non-device 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.[343-346]

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.[344,346,347] 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.[348] Ongoing RCT will provide guidance on this topic (clinicaltrials.gov 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.[349-351] 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 to all patients with HF, and if it is believed to be responsible and/or contributing to the syndrome it should be avoided altogether as there is a dose-dependent effect and individual susceptibility to the deleterious effects of alcohol.[352]

As 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 heart failure should restrict their dietary salt intake to between 2 g/day and 3 g/day (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 heart failure, 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 (i.e. > 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/day should be considered for patients with fluid retention or congestion that is not easily controlled with diuretics (Weak Recommendation, Low Quality Evidence).

Practical tips:

- The appropriate quantity of fluid intake is also a subject of debate. Strict limits should be imposed when there is clear fluid overload or demonstrated sensitivity to fluid intake.
- Severely limiting daily fluid intake to < 1.5 L may have adverse consequences on nutrition, renal function, quality of life without known additional benefit and should be applied selectively.
- Special consideration for hyponatremic patients should be applied.
- Alcohol intake should be avoided if it is a precipitating or contributing factor.
- 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 co-exist.[353,354] Up to 50% of patients with HF may 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.[355]

The presence of AF is associated with a worse prognosis both in terms of overall survival[356,357] and risk of stroke.[358] AF may 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.[359]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*.

7.2.1.1 Primary Prevention of AF

Primary prevention of AF in patients with HF may be achieved through application of established evidence based therapies for HF such as RAAS inhibitors and beta-blockers.[360-363] Aggressive management of co-morbidities linked to both diseases (e.g. hypertension) should be pursued. Once it occurs, classification and management of AF should follow current CCS Guidelines;[364] however there are a number of specific considerations in the HF population that warrant discussion including the merits of rate vs. rhythm control of AF, the role of catheter ablation and the optimal strategy for stroke prevention.

7.2.1.2 Rate and rhythm control strategies

The **A**trial **F**ibrillation in **C**ongestive **H**eart **F**ailure (AF-CHF) trial is the largest study to compare the efficacy of pharmacological rhythm vs. rate control strategies in patients with HF.[359] The study enrolled 1376 patients with HFrEF and NYHA Class I-IV symptoms who had experienced an episode of clinically significant AF in the prior six months. Participants were randomized to either a rhythm control strategy, which could include electrical cardioversion and class III antiarrhythmic agents, or a rate control strategy to include beta-blockers, digoxin and AV node ablation if necessary. After a mean follow-up of 37 months, there was no difference between groups in the primary end-point of death from cardiovascular causes (HR 1.06; 95% CI 0.86-1.03; p=0.59). Similarly, there was no difference in secondary end-points including all-cause mortality, stroke or worsening HF. Based on these results, there is no compelling data in support of a routine rhythm control strategy for patients with HF and AF to reduce morbidity and mortality.

Beta-blockers are the preferred pharmacological agent to control ventricular rate in those with HF and AF, however their impact on mortality in this patient population is less clear. Results from an individual patient data meta-analysis including 3066 subjects with AF and HF RCT, showed no benefit of beta-blockers in this group compared to those patients with HF who were in sinus rhythm (HR 0.97; CI 0.83-1.14).[363] AF was associated with higher mortality than sinus rhythm in the Swedish Heart Failure Registry, which included 18858 patients with HFrEF.[365] A significant relationship between heart rate and mortality was observed above a resting HR of 100bpm for patients with AF. In that study, there was no significant interaction between the use of beta-blockers and the relation between HR and mortality for patients in sinus rhythm or for patients in AF. The use of beta-blockers was associated with lower mortality in both sinus rhythm and AF. For patients in AF receiving beta-blockers, the risk of mortality increased only when heart rate was above 100 bpm.

In patients with persistent tachycardia despite beta-blocker therapy, digoxin may be considered with caution to avoid toxicity.

Guidance on the optimal heart rate while in AF is largely extrapolated based on data from the Rate Control Efficacy in Permanent Atrial Fibrillation (RACE II) trial which included a small subset of patients with HFrEF.[366] There was no difference in clinically meaningful outcomes between those patients randomized to a lenient (resting heart rate <110 beats per minute) or strict

(resting heart rate <80 beats per minute) rate control strategy. These findings are supported by a retrospective combined analysis of the AF-CHF and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trials which showed that heart rate in AF is not predictive of mortality, although rates >115 beats per minute were associated with an increased risk of hospitalization.[367]

Rhythm control of AF is reserved for patients with refractory symptoms and/or in those for whom adequate heart rate control cannot be achieved. Amiodarone is the preferred available pharmacological agent for achieving and maintaining sinus rhythm in patients with HF. A retrospective sub-group analysis of Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) examined the efficacy of amiodarone at achieving sinus rhythm among the cohort of patients in the study with AF at baseline.[368] Compared to placebo, amiodarone was associated with an improvement in conversion and maintenance of sinus rhythm 31% versus 8%, p=0.005) after 4 years of follow-up. Of note, among those patients who remained in AF, the average ventricular rate was lower in those treated with amiodarone, recognizing that amiodarone has a number of longitudinal safety issues.

Catheter ablation of AF appears to be a promising strategy for rhythm control in patients with HF although a meta-analysis suggests that maintenance of sinus rhythm at 2 years approximates only 60%.[369] Data at this stage is drawn primarily from small randomized trials utilizing surrogate endpoints and short follow-up periods. Nonetheless, compared to rate control strategies, catheter ablation has been shown to improve functional capacity, LVEF, peak oxygen consumption, NP levels and quality of life in patients with HF.[370-372]

7.2.1.3 Anticoagulation

Patients with HF and AF are at increased risk of stroke based on the $CHADS_2$ scoring system and should be systemically anticoagulated, in the absence of contraindications, as per CCS AF Guidelines.[364] Two recent meta-analyses demonstrated the superiority of non-vitamin K antagonist oral anticoagulants (NOACs) compared to warfarin among patients with HF both in terms of safety and efficacy.[373,374] As such, NOACs should be the preferred agent for stroke prophylaxis in patients with HF with appropriate consideration for dosing adjustments based on age, weight and renal function.

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).

Recommendation 77: We recommend beta-blockers for rate control particularly in those with HFrEF (Strong Recommendation, Moderate Quality Evidence).

Recommendation 78: We recommend rate-limiting CCBs be considered for rate control in HFpEF (Weak Recommendation, Low Quality Evidence).

Recommendation 79: We recommend the use of antiarrhythmic therapy to achieve and maintain sinus rhythm, if rhythm control is indicated, be restricted to amiodarone (Strong Recommendation, Moderate Quality Evidence).

Recommendation 80: We recommend the addition of digoxin in patients with HFrEF and chronic AF and poor control of ventricular rate and/or persistent symptoms despite optimally tolerated beta-blocker therapy, or when beta-blockers cannot be used (Strong Recommendation, Low Quality Evidence).

Recommendation 81: We recommend that restoration and maintenance of sinus rhythm in chronic HF not be performed routinely, but individualized based on patient characteristics and clinical status (Strong Recommendation, High Quality Evidence).

Recommendation 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 the patient has failed or is unable to tolerate antiarrhythmic therapy (Weak Recommendation, Low Quality Evidence).

Recommendation 83: We recommend oral anticoagulation for AF in patients with HF unless contraindicated, as per current CCS AF guidelines,[375] and not to co-administer antiplatelet agents unless the latter are strongly indicated for other reasons (Strong Recommendation, High Quality Evidence).

Recommendation 84: We suggest that NOACs should be the agent of choice for stroke prophylaxis in patients with HF and non-valvular AF, and that the treatment dose be guided by patient specific characteristics including age, weight and renal function (Weak Recommendation, Moderate Quality Evidence).

Recommendation 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 based on 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 pro-arrhythmia 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.[375]
- In patients with HF with AF, for whom a rate control strategy is employed, the heart rate treatment target remains unclear. Retrospective analyses of large RCTs suggest that rates greater than 110-115 bpm may be associated with worse outcomes.[375]

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.
- Non-dihydropyridine CCBs (e.g., verapamil and diltiazem) should not be used to control heart rate in patients with HFrEF because they can depress cardiac function and worsen HF.
- Dronedarone should not be used in patients with an EF < 35% and/or with recent decompensated HF because of in-creased risk of mortality. Agents such as sotalol, flecainide, and propafenone should also be avoided.
- Beta-blockers and non-dihydropyridine CCBs should not be routinely combined as part of a rate control strategy in patients with HF as this may be associated with high degree AV-block
- In acutely decompensated patients with AF and HFrEF, digoxin is the first choice for heart rate control and beta-blockers may be added when the patient has clinically stabilized
- Among patients with HF receiving digoxin for rate control, trough serum digoxin levels should not exceed 1.0ng/mL

7.2.2 Coronary artery disease and revascularization

Nearly 60% of patients with chronic HF suffer from CAD, and approximately 15% of acute HF cases occur in the setting of an ACS.[376,377] 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 HF with preserved EF. Although ample evidence exists to support PCI in patients with HF due to ACS,[378] there is limited evidence to support its use in the setting of chronic HF to reduce adverse clinical outcomes.[379] A detailed discussion of different imaging modalities, an approach to the diagnosis of CAD and the peri-operative management and the approach to revascularization are covered in sections *7.2.2.1 – 7.2.2.5*.

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

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

Recommendation 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.

7.2.2.1 Diagnosis of CAD in patients with HF

The approach to the assessment of CAD in patients with HF is illustrated in Figure 6.[380] Identification of the etiology of HF has significant therapeutic and prognostic implications. CAD is present in more than 60% of patients with HF and the absence of a history of myocardial infarction or angina is insufficient to rule out CAD as the etiology for HF.[381,382] Presence of CAD is associated with a poor prognosis and has implications regarding revascularization or device therapy. An important distinction must be made between the presence of CAD, which might coexist with HF but not be the primary etiology of the syndrome of HF and ischemic cardiomyopathy, when the principal etiology for HF is CAD. Although CAD might contribute as a comorbid factor in HF, it is largely treated for symptoms and prevention only, whereas ischemic cardiomyopathy is a distinct condition defined by the combination of LV systolic dysfunction due to multivessel CAD or clear evidence of a previous ischemic insult to a large portion of the myocardium and its subsequent remodelling.[382] Surgical revascularization for ischemic cardiomyopathy might have prognostic and symptomatic benefits.[383] As such, it is important to determine the presence and effect of CAD for all patients with HF.

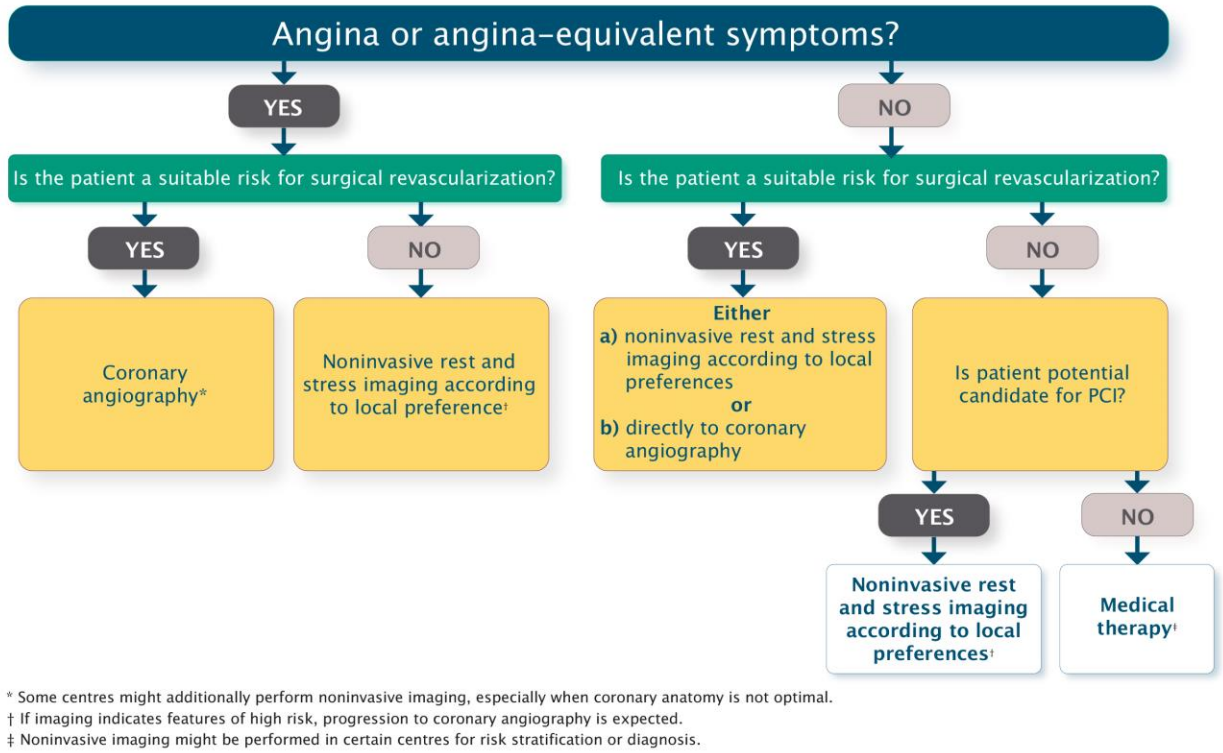

Figure 6: The approach to assessment for coronary artery disease in patients with heart failure. All patients with heart failure are expected to undergo non-invasive measurement of systolic function (not included in this algorithm). PCI, percutaneous coronary intervention.

Three types of ischemic abnormalities portend differential responses to medical therapy (such as b-blockade) and revascularization.[381] These include: (1) reversible ischemic myocardium; (2) hibernating, or viable myocardium, a state in which segments of the myocardium exhibit abnormalities of contractile function[384]; and (3) nonviable myocardium. In theory, these types of myocardium behave differently. Ischemic myocardium is likely to improve function after revascularization (> 80% likelihood), and hibernating and viable myocardium states are less likely (40%-50% likelihood) to improve measured according to segmental wall motion.[385-388] A body of evidence supports the concept that patients with reversible segments experience the best clinical and functional outcomes after surgical revascularization, followed by those with hibernating/viable segments.[388-390] As such, the presence of reversible or viable myocardium might affect the decision to proceed to a revascularization procedure, but will not be the sole determining factor.[391]

7.2.2.2 Imaging for reversible ischemia as a guide to the presence of CAD

Although noninvasive imaging is increasingly used to determine the presence of CAD, coronary angiography is still the gold standard for diagnosis. It has been shown to lead to an etiological reclassification in HF in up to 25% of cases.[376,392] Several noninvasive tests might allude to the presence or absence of CAD. These include exercise or pharmacologic stress perfusion imaging using cardiac magnetic imaging (CMR), nuclear imaging, positron emission tomography (PET), or echocardiography. The diagnostic accuracy for presence of CAD has been reported

from 70% to 90% using nuclear stress imaging.[387,391,393] Sensitivity is typically very high (> 90%) and specificity might be as low as 60%, with PET demonstrating the higher sensitivity and stress echocardiography the highest specificity.[388-391] Stress CMR is an emerging modality that might be used as a screening test to define the need for coronary angiography. However, it is most commonly used for determination of the functional implications of known CAD. Patterns of delayed gadolinium enhancement are usually able to differentiate between ischemic and nonischemic cardiomyopathy.[394] Coronary computed tomography and calcium scoring might accurately identify the presence of CAD, but at present do not provide clinically useful functional data and are of uncertain value.

7.2.2.3 Imaging for hibernating myocardium

Hibernating myocardium is underperfused, hypocontractile, but viable tissue that has the potential for functional recovery with restoration of normal blood flow.[390,395] Therefore, hibernating myocardium can only be defined with certainty after revascularization. Multiple imaging modalities are used to identify the presence of hibernating myocardium and are grouped into 3 categories. First, nuclear imaging studies test metabolic and cellular integrity and PET scanning is considered to be the gold standard. The **P**ET **a**nd **R**ecovery Following **R**evascularization-2 (PARR-2) trial investigators reported improved out- comes after revascularization in patients with > 7% hibernating myocardium.[396] Second, CMR might define scarred and fibrotic myocardium with limited potential for recovery. Kim et al. re- ported a > 75% potential for functional recovery in the absence of scar, and < 2% recovery in segments with more than 75% scar thickness.[393] Finally, dobutamine stress echocardiography (DSE) might be used to measure contractile reserve. The Viability Identification With Dobutamine Administration (VIDA) study investigators reported lower mortality in patients with viable myocardium treated with revascularization compared with those treated medically using DSE.[397] **C**linical **E**valuation of **Ma**gnetic **R**esonance Imaging in **C**oronary Heart Disease (CE-MARC) is the largest, prospective, real world evaluation of CMR and has established CMR's high diagnostic accuracy in CAD and CMR's superiority over single-photon emission computed tomography.[398] Comparative studies between these different imaging modalities report higher sensitivity with PET, and higher specificity with CMR and DSE.

Despite the observational evidence base evaluating these therapies, few adequately powered randomized studies exist. The Medical Imaging Trial Network of Canada (MITNEC) is studying imaging applications in clinical research and practice (www.mitnec.org). A Canadian initiative, the IMAGE-HF Project I-A: Cardiac Imaging in Ischemic Heart Failure (AIMI-HF)[399] (ClinicalTrials.gov, identifier NCT01288560) has a primary objective to compare the effect of imaging strategies on the clinical outcomes. Although the myocardial perfusion literature is robust in terms of predicting surgical risk and the likelihood of experiencing clinical improvement after surgical revascularization, data from the only randomized trial of surgery in ischemic cardiomyopathy failed to demonstrate the utility in identification of patients who would benefit from a surgical strategy.[400]

Practical tips:

- Several noninvasive methods for detection of CAD are in widespread use, including DSE, perfusion CMR, cardiac PET testing, cardiac CT, and nuclear stress imaging. Local

factors (availability, price, expertise, practice patterns) will determine the optimal strategy for imaging.

