Pharmacological therapy of systolic left ventricular dysfunction has evolved over the past 3 decades. Current therapy is focused primarily on the regulation of the renin-angiotensin-aldosterone axis and sympathetic nervous system. Additional targets of pharmacotherapy include vasoconstriction, impaired nitric oxide metabolism, inflammation and improving myocardial function. As therapies in chronic systolic heart failure have evolved beyond diuretics and digoxin, so too has mortality improved. Future directions in the management of heart failure include cell-based and genetic therapy, and further refinement of current therapy through genetics. (Circ J. 2012; 76: 268–277)

**Key Words:** Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Beta-blockers; Heart failure; Sympathetic activation

Cardiovascular disease is the leading cause of morbidity and mortality in the developed world. Heart failure (HF) is an expanding epidemic and is one of the most common diagnoses among hospitalized patients. Roughly 20% of the population over the age of 40 years is at risk for developing congestive HF. The cornerstone of the pharmacological therapy of systolic left ventricular (LV) dysfunction has been neurohormonal antagonists. The regulation of the renin-angiotensin-aldosterone (RAA) axis and sympathetic nervous system have been key elements in the modern treatment HF patients. This review focuses on the current medical management of HF with particular focus on 5 fundamental aspects of the pathogenesis of HF: (a) neurohormonal adaptation and activation of the RAA system, (b) sympathetic activation, (c) vasoconstriction and impaired nitric oxide (NO) metabolism, (d) inflammation, and (e) poor pump function and methods to enhance myocardial performance.

### RAA Blockade

Myocardial damage leads to neurohormonal adaptations that are initially adaptive but ultimately deleterious. Activation of the RAA system leads to pathologic remodeling that results in further structural abnormalities. Norepinephrine, aldosterone and antidiuretic hormone lead to volume expansion in the setting of decreased cardiac output, and high levels of these 3 hormones are associated with poor outcomes.

### Angiotensin-Converting Enzyme (ACE) Inhibitors

The use of ACE inhibitors and angiotensin II blockers is supported by multiple large, randomized controlled trials. As with most HF trials, efficacy of medications initially began with a sicker population (New York Heart Association (NYHA) III–IV symptoms) and subsequently demonstrated benefit in a healthier group of patients. ACE inhibitors initially demonstrated efficacy in NYHA III and IV patients (Table 1).

The CONSENSUS trial demonstrated the benefit of enalapril (2.5–40 mg daily) in advanced HF (NYHA class IV).1 Over the course of 6 months, there was a 40% reduction in mortality (26% in the enalapril group vs. 40% in the placebo group). At 1 year, mortality was reduced by 31%. The reduction in mortality was related to prevention of progressive HF whereas there was no overall decrease in sudden cardiac deaths. In a 10-year follow-up evaluation, enalapril was found to prolong survival by 50% (by 260 days).2

The SOLVD study demonstrated a reduction in mortality and hospitalizations for patients with ejection fraction (EF) <35% and NYHA class II and III symptoms with the addition of enalapril (2.5–20 mg/day). Over an average follow-up of 41.4 months, there was a 16% reduction in deaths (39.7% placebo arm vs. 35.2% in the enalapril arm), and a 26% reduction in the incidence of death or hospitalization. There was little affect on the incidence of arrhythmic death.3 Of note, the initial trial did not demonstrate a mortality benefit in Stage B HF patients (asymptotic LV dysfunction). Over a 12-year follow-up period, there was a 6.5% absolute risk reduction in the death of those patients with Stage B HF (50.9% in the enalapril group vs. 56.4% in the placebo group). In symptomatic patients, there was a 1% reduction in the risk of death (79.8% placebo arm vs. 35.2% in the enalapril arm), and a 26% reduction in the incidence of death or hospitalization. There was little affect on the incidence of arrhythmic death.3 Of note, the initial trial did not demonstrate a mortality benefit in Stage B HF patients (asymptotic LV dysfunction). Over a 12-year follow-up period, there was a 6.5% absolute risk reduction in the death of those patients with Stage B HF (50.9% in the enalapril group vs. 56.4% in the placebo group). In symptomatic patients, there was a 1% reduction in the risk of death (79.8% in the enalapril arm vs. 35.2% in the placebo arm), and a 26% reduction in the incidence of death or hospitalization. There was little affect on the incidence of arrhythmic death.3 Of note, the initial trial did not demonstrate a mortality benefit in Stage B HF patients (asymptotic LV dysfunction). Over a 12-year follow-up period, there was a 6.5% absolute risk reduction in the death of those patients with Stage B HF (50.9% in the enalapril group vs. 56.4% in the placebo group). In symptomatic patients, there was a 1% reduction in the risk of death (79.8% in the enalapril arm vs. 35.2% in the placebo arm), and a 26% reduction in the incidence of death or hospitalization. There was little affect on the incidence of arrhythmic death.3

