Heart failure (HF) is a common condition, affecting 1–2% of the adult population in developed countries. Among those aged 70 years or older, the prevalence of HF is ≥10%.

Despite advances in detection and therapy, HF remains a significant cause of morbidity and mortality. In Canada, HF is reported to be the most common cause of hospitalization in patients over 65 years of age, as well as the cause of 9% of all deaths nationwide. Obviously, there is an urgent need for aggressive measures to reduce the burden of illness associated with this clinical syndrome.

**ETIOLOGY AND PATHOPHYSIOLOGY**

There are many known etiologies of HF, and several risk factors have been identified. Coronary artery disease is cited to be responsible for roughly two-thirds of systolic HF cases (see Table 2, below, for descriptions of systolic and diastolic HF). Hypertension is also a major risk factor in HF development. Some other risk factors include valvular heart disease, diabetes mellitus, hyperlipidemia, excessive alcohol intake, use of certain chemotherapy drugs (e.g., doxorubicin or trastuzumab), physical inactivity, and smoking.

Most patients with HF have symptoms due to left ventricular (LV) myocardial dysfunction. In the presence of LV systolic dysfunction (the most common cause of HF), the body activates several neurohumoral pathways to increase circulating blood volume in an attempt to maintain adequate cardiac output. Two key neurohumoral systems activated are the renin-angiotensin-aldosterone system and the sympathetic nervous system. Initially, activation of these pathways is compensatory and beneficial, but it eventually leads to detrimental effects, including pathologic LV remodelling with dilation, hypertrophy, and impaired contractility.

**CLASSIFICATION AND SYMPTOMS**

Heart failure is often classified according to the New York Heart Association (NYHA) functional classification system (see Table 1). Additionally, patients may be classified based on whether LV ejection fraction (EF) is reduced (HF with reduced EF [HF-REF]) or preserved (HF with preserved EF [HF-PEF]) (see Table 2).

The hallmark manifestations of HF are dyspnea (shortness of breath), fatigue, and edema (fluid retention). Other typical symptoms include orthopnea, paroxysmal nocturnal dyspnea, and reduced exercise tolerance. Less typically, patients may complain of nocturnal cough, wheezing, weight gain, anorexia, palpitations, and confusion (the latter is most likely in the elderly). It is notable that symptom severity can vary substantially during the course of the disease and may not correlate with changes in underlying

### Table 1 – New York Heart Association functional classification

<table>
<thead>
<tr>
<th>NYHA class*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of physical activity; ordinary physical activity does not cause HF symptoms</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in HF symptoms</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity; comfortable at rest, but less than ordinary activity causes HF symptoms</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry on any physical activity without HF symptoms or symptoms of HF at rest</td>
</tr>
</tbody>
</table>

* HF = heart failure; NYHA = New York Heart Association

* Patients in NYHA classes II, III, and IV are sometimes said to have mild, moderate, and severe symptoms, respectively.
cardiac function. Importantly, any deterioration in symptoms indicates a heightened risk of hospitalization and death, and warrants prompt medical attention.

**MANAGEMENT**

The main goals of treatment in patients with HF are to improve/relieve symptoms and signs, reduce morbidity (including hospital admissions), and improve survival. Recommendations for managing patients with HF-REF and HF-PEF are summarized below. In addition to the specific therapies discussed, comorbidities should be appropriately treated, particularly those that are major risk factors for HF and those that directly impact HF symptoms and/or progression (e.g., hypertension, atrial fibrillation, anemia). A thorough discussion of such holistic management is beyond the scope of this review; however, recommendations are provided in guidelines available online (see References, below, for URLs).

**Pharmacotherapy for HF-REF**

There is general consensus among recent guidelines that the foundation of treatment for most patients with HF-REF should be a multidrug regimen consisting of an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin receptor blocker [ARB]) and a beta-blocker. A mineralocorticoid receptor antagonist (MRA) is considered standard additional therapy for individuals who continue to meet NYHA class II–IV criteria despite optimized treatment with an ACE inhibitor (or ARB) and a beta-blocker. Each of the aforementioned drug classes has been shown to improve survival in trials involving patients with HF-REF. These core therapies are generally used in conjunction with diuretics to relieve congestive symptoms/fluid retention. Adjunctive or alternative therapies such as digoxin, isosorbide dinitrate plus hydralazine, and omega-3 polyunsaturated fatty acids may also be beneficial in certain scenarios.