- 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.
- Patients with HF and reduced LVEF are more likely to experience significant improvement in LVEF after successful coronary revascularization if they demonstrate:
    - 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 PET scanning;
    - Reversible ischemia or > 20% of the left ventricle shown as viable using DSE;
    - < 50% wall thickness scarring shown by late gadolinium enhancement on CMR imaging.

7.2.2.4 Disease management, referral, and perioperative care

Care of the patient with HF is best accomplished using an interdisciplinary team approach including a primary care physician, nurse with disease management and HF care skills, pharmacist, and specialists with experience and expertise in HF care. Selection of revascularization will depend on many factors in addition to LVEF and coronary anatomy, such as comorbid conditions (especially frailty and renal dysfunction), access to rehabilitative services, caregiver support, care preferences, and goals of care. Patients with HF are subject to between 2 and 5 times increased procedural risks of elective procedures such as coronary revascularization, whether surgical or percutaneous, compared with similar patients without HF.[401-403] The risk is substantially increased in the settings of nonelective surgery or in the presence of decompensated HF.[403] As such, careful consideration and control of all concomitant medical conditions including optimization of HF are essential before revascularization. These strategies are thought to improve a given patient's clinical status, functional status, and LV function thereby reducing perioperative risk and, in some cases, mitigating the need for concomitant surgical procedures.

RCTs that examined device therapy, CRT and/or ICD, mandated that all planned revascularization be completed at least 3 months before enrollment into the trial.[190,198,203] If a decision to refer for revascularization is made, the team accepting care should include medical and surgical members with expertise and experience in revascularization of patients with chronic HF. For patients with advanced HF, this might require referral to a centre that has an established program and expertise in management of advanced HF, mechanical circulatory support, or cardiac transplantation.[184,404] A multidisciplinary team should be involved with the care from the planning and assessment phase before surgery through the course of hospitalization with a coordinated plan for transitioning to the chronic care setting.

Many clinicians believe that patients who present with HF characterized by significant volume retention will benefit from a period of diuresis which might require adjunctive preoperative inotropic support. Some clinicians advocate for preoperative IABP support. A recent meta-analysis of IABP support suggested a modest clinical benefit but potential harm.[405] Postoperatively, reinstitution of standard HF therapies should be undertaken in a measured

manner. In addition, significant volume overload is often present immediately after surgical revascularization, necessitating concomitant diuresis and increased risk of toxicity associated with medication up titration.

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).

Recommendation 89: We recommend that efforts be made to optimize medical status before coronary revascularization, including optimizing intravascular volume (Strong Recommendation, Low Quality Evidence).

Recommendation 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.[406-409]

The **C**oronary **A**rtery **S**urgery **S**tudy (CASS) enrolled 780 patients with stable ischemic heart disease between 1975 and 1979. Randomization was stratified initially into 3 groups: patients with angina and LVEF > 50%; patients with angina and LVEF < 50%; and asymptomatic patients within 6 months after myocardial infarction.[406] Randomization was further stratified by the number of diseased vessels for the first 2 groups and by the number of diseased vessels and EF in the third group. Although survival was similar in the medical and surgical groups overall at 10 years (79% vs. 82%; $P = 0.25$), survival was greater in patients with angina and LVEF < 50% (59% vs. 80%; $P = 0.01$) and in patients with LVEF < 50% (61% vs. 79% 10-year survival) treated with surgery. This conclusion was based on only 160 patients with LVEF < 50% of whom there were few patients with an EF < 35%.

A similar result was seen in the VA Cooperative Study (N ¼ 686; 595 patients without left main stenosis; 55% of patients had LV dysfunction [LVEF < 50% or regional dysfunction of < 25% of the myocardium]).[407] At 7 years, survival was 63% in medically treated patients compared with 74% in CABG-treated patients ($P = 0.049$). This benefit was attenuated by 11 years (49% vs. 53%; $P = 0.25$). The other major trial was conducted by the European Coronary Surgery Study group, and enrolled 767 male patients with normal LV function.[408] This study identified an overall survival benefit in patients randomized to CABG (92.4% vs. 83.1%; $P = 0.0001$ at 5 years; 70.6% vs. 66.7% at 12 years; $P = 0.04$). In a systematic review and meta-analysis, relative survival advantage was similar in patients with normal or reduced LV function (odds ratio, 0.61 vs. 0.59), although the absolute survival advantage was greater in patients with decreased LV function.[409] An important limitation of these earlier studies is the limited representation of patients with significant LV dysfunction, limited medical and device therapy, and very few patients had symptomatic HF and the results might not be applicable to the contemporary HF population.

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 surgical ventricular reconstruction (SVR) of an akinetic/dyskinetic anterior wall provide better outcomes than isolated CABG for eligible individuals.[410] This study evaluated patients with ischemic cardiomyopathy with or without HF symptoms and randomized them into 3 groups, namely, optimal medial therapy and CABG alone, CABG with the SVR procedure, or neither procedure.

For the first hypothesis, 1212 patients were randomized to medical therapy alone or in combination with CABG.[411] At a median follow-up of 56 months, 17% of patients allocated to medical therapy crossed over to the surgical arm, and 91% of the surgically allocated group underwent CABG within 1 year. For the primary outcome, 41% of those allocated to medical therapy died, compared with 36% in the CABG arm. The secondary endpoint of death from any cause or hospitalization for cardiovascular causes occurred in 68% in the medical therapy group and 58% in the CABG group. Thus, for every 10 patients who underwent CABG in this study, 1 subsequent death or hospitalization was prevented over the course of 4.5 years. After a median of 9.8 years, 359 patients (58.9%) in the CABG group died, as compared to 398 patients (66.1%) in the medical-therapy group, a 16% relative reduction. This reduction was due to a 21% reduction in death from cardiovascular causes. In addition the combined occurrence of death from any cause or hospitalization for cardiovascular causes was 28% lower in the CABG arm. Importantly, these results occurred irrespective of the presence of angina.[412]

For the second hypothesis, 1000 patients who were eligible for SVR in addition to CABG were randomly allocated to receive CABG alone or in combination with SVR surgery. This group (median LVEF 28%; end systolic volume index of 82 mL/m2) experienced a 5% 30-day mortality with a 17-mL/m2 reduction in LV volume. Despite the excellent technical surgical result, there was no reduction in mortality or the composite endpoint of mortality plus repeat hospitalization. Subgroup analyses failed to identify any particular group that might benefit from SVR.[413]

Regardless of how STICH is interpreted, several technical considerations were incorporated into patient selection. First, the presence of at least 1 good coronary target with a critical proximal lesion was required. This did not have to be the left anterior descending artery and indeed, some patients might have been subjected to SVR in the presence of viable, but ischemic inferior and lateral walls. Second, the presence of mitral insufficiency increased the risk of surgical intervention, particularly when accompanied by significant pulmonary hypertension and concomitant tricuspid insufficiency.

More recently, there has been increased attention to the repair of functional mitral regurgitation (MR) in patients with ischemic heart disease. These patients tend to present with mild to moderate systolic dysfunction and restricted mitral leaflets.[413] The data on such patients are conflicting in relation to the increased morbidity and mortality when compared with their peers without functional MR. A single blind RCT assessed mitral repair in patients with mild to moderate systolic dysfunction and moderate MR.[414] In this study, the degree of MR was significantly reduced in the group allocated to CABG plus mitral repair compared with those with CABG alone. The primary end point, peak VO2, was increased by more than 2.0 mL/kg/min. However, no significant reduction in clinical events or mortality was noted, and the dominant clinical feature of the study population was severe MR rather than HF per se. Additional data are needed before consideration of routine mitral repair can be recommended. Similarly, discussion of percutaneous methods for reduction of MR in the HF population is premature and beyond the scope of this update.

Two year results have now been published for the two separate RCTs of surgery for ischemic MR.[415,416] For patients with moderate MR (total sample size 301), the addition of a restrictive annuloplasty to CABG, compared to isolated CABG, resulted in similar mortality (10.0% vs. 10.6%, p=0.78) but greater risk of neurological events and supraventricular arrhythmias. Reduction in the left ventricular end systolic dimensions, the primary study endpoint, was similar in both groups. For patients with severe MR (total sample size 251), CABG with mitral valve repair compared to replacement resulted in similar mortality. Reduction in left ventricular end systolic dimensions, the primary endpoint, was similar in the two treatment arms, while recurrent MR (moderate or greater) was higher with mitral valve repair (58.8% vs. 3.8%, $p<0.001$). Longer term reports from both studies will be very important.

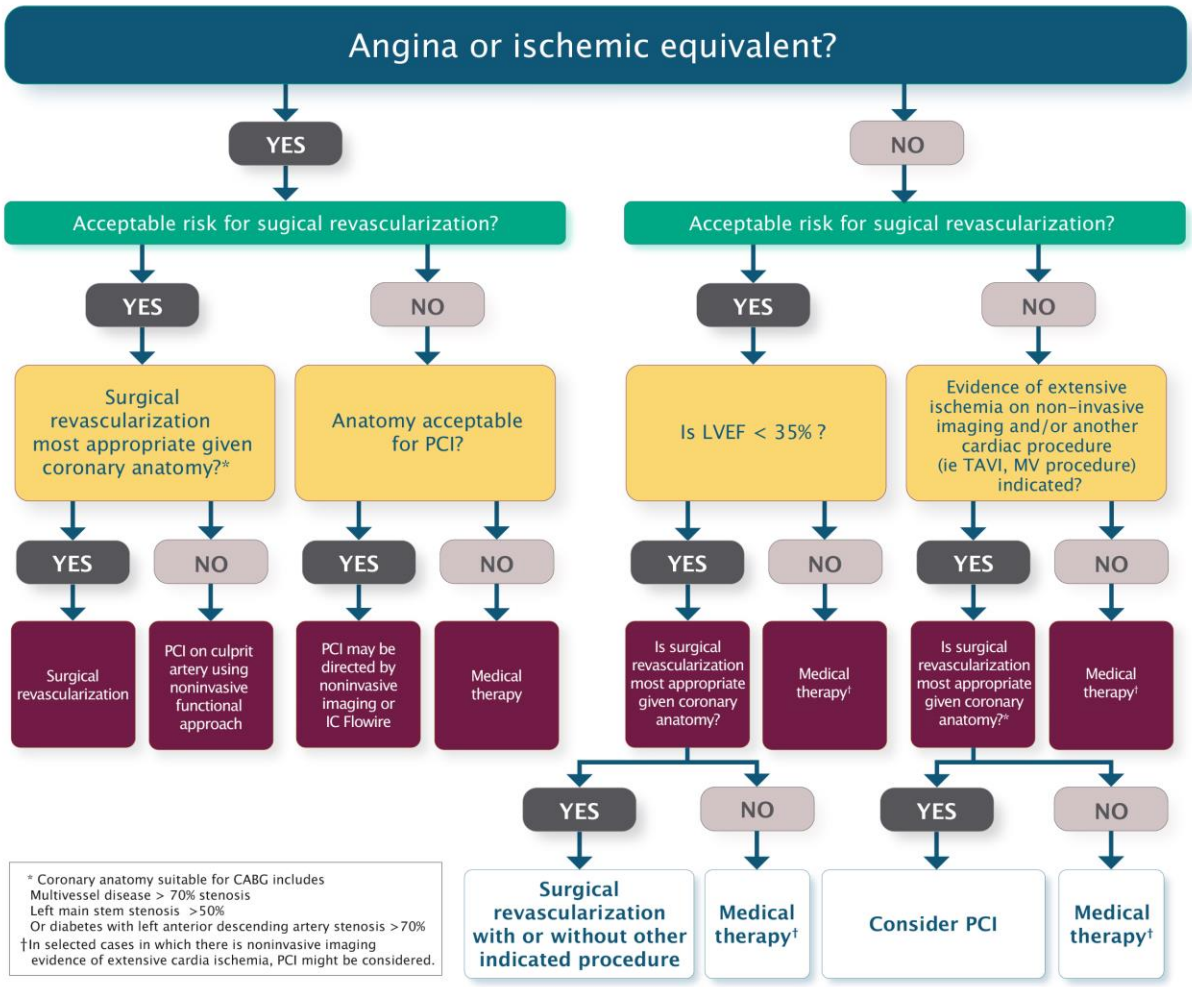

Figure 7: Decision regarding coronary revascularization in patients with heart failure. It is recommended that surgical and interventional cardiology consultation be considered early in this process. CABG, coronary artery bypass grafting; IC, intracoronary; LVEF, left ventricular ejection fraction; MV, mitral valve; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.

More recent studies have included PCI and surgical revascularization together to assess the potential benefit of revascularization compared with medical therapy. A meta- analysis of observational studies (3088 patients, average LVEF of 32%) to determine the importance of either early or late perfusion viability, shown using thallium imaging, PET, or DSE testing before revascularization.[391] In patients with viability, annual mortality was 3.2% in the revascularized patients compared with 16.3% in medically treated patients ($P < 0.0001$). In patients without viability, revascularization was associated with similar annual mortality (7.7%) compared with medically treated patients (6.2%). In an observational study from Canada,[417] 4228 patients with a history of HF were treated medically (n = 1690) or with PCI or surgical revascularization (n = 2538). Only 23% of patients had a normal LVEF and 25% had a LVEF < 35%. Revascularization using PCI or surgery was associated with a 48% lower mortality in

adjusted analyses. Surgery and PCI provided a similar association of a lower mortality in unadjusted analyses.

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%.[418] 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).

It is unclear whether off-pump surgery is associated with lower operative mortality than traditional on-pump CABG for patients with HF. A review of 86 RCTs (10,716 participants) compared on- and off-pump CABG.[419] Overall, off-pump surgery was associated with a greater risk for 30-day mortality (3.7% vs. 3.4%; relative risk, 1.24; 95% CI, 1.01- 1.53; *P* = 0.04). The applicability of this review to patients with HF and impaired systolic function is unclear.

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 and quality of life (Strong Recommendation, Moderate Quality Evidence).

Recommendation 92: We suggest consideration of PCI for patients with HF and limiting symptoms of cardiac ischemia, and for whom coronary artery bypass grafting (CABG) is not considered appropriate (Weak Recommendation, Low Quality Evidence).

Recommendation 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 based on 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 based on clinical need rather than RCT trial data.

Practical tips:

- 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.
- 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.
- In highly selected cases, patients with advanced HF symptoms in association with large areas of dyskinetic and nonviable myocardium might experience clinical improvement with SVR or similar type procedures, when performed by experienced surgeons.
- While mitral valve repair or replacement are both considered acceptable strategies for treatment of severe MR, it should be noted that the addition 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 (CACPR) and CCS joint position statement includes routine cardiac rehabilitation for patients with HF who successfully complete CABG surgery.[420]

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 pre-existing rehabilitation guidelines statements.

7.2.3 Right HF

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.[421] The most common reason for RHF is left-sided HF but occasionally RHF might occur as pure right-sided HF (Table 19).

Table 19: Causes of right heart failure (RHF)

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

RHF, right heart failure; RV, right ventricular.

In HF, RV dysfunction is a strong predictor of mortality.[422,423] 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.[424] In another study of 250 consecutive patients with dilated cardiomyopathy it was shown that reduced RVEF below 45% using MRI was an independent predictor of transplant-free survival and worse prognosis.[425]

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 echocardiogram (TTE). CMR imaging has become the test of choice for noninvasive assessment of RV size, function, viability, potential etiology, and mass.[426] In selected patients with RHF, right heart catheterization should be considered to help determine etiology of RHF and provide PAP, pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance (PVR). Pulmonary arterial hypertension (PH) is defined by a mean PAP of $\geq$ 25 mmHg and increased PVR of > 3 Wood units with a normal PCWP < 15mmHg.[427]

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, as 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 due to the fact that these studies were underpowered or that mechanisms of injury and repair might differ.[428-431]

Patients with RHF secondary to congenital heart disease or secondary to PH should be referred early to specialized clinics for investigations and management.[432,433]

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 may 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.[433]

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.[434,435] 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.

Table 20: Common symptoms, signs and test results in right heart failure (RHF) without pulmonary hypertension and in cor pulmonale

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

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

7.2.3.1 Arrhythmogenic right ventricular cardiomyopathy

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.[436] ARVC is an autosomal dominant inherited

disease with variable penetrance and expression. Prevalence of ARVC is estimated to be 1:1000 – 1:5000[437,438] affecting men more frequently than women with a ratio 1:3.[439]

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 (e.g., 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.[440] Current Task Force Criteria for ARVC diagnosis developed diagnostic criteria based on six categories: typical ECG findings (e.g., epsilon waves), ventricular arrhythmias (left bundle block morphology), morphological and functional changes in RV, 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.

Table 21: Comparison of Original and Revised Task Force Criteria (TABLE 1 from Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533-41)[440] http://circ.ahajournals.org/content/121/13/1533/tab-figures-data

Echocardiography and CMR imaging are the most commonly used tests for the diagnosis of ARVC.[441] Strain echocardiography is one of the newest modalities and it appears to be very effective in the assessment of RV function.[442] CMR imaging if available is a preferred test to echocardiography for ARVC.[443] 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 due to the patchy distribution of the disease.