In addition to the benefits seen in chronic HF, ACE inhibi-
tors have had proven benefit in LV dysfunction following myocardial infarction (MI). In the SAVE trial, captopril was demonstrated to provide a 19% relative risk reduction in mortality in patients with asymptomatic LV dysfunction after MI. Similarly, the AIRE trial demonstrated benefits of ramipril in patients with a history of MI and a history of HF at any time.

Although enalapril demonstrated an overall mortality benefit over the combination of hydralazine and isordil in the V-HeFT II trial, subgroup analysis demonstrated a lack of benefit in black patients. Compared with a combination of hydralazine 300 mg and isosorbide dinitrate 160 mg daily, enalapril 20 mg daily led to significant mortality reduction at 2 years (18% vs. 25%, respectively). Unlike earlier trials, there was a reduction in sudden cardiac death in the enalapril arm, which was more prominent in patients with NYHA class I or II symptoms. There was a greater improvement in peak oxygen consumption and LVEF with hydralazine/isosorbide. Improvements were attenuated in black patients. Likewise, in a pooled analysis of the prevention and treatment arms of the SOLVD trial, there was no reduction in HF hospitalizations among black patients compared with white patients. In an analysis of the SOLVD prevention trial exclusively, enalapril demonstrated a comparable risk reduction in the progression from asymptomatic to symptomatic HF between black and white patients, although black patients were at greater risk for progression. ACE inhibitors may also have a greater benefit for men than for women, especially asymptomatic LV dysfunction.

The effective dose of ACE inhibitors has been studied in several controlled trial. Although the benefit in mortality may be similar at higher vs. lower doses, the use of higher doses decreased the combined endpoint of mortality and hospitalizations. The NETWORK trial, which followed 1,532 patients over 24 months, found no significant difference in the combined endpoint of death, hospitalization from HF or progression of HF between escalating doses of enalapril (2.5 mg twice daily up to 10 mg twice daily). The ATLAS study, however, demonstrated that vs. low-dose lisinopril (2.5–5.0 mg/day), high-dose lisinopril (32.5–35 mg/day) had a greater reduction in the combination of death or hospitalization for any reason (12% lower risk) and 24% fewer hospitalizations for HF over 39 to 58 months among 3,164 patients. In general, ACE inhibitors exhibit a class effect and should be titrated up to a dose of: enalapril 10 mg twice daily, captopril 50 mg 3 times daily, or lisinopril or quinapril 40 mg daily.

### Angiotensin-Receptor Blockade

Angiotensin-receptor blockers (ARBs) have demonstrated benefit in patients who are intolerant of ACE inhibitors or as an alternative agent (Table 2). Although the addition of ARBs to ACE inhibitors has proven benefit in decreasing hospital admission, the combined use of ARBs and ACE inhibitors is questionable given the potential for hyperkalemia.

Compared with ACE inhibitors, ARBs have essentially shown equivalence. The ELITE I trial suggested that treatment with losartan (50 mg daily) resulted in mortality benefits over captopril (50 mg 3 times daily) in patients over the age of 65 years with NYHA class II–IV HF and EF of 40%. This trial’s primary endpoint was not mortality, however. In the ELITE II trial, despite a trend towards lower mortality in patients randomized to captopril (50 mg 3 times daily) over losartan (50 mg once daily), there was no overall difference in the primary endpoint of all-cause mortality, sudden death or resuscitated arrest. Likewise, in the OPTIMAAL trial, captopril (50 mg 3 times daily), when compared with losartan (50 mg daily), demonstrated a trend towards improved mortality in patients with acute MI and evidence of HF or LV dysfunction. The HEAAL trial suggested that the trends favoring captopril over losartan in the ELITE II and OPTIMAAL trial might have been because of underdosing of losartan. Treatment with losartan 150 mg significant reduced the rate of death or HF admissions over losartan 50 mg daily.