Evidence-based dosing strategies for disease-modifying therapies are summarized in Table 3; recommendations and practical tips regarding these agents are provided in Box 1. Recommendations and

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### Table 2: Classification based on left ventricular ejection fraction

<table>
<thead>
<tr>
<th>Classification*</th>
<th>LVEF</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Heart failure with reduced ejection fraction (HF-REF) | ≤40% | • Also referred to as “systolic HF”
| | | • Best understood type of HF in terms of pathophysiology and treatment. RCTs proving therapies to be efficacious in HF have primarily enrolled patients with HF-REF |
| Heart failure with preserved ejection fraction (HF-PEF) | ≥50% | • Also referred to as “diastolic HF”
| | | • To date, efficacious therapies for patients with HF-PEF have not been identified |

HF = heart failure; LVEF = left ventricular ejection fraction; RCTs = randomized controlled trials

* Classifications in addition to those listed have been described: (1) HF-PEF, borderline LVEF (41–49%); (2) HF-PEF, improved LVEF >40% (a subset of patients who previously had HF-REF; further research is necessary to better characterize these patients).

† In systolic HF, cardiac contractility is reduced.

‡ In diastolic HF, cardiac relaxation is impaired and ventricular filling is abnormal.

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### Table 3: Doses of disease-modifying medications for HF-REF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial*</th>
<th>Target†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg tid</td>
<td>50 mg tid</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1.25–2.5 mg bid</td>
<td>10 mg bid</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–5 mg od</td>
<td>20–35 mg od</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg od</td>
<td>4–8 mg od</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–2.5 mg od</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>0.5–1 mg od</td>
<td>4 mg od</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg od</td>
<td>10 mg od</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg bid</td>
<td>25 mg bid†</td>
</tr>
<tr>
<td>Metoprolol CR/XL§</td>
<td>12.5–25 mg od</td>
<td>200 mg od</td>
</tr>
<tr>
<td><strong>Angiotensin receptor blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 mg od</td>
<td>32 mg od</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 mg bid</td>
<td>160 mg bid</td>
</tr>
<tr>
<td><strong>Mineralocorticoid receptor antagonists¶</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg od</td>
<td>50 mg od</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5 mg od</td>
<td>25–50 mg od</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>375 mg tid</td>
<td>75 mg tid</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>20 mg tid</td>
<td>40 mg tid</td>
</tr>
</tbody>
</table>

* In instances where initial recommended doses varied among guidelines consulted, lower doses have been listed.

† If target doses cannot be reached, use maximum tolerated doses.

‡ 50 mg bid if weight >85 kg

§ The metoprolol CR/XL (succinate) formulations are not commercially available in Canada.

¶ Also referred to as aldosterone antagonists.
Box 1 – Recommendations* and practical tips† for disease-modifying medications for HF-REF 1,5,7,9

**Angiotensin-converting enzyme inhibitors**

Recommended use:
- All symptomatic (and previously symptomatic) patients with EF ≤40% (in addition to a beta-blocker)

Tips/comments:
- When initiating therapy, double the dose at intervals of no less than 2 weeks in the community, quicker up-titration may occur in hospital or in other settings where patients are closely monitored
- An increase in serum creatinine is expected upon initiating therapy, there is no immediate need to lower the dose if the increase stabilizes at ≤30%
- Symptom improvement occurs within a few weeks to a few months after starting treatment
- Abrupt withdrawal can lead to clinical deterioration and should be avoided
- The combination of an ACE inhibitor and ARB increases the risk of hypotension, hyperkalemia, and renal dysfunction, and should be used with caution

**Beta-blockers**

Recommended use:
- All symptomatic (and previously symptomatic) patients with EF ≤40% (in addition to an ACE inhibitor)

Tips/comments:
- When initiating therapy, double the dose at intervals of no less than 2 weeks (slower up-titration may be necessary)
- Therapy should generally be initiated in stable patients (e.g., not during or within 4 weeks of a HF exacerbation); attempts should be made to relieve congestion/fluid retention prior to starting therapy
- Major dose reduction or abrupt withdrawal can lead to clinical deterioration and should be avoided
- Symptom improvement may occur slowly after starting treatment, sometimes taking 3–6 months or longer

**Angiotensin receptor blockers**

Recommended uses:
- As an alternative to an ACE inhibitor in patients who: (1) cannot tolerate ACE inhibitor therapy or (2) are already taking an ARB for another indication
- In combination with an ACE inhibitor and beta-blocker for persistently symptomatic patients when a MRA is not tolerated

Tips/comments:
- Tips/comments for ACE inhibitors, above, for statement regarding combined use of an ACE inhibitor and ARB

**Mineralocorticoid receptor antagonists**

Recommended uses:
- All patients with persistent symptoms (NYHA Class II–IV) and an EF ≤35% despite treatment with an ACE inhibitor (or ARB) and beta-blocker
- Following an acute MI in patients with (1) symptoms of HF and an EF ≤40%, or (2) an EF ≤40% and a history of diabetes mellitus

Tips/comments:
- Consider dose up-titration 4–8 weeks after initiation of therapy
- Symptom improvement occurs within a few weeks to a few months after starting treatment
- Hyperkalemia is the main concern with MRA therapy, and risk is increased when therapy is combined with an ACE inhibitor or ARB; vigilant monitoring of serum potassium and renal function is essential
- Interruption of therapy may be necessary during periods of worsening renal function and/or dehydration