Genetic testing can be useful in patients with 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.[444] Beta-blockers have shown effectiveness in reducing adrenergically stimulated arrhythmias.[445]

ARVC patients at high risk for sudden death based on a clinical profile with one or more risk factors for sudden death should be considered for ICD as a primary prevention.[446] For secondary prevention of sudden death in the ARVC population, ICDs are indicated.[447] 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.[448] Patients with suspected or confirmed ARVC should avoid vigorous physical activity like competitive sports, or regular activities associated with symptoms.[449,450]

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.[451]

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 as clinical presentation is often atypical and might mimic other causes of the RHF.[452] Chest x-ray is very helpful in diagnosis of constrictive pericarditis as in 27% of cases, calcification can be seen in the pericardium.[453] In cases where diagnosis of constrictive pericarditis is suspected, a special "constriction protocol" should be requested when ordering an ECHO.[454] 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.[455-457] 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 non-invasive evaluation is indeterminate, the cardiac catheterization with hemodynamic assessment is the test of choice.[458]

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 short course of anti-inflammatory medications or corticosteroids.[459]

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% to 12%, [460,461] 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 right heart failure (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. An echocardiogram 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).

Recommendation 96: We recommend that patients with right heart failure (RHF) secondary to or in association with left heart failure (LHF) should be managed as per LHF guidelines (Strong Recommendation, High Quality Evidence).

Recommendation 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 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).

Recommendation 99: We recommend that right heart catheterization be considered in selected patients with right sided heart failure to determine the true PASP, PVR, TPG, PCWP and to exclude the left sided heart failure as the underlying cause (Strong Recommendation, Low Quality Evidence).

Recommendation 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).

Recommendation 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 center with expertise and experience in the management of these conditions (Strong Recommendation, Low Quality Evidence).

Recommendation 102: We recommend that patients with severe (peak gradient higher than 80 mmHg) or symptomatic moderate (peak gradient 50 mmHg to 79 mmHg) pulmonary valvular

stenosis should be referred or considered for balloon valvuloplasty or surgical intervention (Strong Recommendation, Low Quality Evidence).

Recommendation 103: We recommend bioprosthetic rather than metallic prosthesis for replacement of right sided valvular lesions (Strong Recommendation, Low Quality Evidence).

Recommendation 104: We recommend diagnosis of ARVC be made according to the European Society of Cardiology (ESC)/International Society and Federation of Cardiology criteria (revised in 2010) to establish a diagnosis (Strong Recommendation, Low Quality Evidence).

Recommendation 105: We recommend individuals with ARVC avoid strenuous or high-intensity sports activities (Strong Recommendation, Moderate Quality Evidence).

Recommendation 106: We recommend an implantable cardioverter defibrillator (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).

Recommendation 107: We recommend ICD be considered for the prevention of sudden cardiac death (SCD) in eligible patients with ARVC in whom the risk of SCD is judged to be high (Strong Recommendation, Low Quality Evidence).

Recommendation 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).

Recommendation 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).

Recommendation 110: We recommend CT scan or CMR be performed in all patients with suspected constrictive pericarditis to assess for pericardial thickening (Strong Recommendation, Low Quality Evidence).

Recommendation 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).

Recommendation 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).

Recommendation 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 tips:

- Atrial septal defect may be difficult to diagnose and should be suspected in the setting of unexplained RHF or RV enlargement. Bubble study or transesophageal echocardiography may be required for diagnosis.
- Patients with RHF may not have increased left atrial filling pressures and may be more sensitive to change in reduction of cardiac preload and renal dysfunction. This may manifest as light-headedness or elevation of serum creatinine. Careful monitoring of volume status is necessary.
- Patients with RHF may require increased doses of diuretics, which may lead to increased likelihood of hypokalemia. Judicious use of potassium-sparing diuretics may be useful in the maintenance of potassium homeostasis.
- Carefully selected patients with advanced heart failure and severe pulmonary hypertension while on optimal therapy may be considered for therapy with sildenafil for improvement of symptoms and exercise tolerance.
- Ventilation/perfusion lung scanning should be used as a screening test for CTEPH but CT pulmonary angiography or conventional pulmonary angiography will be required for the confirmation for CTEPH diagnosis.
- Pulmonary function testing with diffusion of carbon monoxide should be performed to determine underlying obstructive or interstitial lung disease.
- Lung biopsy may be considered for diagnosis in cases in which the diagnosis is in doubt and will refine treatment.
- Evaluation for lung and heart-lung transplantation should be considered for end-stage cor pulmonale.
- Patients with trivial (mean gradient lower than 25 mmHg) or mild (gradient lower than 50 mmHg) pulmonary stenosis require no intervention or exercise limitation, but should have periodic follow-up (approximately every five years).
- Patients with right-sided valvular stenosis may have underlying carcinoid syndrome or ingestion of appetite suppressants.
- Arrhythmogenic RV cardiomyopathy (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 heart failure, or in whom characteristic ECG changes or a positive family history of ARVC is noted.
- Up to 40% of patients with ARVC may have a normal ECG on initial presentation, although almost all patients will develop pathological ECG changes within six years
- Interpretation of CMR for ARVC should be performed at experienced centres. An abnormal scan in isolation is not diagnostic for ARVC.
- Endomyocardial biopsy (EBM) of the RV free wall for ARVC should be performed with extreme caution and at an experienced centre due to the high risk of myocardial perforation and cardiac tamponade.

- Antiarrhythmic drugs or catheter ablation should not be used in the place of ICD therapy for patients with ARVC, but may be considered in patients who refuse or who are not candidates for device therapy.
- TTE is insensitive for detecting pericardial thickening but is a useful first test for examining constrictive physiology; transesophageal echocardiography may further improve the sensitivity over the transthoracic approach.
- When extensive calcification of the pericardium is present, CT may be more effective than CMR for measuring pericardial thickness.
- Provocation testing in the cardiac catheterization laboratory, such as rapid volume loading (e.g., intravenous infusion of 1 L of normal saline over 6 min to 8 min) and simultaneous LV and RV measurement during respiration, may unmask hemodynamic signs of constriction in patients with early or occult forms of constrictive pericarditis.
- The diagnosis of pericardial constriction may 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 may be required to assist in the diagnosis.

7.3 Non-cardiovascular 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;[462] other definitions also exist.

Anemia has a prevalence ranging from 10% to 68%;[463,464] 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.[465-469]

The prevalence of anemia is similar whether EF is reduced or preserved.[466,470] 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.[471,472] 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.[473,474] A decline in Hb over time is also associated with mortality and morbidity.[467] 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), GI blood loss and a few therapeutic agents with generally low impact on Hb levels (e.g., ACEis) (Table 22). In HFrEF, increased myocardial remodeling, inflammation, and volume overload have been described as the hallmarks of patients with anemia and HF. [465]

In the CHARM studies, the effectt of anemia on the primary outcome of cardiovascular death or HF hospitalization was slightly less in HFpEF than in HFrEF. [466] However, observational and population-based studies suggest that the effect of anemia on prognosis appears similar for HFpEF and HFrEF.[475,476]

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 (e.g., 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 demonstrated the prognostic impact of anemia. Reversible causes of anemia are common and should be treated.

Practical tip:

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

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 may be artificially elevated in chronic inflammatory states; transferrin saturation may be low in patients with cachexia
Fecal occult blood; upper and lower endoscopy	GI-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.

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[464,477] and a major contributor to exercise intolerance in HF, even in the absence of anemia.[478] 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%.[477] It is estimated that 60% of patients with HF with anemia and 40% of those without anemia have ID.[479] The above definition may 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.[480,481] Hepcidin, soluble transferrin receptor (sTfR) and reticulocyte Hb have been proposed as more sensitive indices to evaluate ID.[479,482,483]

A meta-analysis by Avni and colleagues[484] had reported improvements in quality of life, 6-minute walk distance and all-cause hospitalization with iron replacement therapy. Qian and colleagues[485] reported on the effects of IV iron therapy on clinical outcomes in HF, in a second meta-analysis, including a total of 907 patients from five 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 **Ir**on Deficiency In Co**m**bination With Chronic **H**eart **F**ailure (CONFIRM-HF) (n =301)[486] and **F**erric carboxymaltose **A**ssessment in Patients with **Ir**on Deficiency and Chronic **H**eart **F**ailure (FAIR HF) (n=459).[487] The CONFIRM-HF trial[486] included 301 patients (251 completed the trial) with moderate HF symptoms (NYHA class II-III), LVEF ≤ 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±11m, *P* = 0.002). The benefit was maintained up to 52 weeks. Fatigue, NYHA 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 **Ef**fect 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 VO2 compared with standard of care in patients with HF, EF ≤ 45% and ID.[485,488,489]

In patients with HF with anemia and ID in whom iron repletion is being contemplated, iron supplementation should be considered to improve functional capacity.[490] Oral iron has no known efficacy in this context, and therefore I.V. iron should be considered given the recently presented results from the Oral **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.[491] It is essential that the causes of absolute ID (such as iron loss) have also been investigated and treated by other means when possible (e.g., 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 IV iron repletion on major cardiovascular events (namely death), especially for non-anemic patients with HF and those with HFpEF. Cost-effectiveness also requires further validation with various I.V. iron formulations.

Recommendation 115: We recommend that IV iron therapy be considered for patients with HFrEF and iron deficiency, in view of improving exercise tolerance, quality of life, and reducing HF hospitalizations (Strong Recommendation, Moderate Quality of 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 IV iron therapy on the above outcome measures but there is yet no evidence regarding benefits on mortality. Given the rapid rate of iron repletion using the IV route and the available evidence, this treatment should be considered rather than PO iron repletion. Ongoing hospitalization can provide a good opportunity to facilitate IV iron administration.

Practical tip:

- Iron deficiency 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 may improve the sensitivity and specificity for the diagnosis of iron deficiency; but their clinical utility has yet to be demonstrated.

7.3.1.2 Erythropoietin stimulating agents

Erythropoietin 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 **S**tudy of **A**ne**mi**a in **H**eart **F**ailure Trial (STAMINA-HeFT)[492] and the **R**eduction of **E**vents With **D**arbepoetin Alfa in **H**eart **F**ailure (RED-HF) trial.[493] These 2 trials, and a meta-analysis[494] failed to demonstrate 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.[493] Based on 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 impact on quality of life, which is likely higher for those with lower Hb levels.

[495] Patients with advanced CKD (eGFR< 30 mL/min/1.73m^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 not be routinely used to treat anemia in HF (Strong Recommendation, High Quality Evidence).

Values and preferences: The above recommendation against the use of erythropoiesis-stimulating agents (ESAs) for the treatment of anemia in HFrEF at large was derived from robust data from RCTs.

Practical tip:

- Patients with severe chronic kidney disease or hemato-oncologic conditions may 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 diabetics. Instead, each individual should be assessed for his / 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 may be considered a first-line agent for type 2 diabetes treatment (Weak Recommendation, Moderate Quality Evidence).

Values and preferences: Metformin is the current Diabetes Canada first line treatment for type 2 diabetes.

SGLT-2 inhibitors

Ongoing trials in this area 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 (~10%), however, patients with HF had similar results to the overall trial.[27] There are ongoing trials of SGLT-2 inhibitors specifically enrolling patients with HF that may 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 addition of a GLP-1 agonist in patients with HF. None have shown any additional benefit in patients with HF, with or without diabetes.[496,497]

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: Both pioglitazone and rosiglitazone have been shown in studies to increase the risk for heart failure.

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.[498] Mechanistic hypotheses are discussed elsewhere.[498,499] Both elevated intra-abdominal pressure and central venous pressure are linked to rising serum creatinine levels. Elevated renal vein hydrostatic pressure is an important mechanism in volume expanded patients.[500,501]
When managing these patients the **A**cute **D**ialysis **Q**uality **I**nitiative (ADQI) definition of the CRS should be followed (Table 23).[499,502]

Table 23: Acute Dialysis Quality Initiative (ADQI) classification system of the cardiorenal syndrome[499]

CRS Type	Inciting Event	Secondary Disturbance
Type 1	Acute decompensated heart failure	Acute kidney injury
Type 2	Chronic heart failure	Chronic kidney disease
Type 3	Acute kidney injury	Acute heart failure
Type 4	Chronic kidney disease	Chronic heart failure
Type 5	Co-development of heart failure and chronic kidney disease	

Recommendation 119: We recommend that patients with cardiorenal syndrome (CRS) should be managed by a multispecialty team that has expertise in this area (Strong Recommendation, Low Quality Evidence).

Recommendation 120: We suggest that for patients with persistent volume overload despite optimal medical therapy and increases in loop diuretics, cautious addition 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).

Recommendation 121: We suggest that patients with the cardiorenal syndrome who develop diuretic resistance should be tried on stepped pharmacologic therapy [Figure 10] (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 to 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 a > 2-fold increase in relative mortality risk.[503] The presence of HF in a hemodialysis population portends a poor prognosis with mean survival of < 36 months.[504]

Creatinine clearance calculated by Cockcroft and Gault[505], **C**hronic **K**idney **D**isease **Epi**demiology Collaboration (CKD-EPI) or the MDRD formula[506] estimates the Glomerular filtration rate (eGFR). Standardized and validated criteria may 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 utilized for the classification, and evaluation of CKD (Table 24). It is important to recognize that markers used in the assessment of HF including BNP and NT-pro-BNP may need to be interpreted with caution in the presence of acute renal failure or end-stage renal disease.

Table 24: Standard definition of renal function

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

Adapted from the National Kidney Foundation[506]

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

Practical tips:

- As 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.

- No large, randomized, outcome trials on the use of diuretics have been conducted in patients with renal insufficiency.
- 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.
- Changes in GFR after commencing therapy are not necessarily associated with worsening outcome.
- As a general rule, the serum creatinine can rise or eGFR can fall by as much as 30% from baseline before it becomes necessary to stop or reduce the dose of the ACEis, ARB's or MRA's.

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).

Recommendation 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 re-assessed 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.[507] Early consultation with a nephrologist is recommended for patients with acute kidney injury and in situations where 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* for palliative care). 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. A RCT of carvedilol in 114 hemodialysis patients with a low LVEF and HF symptoms demonstrated a significant reduction in mortality or hospitalization over 2 years and improvement in NYHA and LV remodelling.[508] Cohort data suggest that ACEis are associated with a reduction in all-cause mortality.[509] An RCT of 397 high-risk patients without HF on hemodialysis showed a trend toward a lower event rate with the use of fosinopril.[510] Similarly, ARBs have been tested in an open-label trial in hemodialysis patients[511] and were not reported to reduce clinical events. One randomized trial of 332 patients with HF receiving an ACEi and hemodialysis demonstrated a significant all-cause mortality reduction over 3 years with the ARB telmisartan but with significantly more hypotension and dropouts in the treatment arm.[512] 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[513-515] and 1 small RCT of 16 patients with HF without significant benefits.[516] There are limited safety data and no efficacy data favouring digoxin for patients with HF receving hemodialysis.

Recommendation 125: We recommend starting or continuing the use of ACEi/ARBs, and beta-blockers in patients with heart failure and on chronic dialysis (Strong Recommendation, Moderate Quality Evidence).

Values and preferences: The use of MRAs in hemodialysis patients with heart failure 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.[517] 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.[518-520] 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.[521] However, evidence-based data are sparse and diuretics have adverse effects such as activation of the neurohormonal cascade, electrolyte depletion, and renal injury.[522,523] Venovenous ultrafiltration (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.[524]

In the multicentre randomized controlled **R**elief for **A**cutely Fluid-Overloaded **P**at**i**ents with **D**ecompensated **C**ongestive **H**eart **F**ailure (RAPID-CHF) trial, the feasibility, safety, and efficacy of early UF versus usual care in the management of AHF was assessed.[525] 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 to standard I.V. diuretic therapy in patients with AHF.[526] 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 re-hospitalization 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 impact on HF or all-cause hospitalizations has been performed.

In a randomized trial of UF in decompensated HF with CRS (**Car**idorenal **Res**cue **S**tudy in Acute Decompensated **H**eart **F**ailure (CARRESS-HF)), stepped pharmacologic therapy using I.V. diuretics and other medications in an organized fashion was found to be superior to UF for

the preservation of renal function, with similar weight loss. A higher percentage of patients in the ultrafiltration group had a serious adverse event.[527]

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, based on 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 for the management of intractable edema in decompensated heart failure (Weak Recommendation, Low Quality Evidence).

Practical tip:

- While the routine use of ultrafiltration for volume and symptom control in heart failure is not supported by trial evidence, it could be tried in refractory cases where 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 center 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.[528] There are two 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.[529] OSA results from collapse of 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.[529] About 40% of patients with HF have CSA and 11% have OSA.[529,530] A significant number patients with HF with SDB remain undiagnosed, possibly due to a lack of awareness and limited availability of sleep laboratories. Although nocturnal polysomnography in a sleep laboratory is the preferred diagnostic method,[531] home-based unattended sleep studies have been used as screening tools.[529] Patients with HF should be asked screening questions, such as on snoring and falling asleep during the day.

7.3.4.2 Treatment of sleep disordered breathing

There have been several RCTs of continuous positive airway pressure (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.[529] There are also small RCT of CPAP in CSA, when applied for at least 1 to 3 months, reduced apnoea–hypopnoea index and improved EF and functional class.[529] One study reported a reduction in combined mortality and heart transplantation rate in HF with CSA, but not in patients without CSA,[532] which in part

prompted the conduct of the **Can**adian Continuous **P**ositive **A**irway **P**ressure (CANPAP) trial.[533] This study was terminated early because of a lower than expected event rate. Despite a reported 50% reduction in the apnea–hypopnoea 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.[534] Short-term RCTs have demonstrated abolition of CSA but an inconsistent effect on EF.[528] In the recently published Central Sleep Apnoea by Adaptive **Ser**vo **Ve**ntilation in Patients with **H**eart **F**ailure (SERVE-HF) trial,[535] 1325 patients with an LVEF ≤ 45%, apnea–hypopnea index ≥ 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 endpoint 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) may provide more insight onto the role of servo-ventilation in HF.

