

# Cardiac Diseases and Therapies

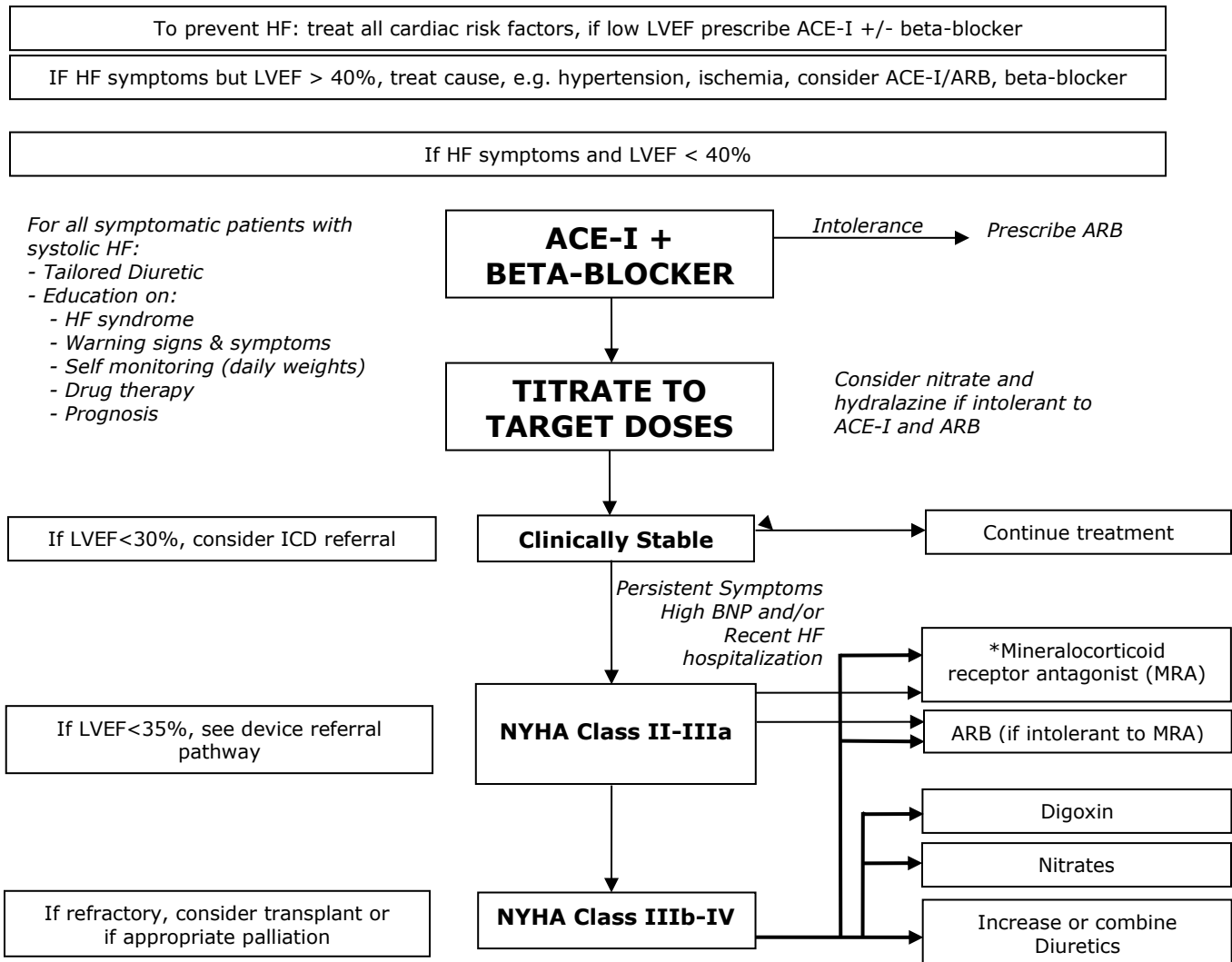
## HEART FAILURE

### CHRONIC HEART FAILURE

#### OVERVIEW

- Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood
- The cardinal manifestations of HF are dyspnea, fatigue, and fluid retention
- HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels or from certain metabolic abnormalities, but most patients with HF have symptoms due to impaired left ventricular myocardial function which includes both reduced and preserved ejection fraction (EF)