**Vasodilators**

Recommended use:
- The combination of isosorbide dinitrate and hydralazine may be considered: (1) for black patients with persistent symptoms despite standard therapy with an ACE inhibitor (or ARB) and beta-blocker (and MRA as appropriate), and (2) as an alternative to an ACE inhibitor or ARB in any patient unable to use/tolerate these therapies

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; EF = ejection fraction; HF = heart failure; HF-REF = heart failure with reduced ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association

* Recommendations provided were summarized/synthesized from guidelines consulted; refer to complete online documents for details of recommendations made in individual guidelines, including grades/level of evidence (see References, below, for URLs).
† Many useful tips and comments in addition to those listed (including ones related to contraindications, precautions, drug interactions, monitoring, and management of adverse effects) are made in the full guidelines; refer to complete online documents for details (see References, below, for URLs). Web tables 11, 12, 13, and 15 from the European guidelines are particularly helpful.
‡ In addition to the listed uses, Canadian guidelines propose ARBs be considered as adjunctive therapy to ACE inhibitors when (β)-blockers are either contraindicated or not tolerated after careful attempts at initiation.
§ Intolerable ACE inhibitor-induced cough is the primary indication for ARB therapy; caution is advised in patients who developed angioedema with an ACE inhibitor.
¶ Also referred to as aldosterone antagonists.
†† Recommendations from Canadian guidelines are more restrictive (based on EF) than those from US or European guidelines; Canadian guidelines also make differential recommendations for eplerenone and spironolactone, whereas US and European guidelines do not.
†‡ According to US guidelines, patients with NYHA class II HF should have a history of prior cardiovascular hospitalization, or elevated plasma natriuretic peptide levels, to be considered for MRA therapy.
‡‡ Refer to online guidelines for detailed recommendations (see References, below, for URLs).

Tips for use of adjunctive therapies are summarized in Box 2.

In instances where a drug with proven mortality or morbidity benefits (i.e., those listed in Table 3) seems to be poorly tolerated (e.g., low blood pressure, low heart rate, renal dysfunction), concomitant drugs that have less proven benefit should be re-evaluated to determine if their dose can be reduced (or the drug discontinued) to allow better tolerance of the proven drug.

Medications that are not specifically used to treat HF-REF per se, but which may be used in patients with other indications for therapy include platelet inhibitors, anticoagulants, and statins. Drugs that should generally be avoided based on risk of HF exacerbation include thiazolidinediones (“glitazones”), traditional non-steroidal anti-inflammatory drugs,
Diuretics
Recommended use:
• Patients with signs and symptoms of fluid retention/congestion (e.g. dyspnea, edema)

Tips/comments:
• Loop diuretics (e.g., furosemide) are preferred for most patients, once acute congestion resolves, use the lowest dose that maintains stable signs and symptoms (continuous treatment may not be necessary for all patients)
• When volume overload persists despite optimal medical therapy (including increased loop diuretic doses), cautious addition of a second diuretic (e.g., a thiazide or low-dose metolazone) may be considered, with close monitoring of daily weight, renal function, and serum potassium
• Symptoms improve quickly, usually within days of starting treatment

Digoxin
Recommended use:
• Digoxin may be considered for: (1) patients in sinus rhythm who continue to have moderate to severe symptoms despite optimized therapy, and (2) patients with chronic atrial fibrillation and poor ventricular rate control despite optimal beta-blocker therapy (or when a beta-blocker cannot be used)

Tips/comments:
• Therapy is typically initiated and maintained at a dose of 0.125–0.25 mg daily, although lower doses may be appropriate for some patients (target plasma drug concentrations in the range of 0.6–1.1 nmol/L [0.5–0.9 ng/mL] have been suggested based on limited evidence)

Omega-3 polyunsaturated fatty acids
Recommended use:
• An n-3 PUFA preparation may be considered as adjunctive therapy in patients with persistent symptoms to reduce the risk of death and CV hospitalizations

Tips/comments:
• In the main study supporting the recommended use, patients received a dose of 1 g n-3 PUFA daily
• The small treatment effect in the main study was only detected after covariate adjustment in the statistical analysis

Pharmacotherapy for HF–PEF
No treatment has been shown to definitively reduce morbidity and mortality in patients with HF–PEF.1 As a result, the main treatment approach is to control potentially etiologic risk factors such as hypertension and myocardial ischemia.17 Control of ventricular rate in patients with atrial fibrillation is also considered important.1 Where appropriate for the aforementioned indications, ACE inhibitors, ARBs, and beta-blockers are reasonable choices.5,7 Diuretics are used to relieve dyspnea and edema.15,7 In contrast to HF–REF, nondihydropyridine calcium channel blockers may be used if indicated.17

Nonpharmacological Interventions
Various lifestyle interventions and device-related or surgical procedures may be indicated for patients with HF. A full review of these interventions is beyond the scope of this review; however, recommendations are provided in guidelines available online15,7 (see References, below, for URLs).

References

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