Recommendation 127: We suggest that patients with HFrEF and central sleep apnea (CSA) not be treated with adaptive servo-ventilator treatment (Weak Recommendation, Moderate Quality Evidence).

Recommendation 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 obstructive sleep apnea (OSA) and CSA using contemporary diagnostic standards (Weak Recommendation, Moderate Quality Evidence).

Recommendation 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 atrial fibrillation (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 tips:

- 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.

- Consider OSA in patients with HF presenting with paroxysmal or recurrent atrial fibrillation, hypertension refractory to optimal HF therapy, high body mass index (BMI), and unanticipated pulmonary hypertension or right ventricular (RV) dysfunction.
- Consider the coexistence of sleep-related breathing disorders in patients with HF when malignant ventricular arrhythmias are detected, particularly at night.

7.4 Acute HF

7.4.1 Diagnosis, evaluations, and investigation

The diagnosis of AHF is based on a constellation of symptoms (e.g., orthopnea and shortness of breath on exertion) and signs (e.g., edema and respiratory crackles) and supported by targeted investigations.[536,537] Physical examination evaluates systemic perfusion and presence of congestion.[182,401,537,538] Laboratory testing, ECG, chest x-ray, and ECHO are all important to obtain relatively efficiently.[401]

Clinicians should consider potential etiology and precipitating factors (Table 3). In many cases (75% to 80%), a precipitant can be found (Table 25).[539,540] Failure to uncover the responsible precipitating factor may 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 may sometimes be normal. An ECG assists in identifying rhythm abnormalities (AF, flutter or bradycardia and ventricular tachycardia), ACS[541], 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 (Figure 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*.[56,401,542,543] Several clinical scoring systems have been derived and validated and combine commonly used clinical features with NP values to improve diagnosis and decision-making.[544,545] One such clinical scoring system (Table 26) was developed from the **Pr**oBNP **I**nvestigation of **D**yspnea in the **e**mergency department (PRIDE) study.[544]

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).

Recommendation 131: We recommend the diagnosis of acute heart failure be established within < 2 hours of the initial contact in the emergency department (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 tips:

- A precipitating cause for AHF should be sought.
- An ECG, blood tests and a chest x-ray should be performed within 2 hours of initial presentation.
- Initial blood tests should include: complete blood count, creatinine, blood urea nitrogen, glucose, sodium, potassium, troponin.
- A transthoracic echocardiogram should be performed within 72 hours of presentation. For patients with a previous echocardiogram, 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 greater than 12 months since the previous echocardiogram.

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

Predictor	**Possible score**	**Your patient's score**
Age > 75 y	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

*Elevated NT-proBNP was defined as > 450 pg/mL if age < 50 years and > 900 pg/mL if age > 50 years.
NT-proBNP, N-terminal pro brain natriuretic peptide.

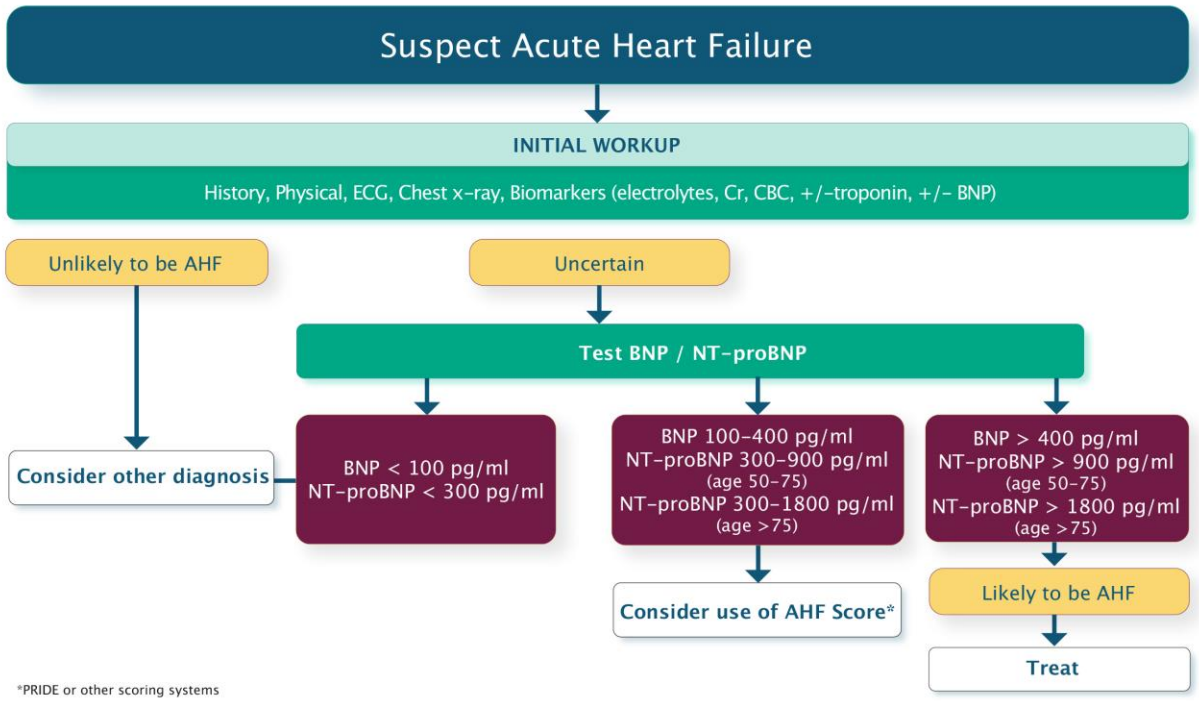

Figure 8: Diagnosis of heart failure in the acute care setting. If acute heart failure (AHF) is suspected, the initial work-up may be supplemented by natriuretic peptide testing and/or an AHF diagnosis score. BNP, B-type natriuretic peptide; CBC, complete blood count; Cr, creatinine; ECG, electrocardiogram; NT-proBNP, N-terminal propeptide B-type natriuretic peptide.

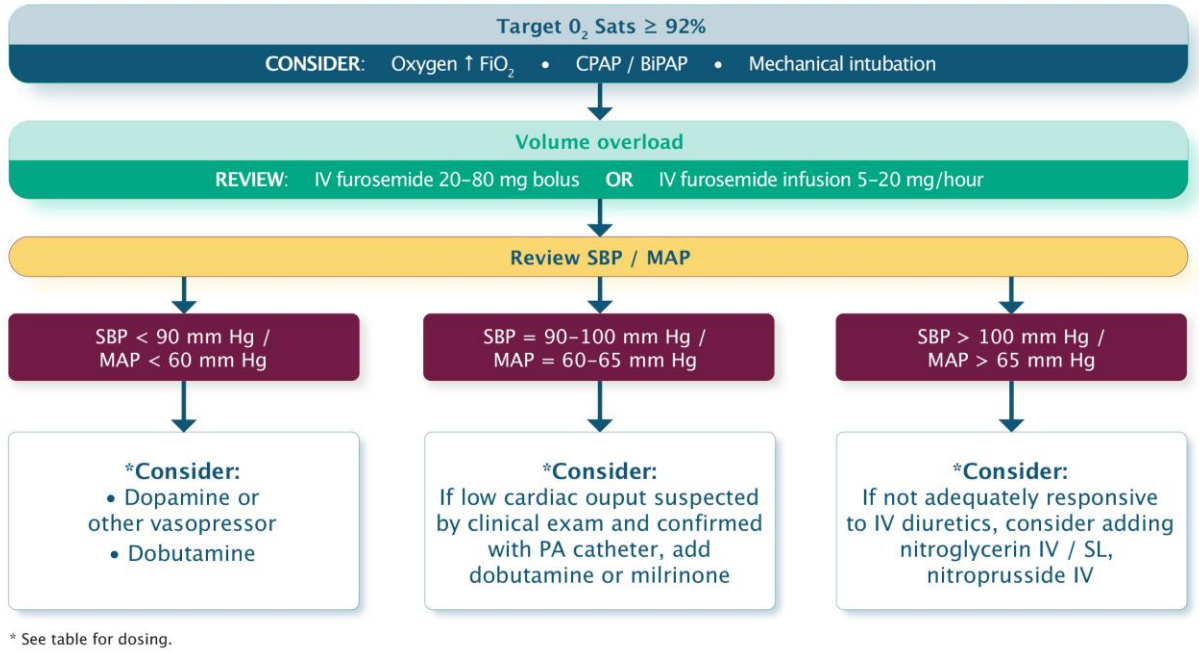

Figure 9: Treatment algorithm for acute heart failure. Decisions regarding the addition of inotropes or vasodilators should be done in consultation with individuals with experience and expertise in the management of patients with AHF, and placed in clinical context. * See Table 27 for dosing. BiPAP, 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 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 Non-adherence	Medication	Diet	Illicit drug or alcohol use
Surgical	Post non-cardiac surgery	Post CV surgical procedure	
Endocrine	Thyroid function	Addition/withdrawal of steroids	
Renal/Hematologic	Worsening renal function	Anemia	
Infectious	Pneumonia, influenza	Endocarditis	Re-activation of myocarditis
Social / Mental Health	Depression / Anxiety	Social stressors	Living conditions

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

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.[546,547] 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 co-interventions (Figure 9).[548-550]

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 demonstrating 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.

Recommendation 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 demonstrating harm with the use of morphine in patients with AHF.

BI-PAP or CPAP should be considered for patients with a high respiratory rate (e.g., > 25 breaths per minute) and persistent systemic arterial hypoxemia despite high flow oxygen administration.[551,552] However, routine use of noninvasive ventilation (NIV) is not advisable. In the **Three** Interventions in **C**ardiogenic **P**ulmonary **O**edema (3CPO) trial,[548] 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 caries 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 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 (SpO2 < 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).[553] 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.[554] 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.[555]

Table 27: Diuretic dosing for the treatment of acute heart failure (AHF)

eGFR	**Patient**	**Initial IV dose***	**Maintenance oral dose**
>=60 mL/min/1.73m^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 IV 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 IV equivalent of oral dose	

eGFR (estimated glomerular filtration rate) is calculated from the Cockroft-Gault, CKD-EPI or Modification of Diet in Renal Disease formula. See section 7.4.2 for details.

*Intravenous continuous furosemide at doses of 5 to 20mg/h is also an option.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HF, heart failure; I.V., intravenous.

Diuretic therapy may be initiated in the ambulance,[556] HF clinic, or in-hospital. Combining loop diuretics with thiazides[557,558] or spironolactone[559] 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.[401] Using stepped pharmacologic diuretic therapy is a useful approach and has been used as the control arm in the CARRESS-HF trial (Figure 10).[527]

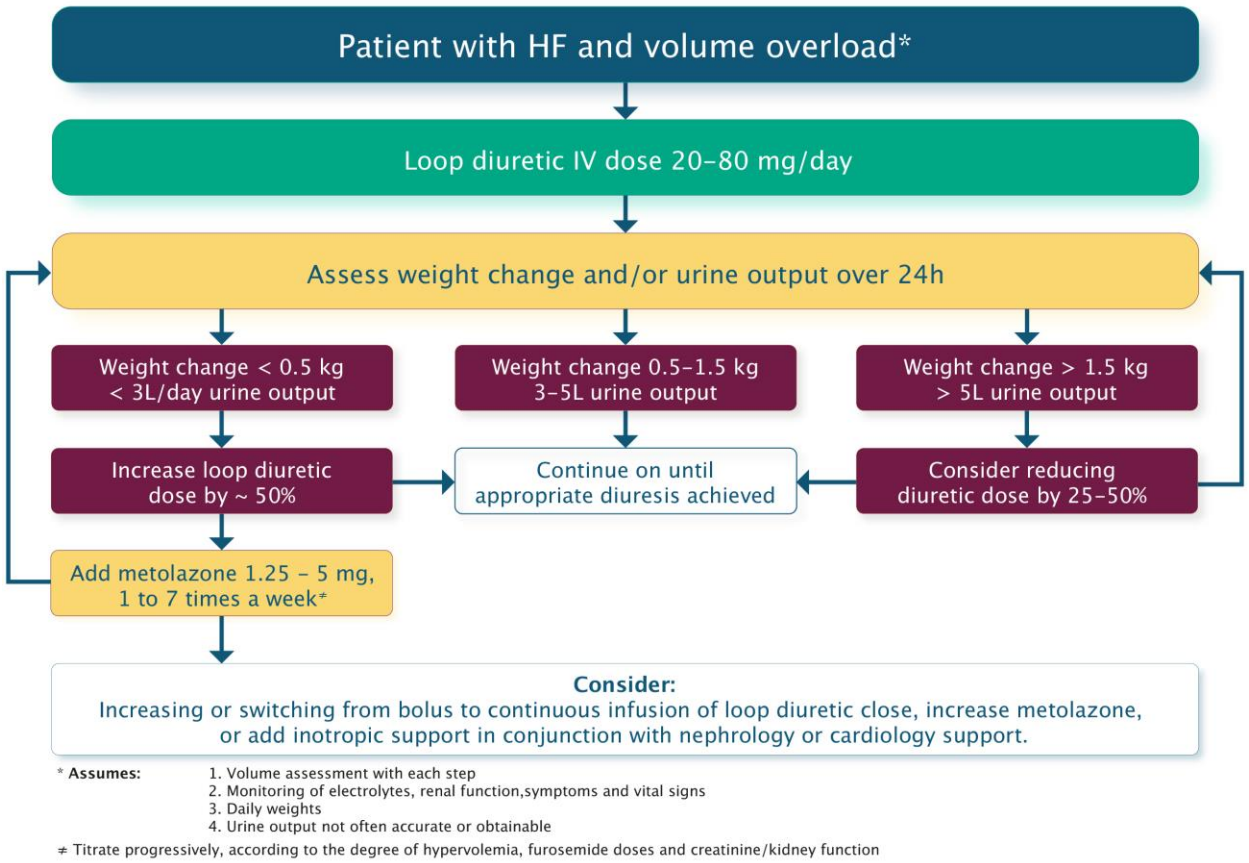

Figure 10: Stepped pharmacological care; treatment algorithm for patients with heart failure (HF) and volume overload. At each decision, clinical assessment should include an assessment of symptoms, volume assessment and appropriate monitoring of vital signs, electrolytes and creatinine. Daily weights are more easily and accurately assessed than urine output. IV, intravenous.

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 versus bolus intermittent dose) for the primary end point of global symptom assessment and creatinine at 72 hours.[553] 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 demonstrated similar findings (Figure 11).[560] 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.[561,562] 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.[561]

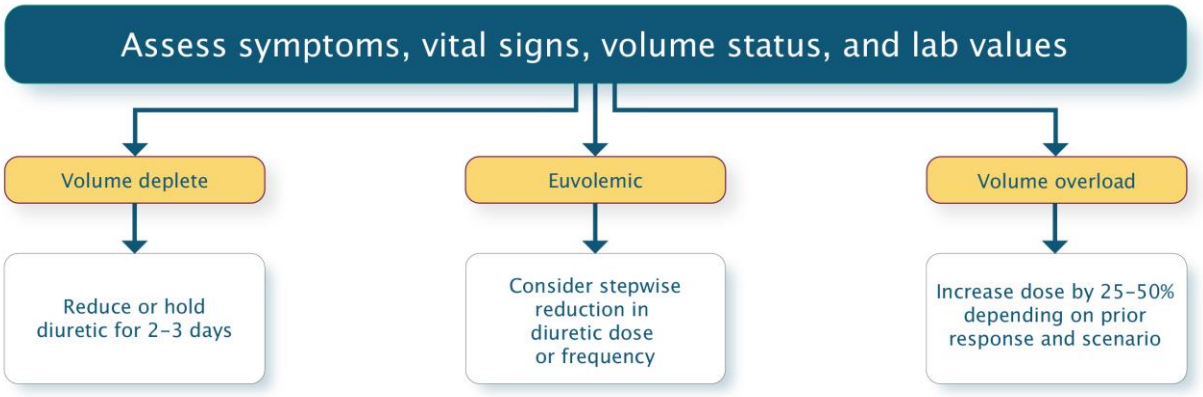

Figure 11: Outpatient diuretic management algorithm for patients with heart failure. At each decision, clinical assessment should include an assessment of symptoms, volume assessment and appropriate monitoring of vital signs, electrolytes and creatinine. Daily weights are more easily and accurately assessed 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 prior response if known, and clinical scenario. See section 7.4.2 and CCS Apps for further practical guidance.

Recommendation 135: We recommend that intravenous diuretics be given as first line therapy for patients with pulmonary or peripheral congestion (Strong Recommendation, Low Quality Evidence).

Recommendation 136: We recommend that for patients requiring intravenous diuretic therapy, furosemide may be dosed intermittently (e.g., twice daily) or as a continuous infusion (Strong Recommendation, Moderate Quality Evidence).

Practical tips:

- When acute congestion is cleared, the lowest dose that is compatible with stable signs and symptoms should be used.
- 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 IV furosemide will need a reassessment of fluid status and may be diuretic resistant.

- Once transitioned from IV to oral diuretic therapy, the stability of symptoms, weight and hemodynamics should be observed for ~24 hours prior to hospital discharge.
- To transition a patient to oral diuretics, be aware that the oral version of furosemide has ~50% bioavailability compared to IV furosemide.