**Figure 1. Algorithm for Prevention and Treatment of Clinically Stable Heart Failure**



\*Mineralocorticoid receptor antagonist – spironolactone, eplerenone  
 Not recommended to combine ACE-I, ARB, and mineralocorticoid receptor antagonist

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#### HEART FAILURE WITH REDUCED EJECTION FRACTION

- The definition varies, but typically guidelines refer to  $EF \leq 40\%$
- Randomized controlled trials in patients with HF have mainly enrolled patients with HF with reduced EF with an  $EF \leq 35\%$  or  $\leq 40\%$ . It is only in these patients that efficacious therapies have been demonstrated to date.

#### Non-Pharmacologic Management

- All patients with symptomatic heart failure should restrict their dietary salt intake to a no-added-salt diet (2 g/day to 3 g/day). Patients with more advanced heart failure and fluid retention may be advised to restrict salt intake further to 1 g/day to 2 g/day (low-salt diet).
- Concomitant restriction of daily fluid intake to between 1.5 L/day to 2 L/day should be considered for all patients with fluid retention or congestion that is not easily controlled with diuretics, or in patients with significant renal dysfunction or hyponatremia
- Daily morning weight should be monitored in heart failure patients with fluid retention or congestion that is not easily controlled with diuretics, or in patients with significant renal dysfunction
- Regular physical activity is recommended for all patients with stable heart failure symptoms and impaired left ventricular systolic function

#### Pharmacologic Therapies

The clinical goals of pharmacologic therapy include:

- 1) Limit or reverse myopathic dilatation  
Neurohormonal blockade
  - Angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), beta-blockers, mineralocorticoid receptor antagonists (MRA), combined angiotensin/neprilysin inhibitor
- 2) Relieve or prevent congestion
  - Diuretics
- 3) Improve functional capacity
  - Diuretics
  - Vasodilators
  - Digoxin
  - Combined angiotensin/neprilysin inhibitor
- 4) Improve survival
  - ACE-I, ARB, beta-blockers, MRA
  - Hydralazine and nitrates (marginal benefit)
  - Combined angiotensin/neprilysin inhibitor

Drug Classification	Drug Name(s) and Dosage Range	Place in Therapy	Precautions/Contraindications	Special Considerations
<b>Diuretics</b>	<u>Loop Diuretics</u>	<ul style="list-style-type: none"><li>• For relief of signs and symptoms of congestion</li><li>• Maintenance of euvolemia for recurrent fluid retention with diuretic</li></ul>	<ul style="list-style-type: none"><li>• Hypokalemia</li><li>• Hyponatremia</li><li>• Hypotension</li><li>• Hypovolemia</li></ul>	<ul style="list-style-type: none"><li>• Monitor efficacy with daily patient weights</li><li>• Monitor electrolytes, particularly <math>K^+</math> and <math>Na^+</math>, and serum creatinine</li><li>• Consider dose reduction for</li></ul>
	Furosemide 20-160 mg po daily, bid or tid			
	Bumetanide 0.5-2 mg po daily to			