Vasodilators have not been shown to convincingly reduce mortality or reduce rehospitalization rates.[563] I.V. isosorbide dinitrate (in conjunction with low dose furosemide) was tested against low dose nitrates with high dose diuretics.[564] 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 added to standard therapy for 3 hours, followed by nesiritide or nitroglycerin added to standard treatment for 24 hours in AHF.[565] 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.[566] 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-acute HF.[567] I.V. serelaxin, a vasodilator, was tested in the The **Pre**liminary study of **Relax**in for the Treatment of **A**cute **H**eart **F**ailure (PRE-RELAX-AHF) 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 versus placebo in 1161 patients with AHF with a SBP >125 mmHg 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 endpoints 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.[568,569]

Recommendation 137: We recommend the following intravenous vasodilators for relief of dyspnea in hemodynamically stable patients (SBP > 100 mm Hg):

i. Nitroglycerin (Weak Recommendation, Moderate Quality Evidence);
ii. Nesiritide (Weak Recommendation, High Quality Evidence);
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 intravenous 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.[401,570-572] 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.[571] New-onset atrial arrhythmias, worsening HF, and symptomatic hypotension requiring intervention occurred more frequently in the milrinone group. A non-significant increase in the number of deaths in-hospital and after 60 days was seen in the milrinone group. A post hoc analysis demonstrated a higher incidence of death or rehospitalization in patients with underlying ischemic HF etiology.[572] Trials using levosimendan have not shown additional benefit compared with placebo;[573] omecamtiv mecarbil is undergoing further testing in RCT.[574] Low-dose dopamine has been studied in the context of AHF[575,576] 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 place high value on the potential harm demonstrated when systematically studied in clinical trials and less value on potential short-term hemodynamic effects of inotropes.

Practical tips:

- Intravenous vasoconstrictor agents (e.g., phenylephrine, norepinephrine) should generally be avoided for AHF management except for patients with hypotensive with SBP < 90 mmHg, associated signs or symptoms, end-organ damage and a significant change from baseline.
- In patients with low SBP (< 90 mmHg), 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 (e.g., the first 8-12 hours) unless an elevated SBP is present, but should be initiated after the acute event (e.g., > 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 beta-blocker upon admission for AHF is considered safe based on the limited data available, including patients on inotropes.[577,578] In an RCT of 169 patients with AHF, patients either discontinued beta-blockade for 3 days or continued the medication unchanged. The trial showed that continuing the beta-blocker was non-inferior for the primary end point of dyspnea and well-being and was associated with a higher rate of beta-blocker prescription at 3 months.[578]

Recommendation 139: We recommend continuation of chronic beta-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 beta-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 beta-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 (e.g., tolvaptan) can rapidly and effectively reduce body weight and restore serum sodium in patients with significant symptomatic hyponatremia with hypervolemia and congestion.[579,580] The use of a vasopressin antagonist has not yet been associated with mortality or rehospitalization reduction.[581] A subgroup of 11% and 3% of the patients in the **E**fficacy of **V**asopressin Antagonism in H**e**art 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.[582]

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.[401] 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 (e.g., 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,[583] 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.[577] 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.[584] One instrument developed from prospectively collected data on 1033 patients with AHF created a nomogram for predicting 5 and 30 day

clinical events.[585] 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.

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 on room air	< 91%	≥ 92%
Systolic blood pressure	< 90-100 mmHg	> 100 mmHg or similar to prior
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
Inter-current 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 multi-disciplinary disease management program
Presenting symptoms resolved	Vital signs resolved and stable for > 24 hrs, especially blood pressure & heart rate	Clear discharge plan for labs, follow-up and other testing
Chronic oral HF therapy initiated, titrated and optimized (or plan for same)	Greater than 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.

Clinical deterioration despite initial therapy requires closer supervision, such as transfer to an intensive care unit.[586] 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.[401] 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.[401] 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.[587] The insertion of a pulmonary artery catheter is not usually necessary for making a diagnosis or ongoing management of AHF.[588-590] 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.[591]

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 may be clinically useful in highly selected cases, such as ongoing heart failure accompanied by cardiorenal syndrome, poor response to therapy or systemic hypotension or as evaluation for advanced therapies (mechanical circulatory support or heart transplantation).

7.5 Special Circumstances

7.5.1 Cardiomyopathies

7.5.1.1 Hypertrophic cardiomyopathy

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,[592] with a risk of sudden death, often at a young age. Most patients with HCM are asymptomatic.[593] 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[594] 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).[594,595]

Table 30: Cardiac hypertrophy including hypertrophic cardiomyopathy versus restrictive cardiomyopathy

	Cardiac hypertrophy	**Restrictive cardiomyopathy**
Prevalence	High	Low
Onset	Late	Early
Gender	Female > male	Male = female
Family history	Uncommon except in HCM	≅ 30%
Hypertension	Common	Uncommon
Obesity	Common	Uncommon
Hypertrophy	Moderate/Marked	None/mild
Echocardiographic/MRI 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 co-morbid condition	Uncommon
Natriuretic peptide	Variable	Elevated
Endomyocardial biopsy	Non-specific	Specific findings

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's ataxia,[596] and LEOPARD syndrome[597]) have also been linked to HCM. Approximately 30% of the cases are diagnosed de novo in elderly patients.[598]

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 non-diagnostic and might provide other structural details.[599] Tissue Doppler imaging may aid in early diagnosis.[600] 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% to 50% of cases and may be latent.[601] 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 tips:

- All first-degree relatives of patients with HCM should be screened for the disease with an ECG and echocardiography.
- Heart failure symptoms in patients with HCM may be due to diastolic dysfunction (most common), outflow tract obstruction (less common), rhythm disturbance, or concomitant valvular or ischemic heart disease (Table 30 - Cardiac hypertrophy including HCM versus RCM).

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.[602,603] 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.[603,604] Myocardial fibrosis, infiltration, or endomyocardial scarring is responsible for the diastolic dysfunction.[604] 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.[602] Amyloidosis is a frequent cause, but many other situations may 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).[604,605] Prognosis of patients varies substantially, but it is generally one of inevitable downward symptomatic progression with a high mortality.[606]

Table 31: Classification of etiologies of restrictive cardiomyopathy

Non infiltrative	Infiltrative
Myocardial	
Idiopathic*, familial, hypertrophic or diabetic cardiomyopathy, scleroderma, pseudoxanthoma elasticum	Amyloidosis*, sarcoidosis*, fatty infiltration, Gaucher's or Hurler's disease, Storage disease, Hemochromatosis, Fabry's 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

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's sign that may be disproportionate to the degree of systolic or valvular dysfunction. Hepatomegaly, ascites and, in more advanced cases, anasarca, may be present. Notably, the apex beat is usually palpable in RCM, but not in constrictive pericarditis.[604] The ECG is frequently abnormal with decreased voltage intraventricular conduction delay, or poor R wave progression mimicking myocardial infarction.[607] Sinus node disease is frequent, and typical characteristics of the sick sinus syndrome are encountered.[608] Arrhythmias, mostly AF, are frequent and may be caused by amyloid deposition.[609]

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 alpha-galactosidase activity are diagnostic.[610] 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, while a high plasma level of ferritin, in combination with increased transferrin saturation (TSAT), suggests hemochromatosis. Ventricular arrhythmias may be a forerunner for sudden death, and a signal-averaged electrocardiogram (ECG) has been suggested to help in identifying patients at risk.[611]

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 may help if cardiac amyloidosis is suspected, and kidney biopsy might also be useful if the estimated glomerular filtration rate 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.[612,613] Unsuspected hereditary amyloidosis might be present in nearly 10% of patients thought to have the primary amyloid light-chain (AL) form.[614] 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 may be reduced in advanced disease. Pericardial effusion is common, but rarely results in tamponade.[615] 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.[616] Doppler echocardiography is useful for the diagnosis, prognosis and should be evaluated carefully in centres with experience and expertise.[617,618]

CMR can precisely image functional, morphological changes,[619] fibrosis,[620] and inflammation[621] and may provide early insight into the disease process and etiology. CMR is useful in

amyloidosis,[622] with subendocardial contrast enhancement associated with nonsuppressible signal of remote myocardium. CMR might increase the sensitivity of myocardial biopsy,[623] and may help to direct treatment.[624] CMR might be helpful in distinguishing between active myocardial disease and clinical remission in systemic lupus erythematosus,[625] documenting the presence of cardiac fibrosis in Churg-Strauss syndrome, a rare form of systemic vasculitis,[626] and detecting early indications of iron overload in thalassemia patients.[627]

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.[628]

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 left ventricular filling pressure that exceeds right ventricular (RV) filling pressure by more than 5 mmHg (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 may be required.[602]

Practical tip:

- Radionuclide ventriculography, CMR and/or echocardiography can be used to noninvasively determine right ventricular (RV) EF and other measures of RV function.

7.5.2 Ethnicity

On the basis of a Statistics Canada 2006 census,[629] 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. [630] However, the use of ethnicity as a way to differentiate patients may be debatable and differential medical treatment based on the color of one’s skin has been associated with detrimental outcomes for ethnic minorities.[631] 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. [632] 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. [632,633]

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,[634] 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 aetiology in subjects from South America. [635] Although it is useful to remember region-specific aetiologies of HF particularly when managing recent immigrants from the regions where the minority groups were resident, it should be remembered that as these regions also constantly undergo epidemiological and economic transitions and the epidemiology of HF is likely to be increasing similar to that of the Western world. The INTERHEART study has demonstrated that the impact of conventional and potentially preventable risk factors on the risk of myocardial infarctions are consistent across different geographical regions and different ethnic groups.[636] This implies that simple measures that can prevent myocardial infarction 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 [637] demonstrates that most immigrant groups to 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.[638]

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. [639] Evidence that different ethnic groups have the same mortality benefit from current standard therapy is scant as 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 beta-blockers in patients from Africa and Asia. [635,640] Given 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.

7.5.2.2 HF in specific ethnic minority populations

The South Asian population

The South Asian population is currently the largest and fastest growing minority group, representing 25% of all minority and 4% of the total population in Canada.[327] South Asians have increased susceptibility to premature mortality from coronary heart disease.[635,641,642] A higher disease burden of coronary heart disease in South Asian individuals might be expected to result in a higher prevalence of HF. In a study conducted in Leicestershire in United Kingdom involving 5789 consecutive patients,[643] admission rates for HF were higher among South Asian than Caucasian patients. South Asians were younger and more frequently had concomitant diabetes than Caucasians. Despite differences in risk factors, clinical outcome was similar. In a matched historical cohort study of patients hospitalized for HF, conducted also in Leicestershire,[641] when compared to Caucasians the South Asian patients had similar rates of CAD but more often had hypertension and diabetes. South Asian patients had a lower mortality than Caucasian patients. A retrospective chart review of South Asians and non-South Asian white patients hospitalized with HF at two Toronto-area community hospitals in Canada demonstrated that South Asians were younger, of lower body mass index and were more often diabetic.[644] In-hospital mortality was also not different although South Asians were more likely to experience atrial and ventricular arrhythmias. In an analysis that compared two HF clinics, one that managed mostly Chinese, the other one South Asians, it was demonstrated that South Asian patients more frequently had a past history of myocardial infarction, multi-vessel CAD on angiogram, and treatment with coronary revascularizations compared to non-Chinese, non-South Asians.[645]

These data therefore suggest that South Asians have more risk factors thereby increasing the risk for premature coronary heart disease which may lead to development of HF at a younger age. As in other ethnic groups, in order to understand and manage a person's illness it is necessary to appreciate the effects of their culture, experiences and environment on the illness.

The Chinese population

The Chinese represent the second largest visible minority comprising of 24% of the minority population in Canada.[327] When managing Chinese patients with HF, their ability to comprehend and speak English and their family values should be considered. Chinese languages are the third most commonly spoken language in Canada and many Chinese do not speak or understand English well, particularly in technical terms. The modern Chinese continue to emphasize the values of family and there is a strong bond between parents, children and family members. A recent survey conducted in Toronto and Vancouver where the majority of Chinese reside revealed that there is a general lack of awareness of the symptoms of stroke and myocardial infarction and risk factors for CVD among the Chinese Canadians.[642] These social and ethnocultural factors may therefore confound the management of the Chinese patients.

There are few long-term prospective studies defining specifically etiologic factors for HF in the Chinese. Available data, by no means definitive, point to hypertension being the most important identifiable risk factor in Chinese with HF. [635,646] In a prospective study of 730 consecutive Hong Kong Chinese patients admitted to hospital with HF, the main identifiable risk factors were hypertension (37%), coronary heart disease (31%), valvular heart disease (15%), cor pulmonale (27%), idiopathic dilated cardiomyopathy (4%), and miscellaneous (10%). In women, hypertension was the commonest cause of HF at all ages but in men aged <70 years, coronary heart disease was equal in frequency to hypertension. Twenty-one percent had diabetes compared to a community rate of 10% for this age group.[647] A subsequent study reported by the same group evaluated 200 consecutive patients with HF using Doppler echocardiography.[648] An LVEF >45% was considered normal. The results showed that 12.5% had significant valvular heart disease. Of the remaining 175 patients, 132 had a LVEF >45%. Therefore, 66% of patients with a clinical diagnosis of HFpEF. Most had an abnormal relaxation pattern in diastole and 14% had a restrictive filling pattern. In the systolic HF group, a restrictive filling pattern was more common (46%). There were no significant differences in the sex distribution, aetiology, or prevalence of left ventricular hypertrophy between these two HF groups. These investigators conclude that HFpEF is more common than HFrEF in Chinese patients and that this may be related to an older age at presentation and the high prevalence of hypertension. In a case-mix study in Toronto, LVEF of Chinese (n=47) and Caucasian patients (n=243) with a diagnosis of HF were compared. [649] Among these patients, there were more Chinese patients with LVEF > 40% than Caucasian patients. The median LVEF was also greater in Chinese and the Chinese patients were older. With the economic growth in the world and the associated socioeconomic changes, a large proportion of Chinese adults now have the metabolic syndrome and obesity has become an important public health problem in China.[650] A recent review[646] from China indicated that in contrast to the Western countries, the prevalence of HF is greater in women than in men which might in turn be related to higher prevalence of rheumatic heart disease which affected women more than men. It is therefore more than likely that antecedent factors for incident HF in the Chinese will approach those of the Western world. A recent study examined the clinical profile of ethnic minority groups among patients with HF managed in two specialized HF clinics that follow a large number of Chinese and South Asian patients respectively.[645] Detailed medical records of 1266 non-Chinese, non-South Asians, 215 South Asians and 151 Chinese patients managed in two specialized HF clinics in Ontario that follow large numbers of South Asian and Chinese patients were reviewed. Compared to non-Chinese, non-South Asians, there were more women in the Chinese patients with HF. South Asian patients had the highest frequency of a history of previous myocardial infarctions and hypertension and the least frequency of concurrent AF. A smaller proportion of Chinese patients had systolic dysfunction that was categorized as Grade II or worse. Chinese patients had the least frequent use of ACE inhibitors but on the other hand had the most frequent use in ARBs. Our data therefore indicate that among patients managed in HF clinics in Ontario, Canada, Chinese and South Asian patients have different patterns of demographics, comorbid conditions, proportion of patients with preserved LVEF and medication use when compared to non-Chinese, non-South Asian patients with HF. Awareness of these differences may help to design future studies and develop differential strategies to prevent and manage HF among the largest and increasing ethnic minority groups in the Western countries.

There are currently no large scale RCTs of pharmacologic and device therapy conducted specifically in Chinese patients with HF. Indeed, the recommendations from the Chinese guidelines on the diagnosis and treatment of chronic HF closely resemble those contained in guidelines in the Western world.[651] The Hong Kong Diastolic Heart Failure Study studied 150 Chinese patients with HF and preserved systolic function and reported no significant additional benefit by adding irbesartan or ramipril to diuretic treatment.[652] It has been stated that Chinese subjects experience a high incidence of cough when treated with ACEis.[653,654] However, most of these studies that reported high incidence of ACEi-induced cough in Chinese patients had involved very small number of patients and did not compare simultaneously Chinese and Caucasian patients. Given the compelling data in support of the benefit of ACE inhibition in HFrEF, a Chinese patient with HF should not be denied the initiation of an ACEi based on anticipated intolerance. The doses of antihypertensive agents prescribed in Asian patients are frequently lower than in Caucasian patients, due in part to a perception of greater sensitivity and therefore higher risk of hypotension in the Asian patients. Unless strong evidence that can change the management of Chinese patients with HF is available, it is prudent to follow the recommendations from guidelines in the Western countries when managing Chinese patients with HF.

The Black population

In the United States, the black population has a higher prevalence of HF than persons of other races; they present with symptoms of HF at younger ages, and are less likely to be due to coronary heart disease than in Caucasians.[655] Two studies have reported on the contemporary epidemiology of HF among African Americans. Observations from the **C**oronary **A**rtery **R**isk **D**evelopment **i**n Young **A**dult (CARDIA) study have indicated that 1 in 100 African-Americans develop HF at an average age of 39, 20 times the rate in Caucasians. Incident HF in the African Americans before 50 years of age was associated with hypertension, obesity, CKD and systolic dysfunction that were already present before age of 35.[656] The incidence, risk factors, and outcomes of HF among African Americans were also examined in the 2934 older individuals without HF in the Health, Aging, and Body Composition (Health ABC) Study.[657] African Americans were more likely than Whites to develop HF. Smoking, left ventricular hypertrophy, fasting glucose levels, systolic blood pressure, decreased albumin, and increased heart rate were more prevalent in African Americans.