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	bid, up to 10 mg/day  *1 mg bumetanide is equivalent to 40 mg furosemide*	withdrawal despite dietary sodium and fluid restriction	observed hypotension or renal azotemia • When acute congestion is cleared, the lowest dose should be used that is compatible with stable signs and symptoms
	<u>Thiazide-like Diuretics</u>  Metolazone 2.5-10 mg daily, up to 20 mg daily (consider increasing dose interval depending on response e.g. 2-3 times/wk)  Hydrochlorothiazide 25 mg daily or bid, up to 200 mg/day	<ul style="list-style-type: none"> <li>• Adjunctive therapy to loop diuretics to improve diuretic efficacy, for patients with persistent volume overload despite optimal medical therapy and increases in loop diuretics</li> <li>• Hypertensive patients with HF and mild fluid retention</li> </ul>	<ul style="list-style-type: none"> <li>• Hypokalemia</li> <li>• Hyponatremia</li> <li>• Hypotension</li> <li>• Hypovolemia</li> <li>• May cause profound diuresis, electrolyte loss, eventual volume depletion</li> <li>• Closely monitor daily patient weights, serum creatinine, and electrolytes (particularly K<sup>+</sup> and Na<sup>+</sup>)</li> <li>• Significant GI upset in select patients</li> </ul>
<b>Vasodilators</b>	<u>Angiotensin-Converting Enzyme Inhibitors (ACE inhibitors)</u>  <i>Evidence-based medications and initial &amp; target doses:</i> Captopril 6.25-50 mg tid  Enalapril 1.25-10 mg bid  Lisinopril 2.5-35 mg od  Perindopril 2-8 mg od  Ramipril 1.25-5 mg bid  Trandolapril 1-4 mg od	<ul style="list-style-type: none"> <li>• In all asymptomatic and symptomatic HF patients with reduced EF</li> <li>• Reduces morbidity and mortality</li> </ul>	<ul style="list-style-type: none"> <li>• Previous hypersensitivity or angioedema</li> <li>• Pregnancy</li> <li>• Bilateral renal artery stenosis</li> <li>• Hyperkalemia</li> <li>• Symptomatic or severe asymptomatic hypotension (SBP&lt;80mmHg)</li> <li>• Renal impairment (SCr &gt;265 µmol/L)</li> <li>• Careful titration in patients with low systemic BP, who are being actively diuresed, or with elevated serum creatinine</li> <li>• Monitor serum creatinine and K<sup>+</sup></li> <li>• Initial elevation of creatinine often normalizes. Elevation of &gt;30% creatinine warrants reduction of ACE-I and/or diuretic dose if possible</li> <li>• Hyperkalemia may limit use</li> </ul>

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<b>Vasodilators (cont'd)</b>	<u>Angiotensin Receptor Blockers (ARB)</u>	<ul style="list-style-type: none"> <li>Alternative for patients who cannot tolerate an ACE-I</li> <li>In addition to ACE-I for patients with NYHA class II-IV HF and reduced EF deemed at increased risk of HF events despite optimal treatment with an ACE-I and beta-blocker</li> <li>Reduces morbidity and mortality</li> </ul>	<ul style="list-style-type: none"> <li>Pregnancy</li> <li>Bilateral renal artery stenosis</li> <li>Hyperkalemia</li> <li>Symptomatic or severe asymptomatic hypotension (SBP&lt;80mmHg)</li> <li>Renal impairment (SCr &gt;265 µmol/L)</li> <li>Angioedema with ACE-I: some cross-reactivity reported</li> </ul>	<ul style="list-style-type: none"> <li>Same as ACE-I</li> <li>Combination treatment with ACE-I requires careful monitoring of serum creatinine and K<sup>+</sup></li> <li>Routine combination of ACE-I, ARB, and MRA should not be used</li> </ul>
	<p><i>Evidence-based medications and initial &amp; target doses:</i></p> <p>Valsartan 40-160 mg bid</p> <p>Candesartan 4-32 mg od</p>	<p><u>Hydralazine</u> 25-50 mg 3 or 4 times daily, up to 300 mg daily in divided doses</p> <p><b>AND</b></p> <p><u>Isosorbide dinitrate</u> 20-30 mg 3 or 4 times daily, up to 120 mg daily in divided doses</p>	<ul style="list-style-type: none"> <li>In addition to standard therapy for black Canadians with NYHA class III-IV HF receiving optimal therapy with an ACE-I and beta-blocker, unless contraindicated</li> <li>Alternative for patients who cannot tolerate an ACE-I or ARB because of intolerance, hyperkalemia, or renal dysfunction with marginal mortality benefit</li> </ul>	<ul style="list-style-type: none"> <li>Contraindicated with phosphodiesterase inhibitors (sildenafil, tadalafil, vardenafil) due to risk of circulatory collapse/severe hypotension (isosorbide dinitrate)</li> <li>Symptomatic or severe asymptomatic hypotension (SBP&lt;80mmHg)</li> </ul>
<b>Beta-Blockers</b>	<i>Evidence-based medications and initial &amp; target doses:</i>	<ul style="list-style-type: none"> <li>In all asymptomatic and symptomatic HF patients with reduced EF</li> <li>Reduces morbidity and mortality</li> </ul>	<ul style="list-style-type: none"> <li>Symptomatic hypotension</li> <li>Symptomatic bradycardia</li> <li>Significant AV block without a permanent pacemaker</li> <li>Severe reactive airways disease</li> </ul>	<ul style="list-style-type: none"> <li>Initiate at low dose and gradually titrate if euvolemic to maximum tolerated dose</li> <li>Avoid abrupt withdrawal</li> <li>Temporary discontinuation may occasionally be necessary in patients with</li> </ul>
<b>Non-selective</b>	Carvedilol 3.125-25 mg bid* *50 mg bid if weight>85 kg			
<b>Beta-1-selective</b>	Metoprolol succinate CR/XL** 12.5-200 mg od **Not available in			