These data imply that young black individuals with risk factors should be a target of more aggressive intervention for HF prevention. Analysis of outcome data from the **S**tudies **o**f **L**eft **V**entricular **D**ysfunction (SOLVD) trials has shown higher mortality and morbidity rates in blacks compared to Caucasians with HF.[658] Whether this reflects differences in baseline characteristics or access of care or socioeconomic factors is not entirely clear. There have been reports which point to access to care and unfavourable clinical characteristics that are independent of HF as factors for poor outcomes.[539]

Long-standing clinical observations have suggested that blacks with hypertension respond less well than Caucasians to ACEis.[659] Concerns remain that differences in the effectiveness of blockade of the renin-angiotensin system might also be present. Several retrospective subgroup analyses of data from randomized trials have added some support to the concept that the response of blacks and Caucasians with HFrEF to ACE inhibition may differ.[660] However, these *post hoc* analyses do not provide sufficient evidence to support a strategy other than routine use

of ACE inhibitors in black subjects with HFrEF. Although the **B**eta-Blocker **E**valuation of **S**urvival **T**rial (BEST) with bucindolol did not find a beneficial effect of β-blockade in blacks,[661] subgroup analysis of data from the US Carvedilol Trials suggests that the beneficial effect of beta-blockers on outcomes in blacks is similar to the effects in the larger population[662] and these findings are supported by other analyses.[663] The totality of data to date therefore still supports the use of beta-blockers in black patients with HFrEF.

Data from the **V**asodilator-**He**art **F**ailure **T**rial (VHeFT) I and II first suggested a racial difference in treatment response between white and black patients with symptomatic LVSD treated with hydralazine-isosorbide dinitrate.[664] Representation of blacks, women, and other minorities in other HF trials has been so poor that even meaningful retrospective subgroup analyses have been precluded. On the basis of the ethnic differences observed in these retrospective analyses, the **A**frican-American **H**eart **F**ailure **T**rial (A-HeFT) was designed as the first HF trial in an all-black cohort. A-HeFT enrolled 1050 black patients with New York Heart Association class III or IV symptoms and with dilated ventricles and systolic dysfunction.[138] Subjects were assigned to receive a fixed combination of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy. The primary end point was a composite score made up of weighted values for death from any cause, a first hospitalization for HF and change in the quality of life. The study was terminated early due to a higher mortality rate in the placebo group. The mean primary composite score was significantly better in the group given nitrate and hydralazine than in the placebo group, as well as its components. These data therefore form the basis for the support for the addition of the combination of isosorbide dinitrate and hydralazine to the standard medical regimen for black patients with HF.

The First Nations population

Data from the 2006 census on Canada's First Nations population counted 1,172,790 First Nations, Métis, and Inuit people, representing 3.8% of Canada's total population. More than half the country's 1.2 million aboriginal people live off reserve. Aboriginal people were four times as likely as non-aboriginal people to live in a crowded dwelling and three times as likely to live in a dwelling in need of major repairs. Life expectancy for First Nations males is 7.4 years less and 5.2 years less for First Nations women compared to other Canadian men and women respectively. There is also evidence to indicate that geographic location, as compared with Aboriginal identity, appears to have a large impact on health status and the use of physician services, with on-reserve Aboriginals reporting lower likelihood of having seen a physician.[665] The **S**tudy of **H**ealth **A**ssessment and **R**isk **E**valuation in **A**boriginal **P**eoples (SHARE-AP) reported a higher frequency of CVD among Aboriginals in Canada and a greater burden of atherosclerosis when compared with Canadians of European ancestry.[666] As with other colonized people, there have been significant social, economic and cultural changes in the past decades which might accounted for an observed increase in hospitalization for CAD .[667] Given the increasing incidence of diabetes that accompanies the transition from traditional to urban lifestyles, [668] the incidence of CVD and therefore that of HF will likely also increase. There are currently few data available that can directly guide the management of HF in the aboriginal population. In patients who have commenced dialysis in Alberta, Saskatchewan, or Manitoba in Canada, the risk of death from HF was higher in Aboriginals than in Caucasians.[669]

When managing Aboriginal patients with HF, health care professionals need to understand how Aboriginal people interpret their illness and respond to treatment, and respect the logic and

rationale of another system of thought where health is perceived as a harmonious order. They need to adapt their treatment plans and education programs to the cultural, social and economic circumstances and to recognize that many communities are geographically remote. They will likely need to adopt a holistic approach in offering advice and care for their patients, respecting local traditions and not to impose their own values.[670] Workers need to recognize the multigenerational legacies of colonization and the importance of local history; to respect traditional beliefs; and to acknowledge the role of the social determinants of health and inadequate resources. Health care workers should work in multidisciplinary teams and include community health representatives. They must be sensitive to cross-cultural care. Aboriginal patients might be operating in a second language and might not be comfortable questioning someone who is perceived to have greater power and knowledge.

In summary, there are important differences across ethnic minority groups in the etiologies of HF and how patients respond to treatment. However, most of the published studies are based on small sample sizes. Given the increasing frequency of HF in these populations and an increasingly multiethnic world, additional studies on HF across different ethnic groups are needed. Furthermore, to be successful in reducing the burden of HF and indeed heart disease at large, and if one is committed to providing the best care for all patients, then one must be cognizant of the health care disparities and if feasible take steps to narrow and eliminate gaps in care as a function of ethnicity. Recommendations and practical tips on the management of patients with HF from the four largest ethnic minority groups in Canada are displayed in Table 32.

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 Asians	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 adding hydralazine-nitrate in those with HF and reduced ejection fraction; uncertainty remains if A-HeFT results apply to all self-identified black populations
Aboriginals	Obesity and diabetes	English, Cree and Ojibwe are among many spoken languages in Canada. May need to involve family members and community representatives	Follow guidelines.

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

7.5.3 Pregnancy

HF during pregnancy has a number of potential etiologies including peripartum cardiomyopathy (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.[671,672] High risk patients should be referred to a multidisciplinary team with expertise in the management of HF and high-risk pregnancy.[673-675]

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 which 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 center with expertise in advanced HF management, including MCS and cardiac transplant. [676,677]

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 auto-transfusion from placenta due to sympathetic stimulation and uterine contraction
Peripheral vascular resistance and blood pressure	Gradual drop, diastolic more such that pulse pressure increases	At lowest point in mid pregnancy	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 3rd trimester values within 1 h of delivery

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 Systolic ejection murmur common; continuous murmur (venous hum, mammary souffle) not common	Opening snap, pericardial rub, S4 Late peaking systolic murmur, diastolic murmur, other continuous murmurs

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.[678,679] There are no data on the use of ARNIs and thus they are not recommended during pregnancy. When beta blockade is used, β1 selective drugs (e.g., metoprolol) should be preferred. Atenolol should not be used.[680] Diuretics can be used if pulmonary congestion is present. Medications that may be used for pregnant women with HF are shown in Table 35. An additional comprehensive list of medications is available at www.motherrisk.org.[676,677]

Table 35: Medications that may be useful for pregnant women with HF

Medication	Use in pregnancy*
Beta-blockers	Should be continued or initiated during pregnancy Requires close fetal monitoring for growth retardation Beta-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

*Avoid all RAAS inhibitors (ACEi, ARB, MRA, ARNI, renin inhibitors)
HF, heart failure.

7.5.3.3 Peripartum cardiomyopathy

PPCM is a diagnosis of exclusion typically defined as HF with an LVEF of less than 45% within one month before delivery to five months post-partum. Pathophysiologic mechanisms are not clearly defined but may include genetic predisposition,[681] oxidative stress and immune mechanisms,[682,683] as well as viral infections[682] and prolactin.[684] Risk factors for the developments of PPCM include multiparity and multiple fetal gestation, advanced maternal age, family history, ethnicity, hypertension, pre-eclampsia, smoking, diabetes, and prolonged tocolytic therapy.[685]

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.[686,687] There have been several case reports and small RCT to evaluate bromocriptine[688] with inconclusive results and uncertain safety.[689-691]

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.[685,692-694] 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.[695,696] 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.[685,697]

Recommendation 142: We recommend that pregnant women (or those in the peripartum period) with acute HF should be managed according to the CCS guidelines for acute HF and should be referred to a tertiary centre with expertise in advanced HF management, including mechanical circulatory support and cardiac transplantation (Strong Recommendation, Low Quality Evidence).

Recommendation 143: We recommend that natriuretic peptides be used for diagnostic and prognostic purposes in peripartum cardiomyopathy (Strong Recommendation, Low Quality Evidence).

Recommendation 144: We recommend that bromocriptine not be used routinely for peripartum cardiomyopathy (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.

Recommendation 145: We recommend that echocardiography be performed in women with worsening or suspected new-onset HF during pregnancy (Strong Recommendation, Low Quality Evidence).

Recommendation 146: We recommend pre-pregnancy counselling in all women with a known history of heart failure or peripartum cardiomyopathy (Strong Recommendation, Low Quality Evidence).

Recommendation 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).

Recommendation 148: We recommend maternal risk assessment and frequency of expert follow-up should be determined using the modified World Health Organization (WHO) risk classification (Strong Recommendation, Low Quality Evidence).

Recommendation 149: We recommend that decisions regarding timing and mode of delivery should be based on obstetrical factors (Strong Recommendation, Low Quality Evidence).

Values and preferences: Caesarean deliveries are not routinely necessary and may additional risk to patients with heart failure. 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 left ventricular function should be advised against future pregnancies due to the high risk of worsening HF and death (Strong Recommendation, Moderate Quality Evidence).

Recommendation 151: We recommend that patients with PPCM who recover normal left ventricular function should be advised regarding the potential for recurrent left ventricular dysfunction in subsequent pregnancies (Strong Recommendation, Moderate Quality Evidence).

Practical tip:

- The risk of thromboembolism associated with PPCM is increased due to the hypercoagulable state of pregnancy, and is highest during the first six weeks postpartum.

Recommendation 152: We recommend that several commonly used cardiac medications should be avoided due to teratogenic effects during pregnancy and with caution during lactation (Strong Recommendation, Moderate Quality Evidence).

Practical tips:

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

- Echocardiography is the preferred imaging modality for heart failure during pregnancy. Post- partum imaging can include cardiac MRI 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 may result in sub-clinical and clinical LV dysfunction. Historically, anthracycline-based chemotherapeutic regimens have been implicated as the major cause of chemotherapy associated cardiotoxicity; however, there is increasing recognition that a variety of chemotherapeutic agents, targeted therapies, and radiation therapy may result in impaired LV function and the clinical HF syndrome.[57] LV dysfunction may be mediated through a number of pathophysiological mechanisms including direct myocardial injury, ischemia or hypertension.[698]

The time course of LV dysfunction may be variable depending on the specific agent implicated, treatment strategy and baseline patient demographics (Table 36).[699-717] In the case of anthracyclines, it has previously been suggested that cardiotoxicity may be idiosyncratic, but there is emerging evidence to suggest that nearly all patients who realize myocardial dysfunction will do so in the first year post-treatment, highlighting the need for aggressive surveillance during this period.[718]

While clinical trials have suggested a relatively low incidence of cardiac dysfunction in cancer patients receiving cardiotoxic chemotherapy, observational studies have suggested much higher rates of LV dysfunction in the real world.[706,719-725] This discrepancy is largely attributable to differences in baseline demographics, definitions of cardiotoxicty and treatment protocols. Moreover, improved cancer survivorship has enabled a better understanding of the long-term cardiotoxic effects of cancer treatment.

The CCS recently published guidelines for evaluation and management of cardiovascular complications of cancer therapy.[57] Specific recommendations, from that document, related to the development and treatment of LV dysfunction are presented here 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.[57]

Table 36: Cancer Therapies Associated with LV Dysfunction

Anti-Cancer Therapy	Major Mechanisms	Signs & Symptoms of Toxicity	Therapy Associated Risk Factors	References
Anthracyclines (Doxorubicin, Daunorubicin, Idarubicin, Epirubicin,	Proposed mechanisms: (1) Reactive oxygen/free radical generation	Classified into: (1) Acute Toxicity: reversible, shortly after infusion, toxicities include	(1) Greater risk for doxorubicin than for idarubicin or epirubicin (2) IV bolus administration (3) High peak	3-12

Mitoxantrone)	(2) Transcriptional change in myocyte ATP pathway (3) Decreased mRNA expression, reduced contractility (4) Topoisomerase IIβ interference	arrhythmias, QT prolongation +/-HF (2) Early-onset chronic progressive: during treatment and up to 1 year post, 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	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 RF is cumulative dose Rates of HF: Doxorubicin 400mg/m2 = 3-5% 550mg/m2= 7-26% 700mg/m2 =18-48% Maximal cumulative doses (mg/m2): Doxorubicin: 400-450 Daunorubicin: 600mg/m2 Idarubicin : 100mg/m2 Epirubicin: 800-900 mg/m2 Mitoxantrone: 160 mg/m2	
Cyclophosphamide	Proposed mechanisms: (1) Direct endothelial injury (2) Toxic metabolites resulting in myocardial injury (2) Ischemia from intracapillary micro-emboli (3) Coronary vasospasm	Include: (1) Arrhythmias (2) Non-specific ST-T abnormalities (3) Pericardial effusion (4) Hemorrhagic myopericarditis (5) Symptomatic HF Occurs within 1-14 days of dose administration and often last for a few days	(1) High dose Cyclophosphamide: 120-200mg/kg or >1.5 g/m2/day (2) History of anthracyclines or Mitoxantrone therapy (3) Mediastinal radiation Toxicity related to single rather than cumulative drug dose	10-12
Ifosfamide	Proposed mechanisms similar to that of cyclophosphamide due to structural and mechanistic similarities	(1) Arrhythmias (2) Non-specific ST-T changes on ECG (3) HF Acute HF typically presents within 6-23 days of first ifosfamide dose	(1) Potentially dose related: doses > 150mg/kg or > 12.5 g/m2 Toxicity related to single rather than cumulative drug dose	10, 12

Docetaxel	Myocyte damage	(1) HF (2) Ischemia		10, 12, 14
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-months)	(1) Concurrent anthracycline therapy	6, 10, 11, 13-15
Sorafenib	Similar mechanism to Sunitinib Toxicity is generally reversible and responsive to medical treatment	(1) MI (2) Hypertension (3) HF/LV dysfunction Less cardiac dysfunction than Sunitinib		6, 10, 13, 16, 17
Imatinib	Proposed mechanisms: (1) Mitochondrial damage (2) Protective mitochondrial pathway inhibition	(1) LV dysfunction		13, 15
Dasatinib	Proposed mechanisms: (1) Mitochondrial damage (2) Protective mitochondrial pathway inhibition	(1) HF/LV dysfunction		13, 14

Lapatinib	Proposed mechanisms: (1) Targeting of HER1/EGFR & HER2 receptors	(1) LV dysfunction (2) Symptomatic HF (3) QTc prolongation Relatively low incidence of adverse cardiac events	(1) Prior anthryacyline or trastuzumab therapy	11, 14
Trastuzumab	Proposed mechanisms: (1) Inhibition of HER2 (Erbβ2) signaling may interfere with growth and signaling of cardiomyocytes and may induce mitochondrial damage Toxicity is generally reversible	(1) HF/LV dysfunction	(1) Concurrent paclitaxel or anthracycline based therapy (2) Cumulative anthracycline dose >300mg/m2) (3) Concomitant use of antihypertensive drugs Toxicity is generally not dose related	10, 11
Bevacizumab	Proposed mechanisms: (1) Inhibition of VEGF signaling resulting in uncontrolled HTN (2) Risk of HF through impaired adaptive response to pressure overload (3) Decreased NO and prostacyclin production and expose 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	10, 11, 18-21
Radiation therapy		(1) CAD (2) Valvular disease (3) Pericardial disease (4) Restrictive cardiomyopathy (5) Conduction system disease		6, 7

AC, doxorubicin & cyclophosphamide; AMPK, adenosine monophosphate-activated protein kinase; ATE, arterial thrombotic event; ATP, adenosine triphosphate; AV, atrio-ventricular; CAD, coronary artery disease; DHP, dihydropyrimidinase; ECG, electrocardiogram; CMP, cardiomyopathy; EGFR, epidermal growth factor receptor; HER1 and HER2, human epithelial growth factor receptor 1 and 2; LVD, LV dysfunction; LVEF, LV ejection fraction; MI, myocardial infarction; NO, nitric oxide; VEGF, vascular endothelial growth factor;.

Recommendation 153: ***(CCS 2016 Cardio-oncology #2):*** We recommend that patients who receive potentially cardiotoxic cancer therapy undergo evaluation of LV ejection fraction

(LVEF) before initiation of cancer treatments known to cause impairment in LV function (Weak Recommendation, Moderate Quality Evidence).

Recommendation 154: ***(CCS 2016 Cardio-oncology #5):*** We suggest that serial use of cardiac biomarkers (e.g., 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).

Recommendation 155: ***(CCS 2016 Cardio-oncology #6):*** We suggest that in patients deemed to be at high risk for cancer treatment-related LV dysfunction, an ACE inhibitor or ARB , and/or beta-blocker, and/or statin be considered to reduce the risk of cardiotoxicity (Weak Recommendation, Moderate Quality Evidence).

Recommendation 156: ***(CCS 2016 Cardio-oncology #10):*** We recommend that in cancer patients who develop clinical HF or an asymptomatic decline in LVEF (e.g., > 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).