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Canada

Bisoprolol  
1.25-10 mg od

shock

- NYHA class IV patients should be stabilized before initiation of a beta-blocker
- Should ideally use a beta-blocker that is proven to be beneficial in clinical trials

#### Digoxin

Digoxin  
0.0625-0.25mg od

- In patients in sinus rhythm who continue to have moderate to severe symptoms, despite optimized HF therapy
- In patients with chronic atrial fibrillation and poor control of ventricular rate despite optimal beta-blocker therapy, or when beta-blockers cannot be used
- Reduces hospitalizations and relieves symptoms
- No mortality benefit
- Significant sinus or AV block without a permanent pacemaker
- Reduced renal function
- Hypokalemia
- Hypomagnesemia
- Narrow therapeutic range - target for HF 0.6-1.2 nmol/L (0.5 to 0.9 ng/ml)
- Monitor digoxin levels within one week of starting therapy, with dose change, when interacting medications are started or stopped, or if toxicity is suspected
- 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
- Many drug interactions (e.g. amiodarone can increase digoxin levels)
- Monitor heart rate particularly in combination with other negative chronotropes

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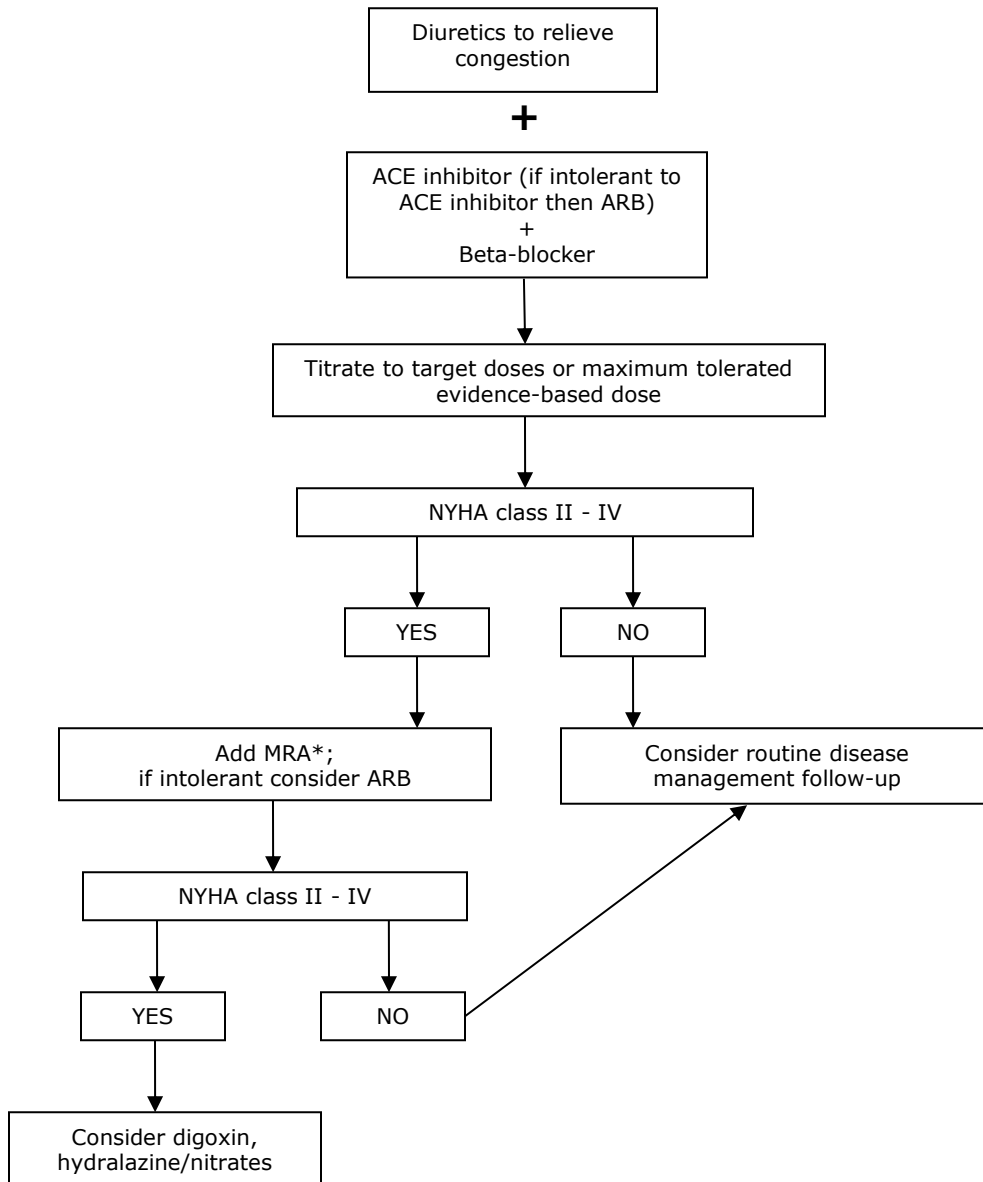
<b>Mineralo-corticoid Receptor Antagonists (MRA)</b>	<p>Spironolactone 12.5-50 mg od</p> <p>Eplerenone 25-50 mg od</p>	<ul style="list-style-type: none"> <li>• In patients &gt; 55 years with mild to moderate HF during standard HF treatments with reduced EF and recent (6 months) hospitalization for CV disease or with elevated BNP or NT-proBNP levels</li> <li>• In post-MI patients with reduced EF and HF or reduced EF alone in the presence of diabetes</li> <li>• In patients with reduced EF and severe chronic HF (NYHA III-IV) despite optimization of other recommended treatments</li> <li>• Reduces morbidity and mortality</li> </ul>	<ul style="list-style-type: none"> <li>• Hyperkalemia (<math>K^+ &gt; 5.0</math> mmol/L)</li> <li>• Renal impairment (<math>CrCl &lt; 30</math> mL/min)</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor <math>K^+</math> and serum creatinine closely</li> <li>• Consider discontinuing or reducing potassium supplementation prior to initiation</li> <li>• Routine combination of ACE-I, ARB, and MRA should not be used</li> <li>• Less gynecomastia or breast pain with eplerenone (&lt;1%) vs spironolactone (10%)</li> <li>• Watch for drug interactions with eplerenone (CYP 3A4 substrate)</li> </ul>
<b>Neutral endo-peptidase inhibitor/angiotensin II AT<sub>1</sub> receptor blocker</b>	<p>Sacubitril/Valsartan (ENTRESTO)</p> <p>24.3 mg Sacubitril / 25.7 mg Valsartan bid</p> <p>48.6 mg Sacubitril / 51.4 mg Valsartan bid</p> <p>97.2 mg Sacubitril / 102.8 mg Valsartan bid (target dose)</p>	<ul style="list-style-type: none"> <li>• In patients with mild to moderate HF, an <math>EF \leq 40\%</math>, an elevated natriuretic peptide level or hospitalization for HF in the past 12 months, a serum potassium &lt; 5.2 mmol/L, and an <math>eGFR \geq 30</math> mL/min and treated with appropriate doses of guideline-directed medical therapy in place of an ACE-I or an ARB, with close surveillance of serum potassium and creatinine</li> </ul>	<ul style="list-style-type: none"> <li>• Renal impairment (<math>eGFR &lt; 30</math> mL/min)</li> <li>• Severe hepatic impairment (Child-Pugh C)</li> <li>• History of angioedema</li> <li>• Hypotension</li> <li>• Hyperkalemia</li> <li>• Pregnancy</li> <li>• Bilateral renal artery stenosis</li> </ul>	<ul style="list-style-type: none"> <li>• Must not be administered concomitantly or within 36 hours of ACE-I (risk of angioedema)</li> <li>• Adverse effects include hypotension, hyperkalemia, renal impairment, angioedema</li> <li>• Cost: \$7.24/day</li> <li>• Non-formulary status at UHN</li> </ul>