Recommendation 157: ***(CCS 2016 Cardio-oncology #12):*** We suggest that patients at high risk of cancer therapy related CVD or patients who develop cardiovascular complications during cancer therapy (e.g., > 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 based on established histological, immunological and immunohistochemical criteria.[726,727]

The incidence of myocarditis is not well established as many patients with clinically suspected myocarditis do not undergo EMB or CMR. In patients with unexplained non-ischemic cardiomyopathy, the biopsy proven myocarditis was demonstrated in 9-16% of cases.[728,729] 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).[730,731]

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 low or normal troponin does not rule out myocarditis. The sensitivity of elevated troponin I in biopsy proven myocarditis in the Multicenter Myocarditis Treatment trial was 34% and specificity was 82%.[732] The ECG findings may include arrhythmias (ventricular or supraventricular), atrioventricular block, pattern of acute injury or pericarditis, nonspecific repolarization abnormalities or, rarely, may be normal. Echocardiographic findings may include segmental or global LV dysfunction, RV dysfunction, or pericardial effusion.[733]

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 to 100% [734] and is also not specific for acute vs. chronic/healed myocarditis.[735]

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.[734] Myocardial mapping as a novel CMR approach might further improve diagnostic accuracy;[736,737] 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 PCR in addition to histological criteria increases the diagnostic value of EMB.[738,739] 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 may help establish diagnosis but has known safety considerations and diagnostic yield issues. EMB is also indicated in patients with a 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.[740]

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 versus 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 versus prednisone and either azathioprine or cyclosporine. At 12 months there was no survival benefit and no significant difference in LV function improvement.[728] 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 the echocardiographic parameters.[741] There are no large, randomized, placebo-controlled studies looking at the 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.[742-744]

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.[745,746]

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 may be useful for predicting outcomes.[747] Persistent inflammation at four weeks follow-up indicates a worse prognosis in patients with no further inflammation. Patients demonstrating a positive clinical response to therapy, including improvement in or normalization of cardiac dysfunction, should also undergo clinical follow-up within approximately three to six months to confirm clinical stability. Patients demonstrating 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:

- Cardiogenic shock due to LV systolic dysfunction (global or regional), where etiology is not apparent.
- Acute or subacute development of LV systolic dysfunction (global or regional), where etiology is not apparent.
- Evidence of myocardial damage not attributable to epicardial CAD or another cause (Strong Recommendation, Low Quality Evidence).

Recommendation 159: We recommend referral to a center with experience and expertise in the assessment and management of myocarditis should be considered for patients with suspected myocarditis (Strong Recommendation, Low Quality Evidence).

Recommendation 160: We recommend 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).

Recommendation 161: We recommend that all patients with suspected myocarditis have CMR where available and in the absence of contraindications (Strong Recommendation, High Quality Evidence).

Recommendation 162: We suggest EMB be considered for patients presenting with a) new-onset (less than two weeks duration) heart failure of undetermined etiology with hemodynamic compromise, b) heart failure and high-grade heart block, c) heart failure with recurrent ventricular arrhythmias or d) heart failure unresponsive to medical therapy (Weak Recommendation, Low Quality Evidence).

Recommendation 163: We recommend best medical therapy, including supportive care for the treatment of myocarditis (Strong Recommendation, Low Quality Evidence).

Recommendation 164: Routine use of general or specific immunological therapies directed toward myocarditis are not recommended, as this has not been shown to alter outcomes, and may lead to side effects or complications (Strong Recommendation, Moderate Quality Evidence).

Recommendation 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 by PCR (Weak Recommendation, Low Quality Evidence).

Recommendation 166: We recommend that the antiviral therapy should not routinely be used in patients with myocarditis (Strong Recommendation, Low Quality Evidence).

Recommendation 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 tips:

- Clinical signs and symptoms of myocarditis may be highly variable.
- Other potential causes of cardiac dysfunction must be ruled out before a diagnosis of myocarditis can be made; additional tests may include cardiac catheterization or CMR, with or without RV biopsy.
- Biomarker and 12-lead ECG findings in patients with myocarditis may mimic those of acute myocardial infarction or acute pericarditis.
- Patients with suspected myocarditis should have troponin I or T and BNP or NT-proBNP measured.
- Treatment with immunosuppressive agents should be implemented by centers/physicians with considerable experience in managing these cases
- Patients with persistence of heart failure symptoms or ventricular dysfunction should be followed in a multidisciplinary heart failure/ function clinic, and referred to specialized centres when appropriate.

- Precise diagnostic criteria for acute myocarditis have not been prospectively validated; however, the criteria consider four major elements in determining the potential for the presence of acute myocarditis. They are:
    1. Symptoms and clinical findings consistent with acute or recent myocardial damage.
    2. Evidence of myocardial injury in the absence of a demonstrable epicardial coronary cause.
    3. Evidence of hyperemia, edema or irreversible injury on CMR images.
    4. Presence of inflammatory cell infiltrate or positive viral genome signal on examination of EMB specimens.
- 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 Heart Failure

The management of HF should be delivered within an integrated system of care on the basis of chronic disease management and prevention principles.[748] 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.[463,749-752] Similarly, frailty affects up to 50% of older patients with HF, in whom it is associated with non-specific clinical features, acute care utilization, poor quality of life, worse outcomes from concomitant conditions, and mortality.[753]

Recommendations regarding HF therapy apply to older patients and should not be restricted on the basis of age alone.[180,182,754-761] 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 towards target doses.[749,762] Orthostatic hypotension is frequent among frail older patients, but if recognized, can be managed to allow for greater use of evidence-based HF therapies.[749,763,764]

Frailty has important ramifications on the organization of HF care. It is central to defining patient goals and thus on decision-making related to advance care planning, surgical treatments, implantable device therapy, medication deprescribing, or other treatments not compatible with these goals.[765,766] 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.[765] Instruments that address key underlying factors related to frailty might be more clinically useful than performance measures, including the Edmonton Frail Scale,[767] the Clinical Frailty Scale,[768]

and scales embedded with the interRAI instruments broadly implemented across multiple care sectors in Canada.[765,769]

An international multidisciplinary working group established, through consensus, ARISE-HF,[752] 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 may affect treatment, adherence to therapy, follow-up or prognosis (Strong Recommendation, High Quality Evidence).

Practical tips:

- Depression in older patients with HF should be suspected when chronic physical complaints persist despite optimal HF therapy.[770]
- Measuring orthostatic vitals may identify individuals at risk of falls.
- Managing fall risk related to orthostatic hypotension:
    - Minimize diuretics and other vasodilators by optimizing first-line HF therapy;
    - Consider a medication review with a pharmacist; and
    - Promote physical activity, which may reduce the risk of orthostatic hypotension.
- Screening, prevention and management of delirium is a standard of care for all acutely ill older patients, including those with HF.[771]
- Cognitive impairment, even when mild, may interfere with HF self-care.
- Patients with HF over the age of 65 years should be screened for cognitive impairment.[772,773]
- If cognitive impairment is identified, a capable substitute decision-maker should be designated.
- HF therapies in frail or older patients should be similar to those in younger patients,
- In frail older patients, HF medications may be introduced at lower doses and titrated more slowly.
- Clinicians should be alert for drug-drug, drug-disease interactions, and therapeutic competition, where the care of one comorbidity is exacerbated by the care of another.[762]
- 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 Advance Care Planning discussions should be initiated early in the course of illness.[749,774-778] 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 (e.g., 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).[779,780] Palliative care is the promotion of physical and psychosocial health, regardless of diagnosis or prognosis (Table 38).[404] 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).[769,781-792] 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.[774-778,793-802]

Table 37: Additional symptoms experienced by patients with advancing heart failure (HF)

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;

Table 38: Palliative care for heart failure (HF) defined

Palliative care for HF defined
Palliative care is a patient-centered and family-centered 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.

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

Table 39: Tools to assess the quality of life or symptom burden in patients with heart failure (HF)

Tool Name	Description
Disease-specific patient QOL	
Minnesota Living with Heart Failure Questionnaire (MLHFQ)	21 item, Likert scale, self-administered, overall rating, physical and emotional
Kansas City Cardiomyopathy Questionnaire (KCCQ)	23 item, Likert scale, self-administered, physical function, symptoms social function, self-efficacy and quality of life

Generic QOL tools: patient and caregiver	
Short Form 12 (SF12)	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 Form36 (SF36)	36 items with 8 scales in physical and mental health
Euro QOL (EQ-5D) and Visual Analogue Scale (EQ-VAS)	EQ 5D- 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). 3 Level (EQ-5D-3L) or 5 Level (EQ-5D-5L) 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 – Patient	
Edmonton Symptom assessment scale (ESAS)	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 (CRA)	Generic, 24 items, multidimensional tool, positive and negative caregiver reactions. 5 dimensions (schedule, financial, family, health, self-esteem)
Dutch Objective Burden Inventory (DOBI)	Disease specific. Multi-dimensional (personal care, practical care, motivational support, emotional support)
Caregiver Burden Scale (CBS)	Generic, 15 item, self-administered, difficulty and demand summary scores
Zarit Burden Inventory (ZBI)	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

	Pharmacological	**Nonpharmacological**
Dyspnea	Optimized CCS HF guideline therapy • Inotropic agents or mechanical circulatory support devices if consistent with advance care plans (inotropes may 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 WHO ladder (avoiding NSAIDs) Opioids	Physical therapy, occupational therapy, massage If related to ICD discharge, consider adjusting settings or deactivation
Gastrointestinal	Consider ascites, digoxin toxicity	
Nausea	pro-motility agents (e.g. metoclopramide 10 mg po/sc tid with meals) target chemoreceptor trigger zone: Haloperidol 0.5 mg q12h; 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 (e.g. 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, nutrition and hydration
Considerations at the end-of-life **Myoclonus,**	Consider discontinuation of medications no longer consistent with goals of care, e.g. statins Consider and treat underlying	Consider discontinuation of shock therapies, inotropic agents, or Mechanically Assisted Circulation

seizures	precipitants Terminal sedation	

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.

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).

Recommendation 170: We recommend that the provision of palliative care to patients with HF should be based on a thorough assessment of needs and symptoms, rather than on individual estimates of remaining life expectancy (Strong Recommendation, Very Low Quality Evidence).

Recommendation 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 tips:

- The timing of ACP discussions should consider the high mortality rate in the year following a first HF hospitalization.
- The substitute decision-maker should be involved ACP discussions.
- 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).
- Care preferences and goals of care should be regularly discussed with patients and documented, with emphasis shifting from quantity to quality of life.
- 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.
- Symptoms and psychosocial burden (e.g., depression, fear, anxiety, social isolation, home supports and need for respite care) should be regularly evaluated, and a palliative care referral considered.
- 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.[803-805] 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.[806-808]

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).

Recommendation 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).

Recommendation 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 tips:

- Patients with HF should have regular follow-up assessments, with their intensity and frequency of tailored according to individual risk and stability (Table 41).
- 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 (Figure 12). Emerging needs, such as disability, other health concerns (Table 42), caregiver burden, and advance care plans should be reviewed as well.
- Follow-up methods may include telemonitoring, structured telephone support, or home visits, all of which have variable evidence to support this and should be localized.[809,810]
- HF management includes coaching patients and informal caregivers on self-care skills, through experiential learning, practice and support.[811,812]
- 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.[813]
- Home-based HF management, which can include Hospital-at-Home care, may be beneficial for highly selected patients.[814,815]

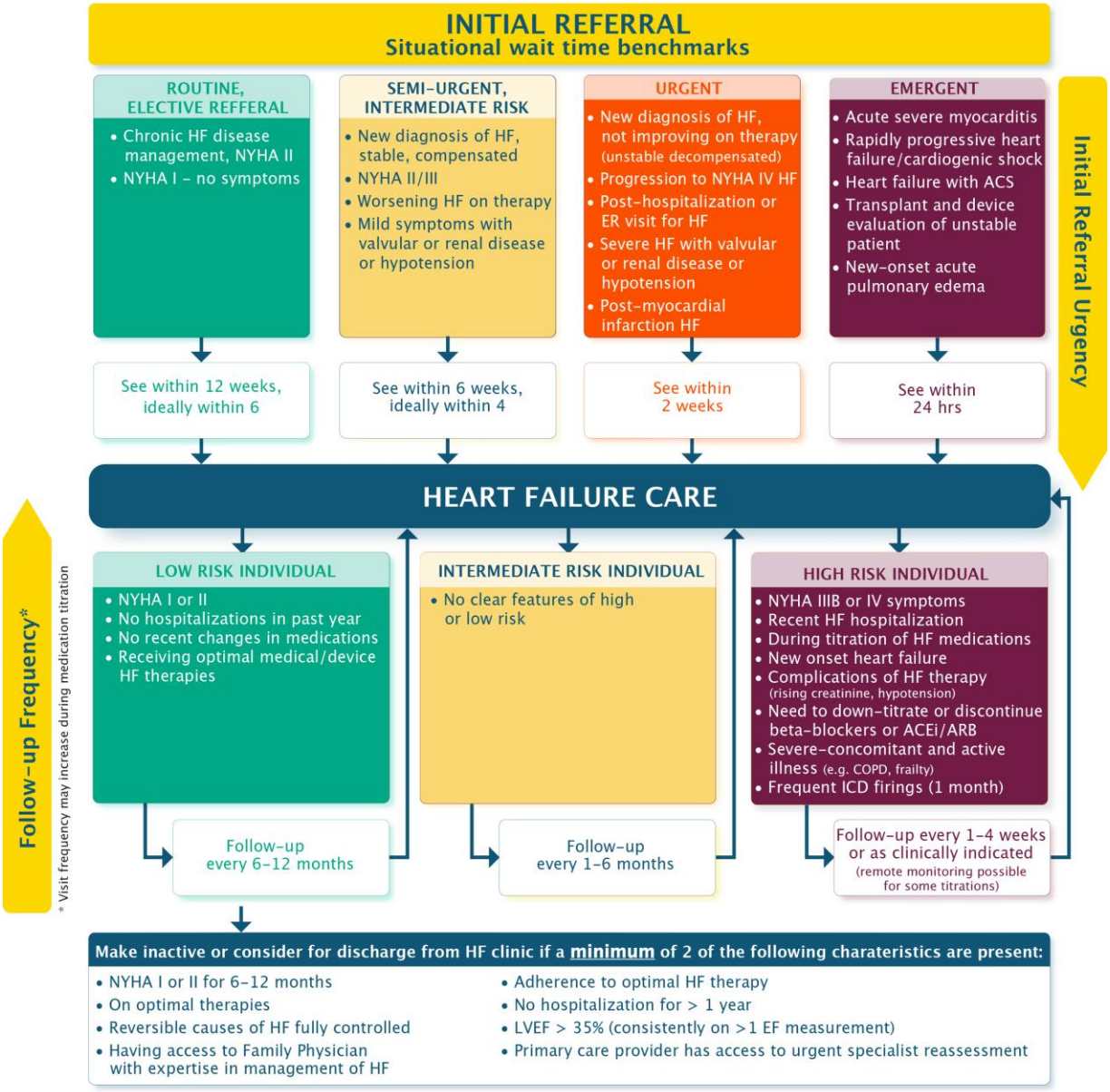

Figure 12: Referral and follow-up frequency for patients with heart failure (HF). Recommended initial referral wait time and follow-up frequency. ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease;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

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.

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	Prednisone, 0.5 mg/kg daily with rapid taper over	No adjustment needed

	with colchicine	7-14 days	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 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.

8.3 Systems level considerations

Integration is a system-wide process of combining social and health services in order 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.[816-818] 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.[819] 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.[820] 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.[820-824] Further, integration of multidisciplinary palliative care services in the care of patients with advancing HF can reduce symptom burden and health system utilization.[825-827] Features of integrated care model for patients with HF are described in Table 43.

Proper execution of care transitions from hospital to the community is particularly important, as patients with HF have high rates of re-admission. Older patients with multimorbidity, frailty and previous HF hospitalizations are at increased risk for readmission.[828] Important elements of successful transitional care programs have been identified and should be considered based on local resources which are outlined below.[829-835]

1. Timely hospital discharge planning;

2. Interprofessional teamwork, communication, and collaboration, including standardized procedures for handoff to post-hospital providers;
3. Timely, clear, and organized information;
4. Medication reconciliation and adherence;
5. Engaging social and community support groups;
6. Monitoring and managing signs and symptoms after discharge, and delivering patient and informal caregiver education;
7. Early and intense outpatient follow-up, including home visits and structured telephone support; and
8. Advance care planning and palliative and end-of-life care.

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

Table 43: Necessary features of successful health system integration

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-centered 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 which are anchored in primary care.
Human Resource Elements	In addition to clinical staff, additional resources should include • Program support a coordination, commensurate with its size and scope; • Access to Continuing Medical Education 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	Measurement and submission of mandated quality measures to

Improvement and Outcome Measurement	appropriate authority; Measurement of Quality Indicators, as defined by the Canadian Cardiovascular Society Quality Indicators Working group for Heart Failure.[836] (http://ccs.ca/images/Health_Policy/Quality-Project/Definition_HF.pdf)

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".[837] 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.[838-840]
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.[836-838] 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.[841,842]
- 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 which 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*, and in Table 44.

9.2 Quality assurance considerations for HF care

Chronic HF has been identified as a priority condition for quality assurance.[837] Although many examples exist showing improvements in HF related outcomes,[843] many patients with HF still fail to meet the standards set out in the CCS Recommendations on HF.[844-848] This is likely due to several important characteristics of HF, which include the advanced patient age and degree of underlying CVD, unpredictable illness trajectory, as well as a high degree of comorbid conditions and social isolation.[849]

9.3 What performance indicators have been developed for HF?

Accordingly, several organizations have developed performance indicators such as the Canadian Cardiovascular Outcomes Research Team / Canadian Cardiovascular Society (CCORT/CCS),[850] the American College of Cardiology / American Heart Association (ACC/AHA),[851] the Joint Commission on Accreditation of Healthcare Organizations (JCAHO),[852] and the Assessing the Care of Vulnerable Elders (ACOVE) Project.[853] These are summarized in Table 44. It is unclear which, if any set of performance measures is superior in gauging the quality of HF care. The CCS Quality Indicators for HF were published in 2015[836] and include 6 key performance indicators (KPI) for inpatient care: Daily assessment of serum electrolytes, BUN and creatinine, documentation of chest X Ray, in-hospital use of ACEi or ARB in eligible patients, documentation of an assessment of left ventricular systolic function, documentation of patient education and documentation of 30-day readmission rate in those discharged alive. The last KPI regarding hospital readmission is unique to the CCS Quality Indicator list.