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**Figure 2. Algorithm for Pharmacologic Treatment of Symptomatic Heart Failure with Reduced Ejection Fraction**



\*MRA - mineralocorticoid receptor antagonist

### Treatment of Asymptomatic Heart Failure with Reduced Ejection Fraction

- Treat all cardiac risk factors
- Prescribe ACE inhibitor and beta-blocker

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#### NOVEL THERAPIES

##### Sacubitril/Valsartan (LCZ696)

- Combined angiotensin/neprilysin inhibitor
- Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, such as natriuretic peptides, bradykinin, and adrenomedullin
- Inhibition of neprilysin increases the levels of these vasoactive peptides, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodelling
- In the PARADIGM-HF trial which enrolled patients with NYHA class II-IV HF with reduced EF on recommended HF medical therapy, LCZ696 (combined angiotensin receptor blocker neprilysin inhibitor) was superior to enalapril at reducing mortality, hospitalization for HF, and HF symptoms
- The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but a smaller risk of renal impairment, hyperkalemia, and cough than the enalapril group
- Recommended for patients with mild to moderate HF, an EF  $\leq$  40%, an elevated natriuretic peptide level or hospitalization for HF in the past 12 months, a serum potassium  $<$  5.2 mmol/L, and an eGFR  $\geq$  30 mL/min and treated with appropriate doses of guideline-directed medical therapy in place of an ACE inhibitor or an angiotensin receptor blocker, with close surveillance of serum potassium and creatinine
- Recently approved in Canada in October 2015 for the treatment of HF with reduced EF in patients with NYHA class II or III

##### Ivabradine

- Selective inhibitor of the  $I_f$  current in the sinoatrial node
- Raised resting heart rate is a risk factor for adverse outcomes in HF
- In the SHIFT trial which enrolled patients with stable symptomatic chronic HF with reduced EF on recommended HF medical therapy (including beta-blockers if tolerated) who were in sinus rhythm with HR  $\geq$  70 and who had been admitted to hospital for HF within the previous year, ivabradine reduced the composite endpoint of cardiovascular death or hospital admission for worsening heart failure compared to placebo
- Fewer serious adverse events occurred in the ivabradine group than in the placebo group
- Symptomatic and asymptomatic bradycardia and visual disturbances (phosphenes) were more frequent in the ivabradine group
- Not currently approved in Canada, but approved by FDA for treatment of HF with reduced EF