Table 44: Summary of performance indicators for heart failure by 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 beta-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 ICD in eligible patients									**X**
Use of CRT in eligible patients									**X**
Avoid 1st and 2nd 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 one 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									
HF 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**		

Please refer to primary references for specific details regarding inclusion and exclusion criteria, and implantation requirements for each quality indicator.

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.

9.4 What care improvement mechanisms should be considered?

Numerous initiatives to improve the management of HF have been developed and evaluated in different care settings, and have met with varying degrees of success. Strategies employed in these initiatives have included passive dissemination of educational information to health care providers and patients, computerized order sets, automatically generated suggestions for care interventions, automated reminders attached to echocardiography results, as well as intensive education, direct feedback, and care support from expert clinicians.[854-864] Strategies that rely on passive dissemination of information are at best modestly effective.[855,860,861] More proscriptive strategies, either through computerized order sets of direct feedback or support from specialists, may be somewhat more successful. Involvement of end-users in the development of strategies for improving HF care may increase their likelihood of success.[857,865] A systematic review of computerized decision support for prescribing suggests that most studies assessed resulted in improved prescribing, though few reported on patient-relevant outcomes.[866] Another systematic review suggests that strategies that combine practice audits with feedback regarding gaps between the care provided for a particular condition and clinical practice guidelines have small to moderate effects in improving care quality.[867] However, the effects may be larger when baseline adherence to clinical guidelines is low and intensity of audit and feedback is high. Multimodality or multifaceted interventions are much more likely to succeed.[867] Several recent reviews suggest that several features are common to successful programs. These include use of interdisciplinary teams, use of evidence-based therapies for HF in eligible patients, care centered around both in-hospital and post-discharge setting, early and repeated assessments, (including home care, case management or multidisciplinary disease management approaches), and provision of timely and effective communication at each stage of care transfer appears to allow greatest gain in terms of quality of care and clinical outcomes. Interestingly, isolated technology-based approaches such as telemedicine and telemonitoring have not yielded added benefit when tested rigorously.

9.5 Experience with large scale quality improvement projects in HF populations

Results from a study of 3657 U.S. hospitals, in which hospital-reported performance measures were linked to Medicare claims data, suggests that two HF care quality indicators (assessment of left ventricular function and use of ACEis in patients with LVSD), were marginally associated with improvements in mortality rates at 30 days and one year.[868]

The **O**rganized **P**rogram **t**o **I**nitiate Lifesaving Treat**m**ent in Hospital**ize**d Patients with **HF** (OPTIMIZE-HF) was a large prospective registry targeting hospitalized patients admitted with or develop HF during hospitalization.[869] An overlying quality assurance initiative was offered to institutions including workshops and rounds, evidence-based care pathways, and a web-based tool provides participating institutions with real-time quality-of-care reports and benchmark comparisons with other institutions. An increased rate of KPI conformity was noted for several KPIs including use of beta-blockers, aldosterone antagonists, statins, and anticoagulants in eligible patients, as well as for discharge education, smoking cessation counseling, and

assessment of left ventricular function. [869-871] The use of computerized tools was associated with lower inpatient mortality (4.1% vs. 2.5%, p<0.001), post-discharge mortality and readmissions (34.8% vs. 38.2%, *P* = 0.02, which was no longer significant after propensity risk adjustment).[871] Of all KPIs, only beta-blocker prescription was associated with a 52% reduction in mortality (95% confidence interval 0.21-0.70) at 90 days.[872] Only use of ACEis for patients with LVSD was associated with reduced combined mortality and rehospitalization at 3 months. Despite intensive application of KPI improvement initiatives, substantial unexplained variability in quality of care persisted.[870]

The Registry to **Improve** the Use of Evidence-Based **HF** Therapies in the Outpatient Setting (IMPROVE-HF) addressed quality assurance for patients with HF or MI with impaired LV function in participating outpatient cardiology clinics (chronic, stable outpatient phase).[873,874] Change tools included mandatory educational programs, development of practice-specific clinical pathways, and periodic chart reviews coupled with web-based feedback and comparison with regional and national benchmarks.[873] Similar improvement in KPI conformity was noted in this observational, non-randomized program.

Finally, ADHERE was a prospective observational study enrolling adult patients hospitalized with HF.[521,875] The study utilized JCAHO performance indicators, which, through web-based quarterly audits, were then fed back to participating centres with comparison to national benchmarks.[521] Modest improvements in KPI conformity and mortality were noted, but not compared to the existing improvements over time and were not compared to a control group.[876,877]

The prospective **G**et **W**ith **t**he **G**uidelines Program (GWTG) HF registry and performance improvement program has been in place since 2006.[878] In this institutionally based program, the unit of allocation was at the hospital level rather than the individual level, and data collection occurred at nearly 1000 hospitals (with data from several hundred thousand patients) participating in performance improvement initiatives as well those that did not. The result is that comparisons in quality of care measures and outcomes could be made between institutions that initiated quality assurance projects and those that did not. Results from several large interventions suggest that modest improvements in quality of care can be shown using multimodality interventions and that unimodal interventions are not effective.[879-885]

Educational/decision support as single interventions targeting health care workers provide a good example of the latter type.[886-893] Participation and KPI conformity tend to be variable. Thus, such programs may constitute a natural component of a larger comprehensive effort.[894-899]

A recently published cluster randomized controlled study assessed the value of a publicly released report card on the quality of care provided to patients with acute myocardial infarction and HF in 86 hospital corporations in Ontario.[900] The development and nature of quality improvement initiatives was left up to the participating hospital corporations. The intervention showed only a small but statistically significant improvement in the use of ACEi and ARBs. HF mortality rates at one year were not significantly improved. Similarly, pay for performance[901] has been a part of UK based quality assurance for primary care and for hospitals. This has met with very modest success: in the US Medicare based payment schemes (including pharmacy access

programs)[902] with both incentives and penalties for increased 30-day readmissions has also met with modest success.[903]

9.6 Can quality assurance initiatives produce meaningful improvements in the outcomes of patients with HF?

The relationship between specific performance measures and patient outcomes is frequently poor.[883,885] Many of the commonly assessed performance indicators have not been shown in clinical trials to reduce mortality and prevent hospitalization in patients with HF.[904,905] Some performance indicators, such as smoking cessation counseling may have been met but delivery may have been suboptimal.[905]

Furthermore, outpatient performance indicators have only been evaluated in the context of specialist cardiology practices.[874] For example, the benefits of better in-hospital care may be undone by suboptimal transitional care or outpatient disease management. Previous updates of the CCS HF guidelines have addressed disease management, transitional care, and end-of-life planning and care, formulating recommendations that could form the basis for new performance indicators (see Table 7).[182,401,906] Whatever their source, performance indicators are more likely to be effective if stakeholders are actively involved in their development and application, and if they are sensitive to the organizational context in which they are used.[907]

The results of several large meta analyses/systematic reviews consistently indicate several features of quality assurance programs are associated with improved clinical outcomes[908] in patients with recently hospitalized with HF.[831,909] These include disease management programs, Nurse Case Managers[910] and programs with home visits.[831] Hospital interventions associated with lower 30- day readmission rates were associated partnering with outpatient physician groups for continuity,[830] partnering with other local hospitals, medication reconciliation, early post hospital follow up, early effective communication (discharge summary) availability, and processes to follow test results.[908]

9.7 Who should participate in quality assurance?

Quality assurance principles could be applied at any level of health care delivery, from the individual practitioner, to group family or specialty practices and clinics, hospitals, and regional or provincial health authorities. However, the costs of quality assurance programs can be substantial barriers to their implementation.[905] Paradoxically, providers and institutions with low baseline adherence to the guidelines, and who are thus most likely to benefit from quality assurance initiatives, may be the least likely to willingly pay for and implement such programs. In the United States, financial incentives have been utilized to promote quality assurance, including linking full Medicare reimbursements with the collection and submission of performance indicators.[905] In Canada, professional agencies such as the Royal College of Physicians and Surgeons recognize Personal Practice Reviews as valid continuing professional development activities (http://www.royalcollege.ca). A broader national framework and incentives has been developed to facilitate the implementation of quality assurance initiatives.[836,911-913]

Recommendation 176: We recommend that health care systems should provide for quality assurance in both the process and content of care provision (Strong Recommendation, High Quality Evidence).

Recommendation 177: We recommend that quality assurance programs should include elements listed below to allow for assessment of patient, provider and health care institutional outcomes (Strong Recommendation, Moderate Quality Evidence):

- Measurement of evidence-based key performance indicators to assess system performance and outcomes.
- Robust measurement of important clinical and system of care outcomes.
- Intervention supports such as clinical tools to facilitate best practices.
- Performance feedback and education to HF care professionals and administrators.

Practical tips:

- Selection of performance indicators with outcome data from randomized clinical trials, such as those listed in the CCS Quality Indicators E- Library- Heart Failure, is preferred.
- Institutional quality improvement strategies that include the following features have been shown to improve outcomes:
    - Reliance on a set of multi-modal 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 following the period of practice change
    - Both administrative and physician champions
- It is unclear if any single intervention is superior to another. Use of multiple simultaneous interventions provides a larger effect size.
- 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 post- acute care in combination
    - Timely and accurate communication between health care providers
- 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
- 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 HFmrEF 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 (e.g., 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 (e.g., 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 LVADs in the context of changing medical and device therapy?
11. Should patients with a non-ischemic 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 ultrafiltration?
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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Abbreviations and acronyms

ACE: Angiotensin-Converting Enzyme
ACEi: Angiotensin-Converting Enzyme Inhibitor
ACS: Acute coronary syndrome
ADHERE: Acute Decompensated Heart Failure National Registry
ADVENT-HF: Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure trial
AF: Atrial Fibrillation
AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management trial
AF-CHF: Atrial Fibrillation in Congestive Heart Failure trial
A-HeFT: African-American Heart Failure Trial
AHF: Acute Heart Failure
AIMI-HF: Project I-A: Cardiac Imaging in Ischemic Heart Failure
ARB: Angiotensin Receptor Blocker
ARNI: Angiotensin Receptor Neprilysin Inhibitor
ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy
ASCEND-HF: Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial
AVID: Antiarrhythmics Versus Implantable Defibrillators study
BEAUTIFUL: Ivabradine for patients with stable coronary artery disease and left ventricular systolic dysfunction trial
BEST: Beta-Blocker Evaluation of Survival Trial
BI-PAP: Bilevel positive airway pressure

BLOCK HF: Biventricular versus Right Ventricular Pacing in Patients with Left Ventricular Dysfunction and Atrioventricular Block study
BMI: Body Mass Index
BNP: B-type natriuretic peptide
BTC: Bridge to candidacy
BTT: bridge to transplantation
CABG: Coronary artery bypass grafting
CACPR: Canadian Association of Cardiac Rehabilitation
CAD: Coronary Artery Disease
CARDIA: Coronary Artery Risk Development in Young Adult study
CCS: Canadian Cardiovascular Society
CE-MARC: Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease
CF: Continuous flow
CHARM- Preserved: Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction Trial
CHF-STAT: Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy
CKD: Chronic Kidney Disease
CMR: Cardiac Magnetic Resonance
COPD: Chronic Obstructive Pulmonary Disease
CORONA: The Controlled Rosuvastatin Multinational Trial in Heart Failure study
CPAP: continuous positive airway pressure
CRS: Cardiorenal syndrome
CRT: Cardiac Resynchronization Therapy
CVD: Cardiovascular disease
DIG-trial: The effect of digoxin on mortality and morbidity in patient with heart failure
DM: Diabetes Mellitus
DOSE : Diuretic Optimization Strategies Evaluation trial
DSE: dobutamine stress echocardiography
DT: destination therapy
ED: Emergency department
ECG: Electrocardiogram
ECMO: extracorporeal membrane oxygenation
ECV: extracellular volume
eGFR: Estimated Glomerular Filtration Rate
EF: Ejection Fraction
EFFECT-HF: Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Iron Deficiency and Chronic Heart Failure
EGE: early gadolinium enhancemen
EMB: Endomyocardial Biopsy
EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure

EPPY: events/patients per year
ESAs: Erythropoietin Stimulating Agents
ESC: European Society of Cardiology
FCM: Ferric carboxymaltose
GCM: Giant cell myocarditis
GDMT: Guideline Directed Medical Therapy
GFR: Glomerular filtration rate
GI: Gastrointestinal
GRADE: Grading of Recommendations Assessment, Development, and Evaluation standards
GWTG: Get With the Guidelines Program
Hb: Hemoglobin
HCM: hypertrophic cardiomyopathy
HF: Heart Failure
HF-ACTION: Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HFrEF : Heart failure with preserved ejection fraction
HR: Hazard ratio
hsTn: High-sensitivity Troponins
HVAD: HeartWare ventricular assist device
IABP: intraaortic balloon pump
ICD: Implantable Cardioverter-Defibrillator
ID: Iron deficiency
IMPROVE-HF: Registry to Improve the Use of Evidence-Based HF Therapies in the Outpatient Setting
INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support group
INTrEPID: Chronic Mechanical Circulatory Support for Inotrope-Dependent Heart Failure Patients Who Are Not Transplant Candidates trial
IRONOUT HF: Oral Iron Repletion effects ON Oxygen UpTake in Heart Failure study
ISAR-Shock: A Randomized Clinical Trial to Evaluate the Safety and Efficacy of a Percutaneous Left Ventricular Assist Device Versus Intra-Aortic Balloon Pumping for Treatment of Cardiogenic Shock Caused by Myocardial Infarction
ISFC: International Society and Federation of Cardiology
KPI: Key performance indicator
LBBB: left bundle branch block
LGE: Late gadolinium enhancement
LV: Left Ventricle
LVAD: Left ventricle assistant device
LVEF: Left Ventricular Ejection Fraction
LVSD: Left Ventricular Systolic Dysfunction
MADIT II: Multicenter Automatic Defibrillator Implantation Trial II
MCS: Mechanical Circulatory Support
MET: Metabolic equivalent of task

MI: Myocardial Infarction
MIT-NEC: Medical Imaging Trial Network of Canada
MR: mitral regurgitation
MRA: Mineralocorticoid Receptor Antagonist
NIV: noninvasive ventilation
NOACs: non-vitamin K antagonist oral anticoagulants
NPs: Natriuretic peptides
NYHA: New York Heart Association
OPTIME-CHF: Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure trial
PAH: Pulmonary arterial hypertension
PAP: Pulmonary artery pressure
PARR-2: PET and Recovery Following Revascularization-2 trial
PCI: Percutaneous coronary intervention
PCT: Procalcitonin
PCWP: Pulmonary capillary wedge pressure
PEP-CHF: Perindopril in Elderly People with Chronic Heart Failure Trial
PET: positron emission tomography
PONTIAC: NT-proBNP Selected PreventiOn of cardiac eveNts in a population of diabetic patients without A history of Cardiac disease study
PPCM: Peripartum cardiomyopathy
PVR: Pulmonary vascular resistance
RAAS: Renin-Angiotensin-Aldosterone System
RACE II: Rate Control Efficacy in Permanent Atrial Fibrillation trial
RAFT: Resynchronization for Ambulatory Heart Failure Trial
RAFT-PermAF: Resynchronization/Defibrillation for Ambulatory Heart Failure Trial in Patients With Permanent Atrial Fibrillation
RAPID-CHF: Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure trial
RCM: Restrictive Cardiomyopathy
RCT: Randomized Controlled Trial
RED-HF: Reduction of Events With Darbepoetin Alfa in Heart Failure trial
REMATCH: Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial
RHF: Right heart failure
ROADMAP: Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management trial
RVAD: right ventricle ventricular assist devices
RVEF: right ventricular ejection fraction
SBP: Systolic Blood Pressure
SCD: sudden cardiac death

SCD-HeFT : Sudden Cardiac Death in Heart Failure Trial

SENIORS: Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure trial

SERVE-HF: Central Sleep Apnoea by Adaptive Servo Ventilation in Patients with Heart Failure trial

SHARE-AP: Study of Health Assessment and Risk Evaluation in Aboriginal Peoples

SHIFT: Ivabradine and outcomes in chronic heart failure

SOLVD: Studies of Left Ventricular Dysfunction trial

SPRINT: Systolic Blood Pressure Intervention Trial

STAMINA-HeFT: Study of Anemia in Heart Failure Trial

STOP-HF: Saint Vincent **S**creening **to P**revent **H**eart **F**ailure

STICH: Surgical Treatment of Ischemic Heart Failure trial

STS: Society of Thoracic Surgeons

SVR: Surgical ventricular reconstruction

TOPCAT: Treatment of Preserved CArdiac Function Heart Failure with an AldosTerone Antagonist trial

TSAT: Transferrin saturation

TTE: Transthoracic echocardiogram

UNLOAD: Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure trial

VA: Veno-arterial

VADs: ventricular assist devices

Val-HeFT: Valsartan in Heart Failure Trial

VHeFT: Vasodilator-Heart Failure Trial

VIDA: Viability Identification With Dobutamine Administration study

3CPO: Three Interventions in Cardiogenic Pulmonary Oedema trial

WHO: World Health Organization