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#### DEVICE THERAPY

##### Implantable cardioverter-defibrillator (ICD)

- Primary ICD therapy improves survival in patients with NYHA II-III ischemic and nonischemic HF with  $EF \leq 35\%$  and in patients with a previous MI with  $EF \leq 30\%$
- There is no survival benefit early after an MI

*Recommended for primary and secondary prevention in patients with:*

- Ischemic cardiomyopathy, NYHA class II-III,  $EF \leq 35\%$  at least 1 month post MI and at least 3 months post coronary revascularization procedure
- Ischemic cardiomyopathy, NYHA class I,  $EF \leq 30\%$  at least 1 month post MI and at least 3 months post coronary revascularization procedure
- Nonischemic cardiomyopathy, NYHA class II-III,  $EF \leq 35\%$ , measured at least 9 months after optimal medical therapy
- HF with reduced EF with a history of hemodynamically significant or sustained ventricular arrhythmia
- **NOT** recommended in NYHA class IV patients who are not expected to improve with any further therapy and who are not candidates for cardiac transplant or mechanical circulatory support

##### Cardiac resynchronization therapy (CRT)

- Can improve left ventricular structure and function and reduce morbidity and mortality in NYHA class II to ambulatory class IV HF patients with reduced EF who are in sinus rhythm with a wide QRS (specified below) and left bundle branch block (LBBB) QRS morphology

*Recommended for patients with:*

- NYHA class III and ambulatory NYHA class IV HF despite optimal medical therapy, in sinus rhythm with QRS duration  $\geq 130$  ms and LBBB QRS morphology and  $EF \leq 35\%$
- NYHA class II HF despite optimal medical therapy, in sinus rhythm with a QRS duration  $\geq 130$  ms with LBBB QRS morphology and  $EF \leq 30\%$

*Considered for patients with:*

- NYHA class II, III, and ambulatory NYHA class IV HF, in sinus rhythm,  $EF \leq 35\%$ , and QRS duration  $\geq 150$  ms with non-LBBB QRS morphology

##### REFER patient to HF clinic disease management program for the following services:

- Multidisciplinary management
- Medication titration
- Referral for electrophysiological services
- Referral for advanced therapies – VAD (ventricular assist device) and heart transplant evaluation
- Referral for palliative care support

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#### Indications for referral to HF specialist for consideration of advanced therapies (VAD and heart transplant):

- Multiple markers of poor prognosis
- Inotrope dependency
- Difficulty titrating HF therapy

#### Typical VAD criteria

Patients with advanced HF, including those, despite optimal treatment, continuing to exhibit NYHA IIIb 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
- Evidence of progressive end organ dysfunction due to reduced perfusion not due to inadequate ventricular filling pressures
- Recurrent HF hospitalizations (>3 in 1 year) not due to a clearly reversible cause
- Need to progressively reduce or eliminate evidence-based HF therapies such as ACE inhibitors or beta-blockers, due to symptomatic hypotension or worsening renal function
- Requirement of inotropic support

#### HEART FAILURE WITH PRESERVED EJECTION FRACTION

- Prevalence is approximately 50% of patients with HF
- Diagnosed when typical clinical HF findings are accompanied by preserved EF and the absence of significant valvular abnormalities
- Preserved EF has been variably classified as EF >40%, >45%, >50%, and ≥55%
- More prevalent in the elderly, women, and in patients with a history of hypertension
- Less mortality but similar morbidity (especially HF hospitalizations) as HF with reduced EF
- Very limited evidence-based outcome-modifying therapies

#### General Approach to Treatment

- Control the risk factors potentially etiologic for the syndrome, such as hypertension and myocardial ischemia
- Control symptoms of congestion with diuretics
- Control heart rate with beta-blockers and rate-lowering calcium channel blockers (non-dihydropyridines)
- ACE inhibitors and ARBs may be used if there are other non-HF indications for their use
- Use of MRA for patients who have had an increased natriuretic peptide level

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This information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about Cardiovascular illness and the treatments in question.

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