In patients intolerant of ACE inhibitors, valsartan, losartan and candesartan have proven benefits in mortality reduction. The CHARM-alternative study demonstrated a reduction in cardiovascular death and HF hospital admissions when candesartan (target dose of 32 mg daily) was compared with placebo in patients with LVEF <40% and NYHA class II–IV symptoms. This reduction was similar to that seen in the SOLVD trial, despite more contemporary therapy with β-blocker (55% use) and spironolactone (24% use). Similar benefits were demonstrated in a subgroup analysis of the Val-HeFT study, in which patients intolerant of ACE inhibitors receiving val-

### Table 1. ACEIs in Systolic HF: Randomized Trials

<table>
<thead>
<tr>
<th>Treatment, trial by year</th>
<th>Disease severity</th>
<th>Intervention</th>
<th>Baseline therapy*</th>
<th>Trial duration (years)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS (1987)</td>
<td>IV</td>
<td>Enalapril 20 mg BID</td>
<td>Spironolactone</td>
<td>0.54**</td>
<td>Death</td>
</tr>
<tr>
<td>SAVE (1992)</td>
<td>≤40 and post-MI</td>
<td>Captopril 50 mg TID</td>
<td>–</td>
<td>3.5</td>
<td>Death</td>
</tr>
</tbody>
</table>

*At least 50% of patients enrolled in the study had these drug groups as baseline therapy.

**Early termination because of demonstrated benefit in the experimental group.
The use of aldosterone antagonists in HF has been standard since the publication of the RALES (Randomized Aldactone Evaluation Study) trial in 1999 (Table 3). The use of aldosterone antagonists is supported by the fact that the myocardium contains mineralocorticoid receptors and that aldosterone production is stimulated proportionally to the degree of HF. aldosterone can stimulate angiotensin II production, which can promote cardiac fibrosis. Higher concentrations of markers of collagen synthesis have been associated with higher rates of death, and a reduction in procollagen type II amino-terminal peptide has correlated with improvements in LV remodeling which may be arrhythmogenic. Additionally, overexpression of cardiac mineralocorticoid receptors can lead to ion channel remodeling, prolonged ventricular repolarization and ventricular arrhythmias. The RALES study, patients with an EF <35% with NYHA class III–IV HF who had serum creatinine <2.5 mg/dl and potassium <5 mEq/L were randomly assigned spironolactone 25 mg/day vs. placebo. Patients were followed over an average of 24 months after which the trial was halted early because of benefits in the treatment arm. There was a 30% reduction in deaths among the spironolactone group secondary to a lower risk of progressive HF and sudden cardiac death. There was also a significant improvement in HF symptoms among the treatment group. Although the incidence of hyperkalemia was minimal in both groups in the RALES trial, a subsequent Canadian population-based time-series analysis among adults 66 years and older demonstrated increases in hyperkalemia-associated morbidity and mortality after the publication of the trial. This increase correlated to additional prescription for aldosterone antagonists.

**Aldosterone Antagonists**

The use of aldosterone antagonists in HF has been standard

### Table 3. ARBs in Systolic HF: Randomized Trials

<table>
<thead>
<tr>
<th>Treatment, trial by year</th>
<th>n</th>
<th>Disease severity</th>
<th>Intervention</th>
<th>Baseline therapy*</th>
<th>Trial duration (years)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val-HEFT (2001)</td>
<td>5,010</td>
<td>II–IV</td>
<td>Valsartan 160 mg BID</td>
<td>ACEI</td>
<td>1.9</td>
<td>Death and morbidity</td>
</tr>
<tr>
<td>CHARM-Added (2003)</td>
<td>2,548</td>
<td>II–IV and ≤40</td>
<td>Candesartan 32 mg once daily</td>
<td>ACEI and BB</td>
<td>3.4</td>
<td>CV death or unplanned hospital admission for HF</td>
</tr>
<tr>
<td>CHARM-Alternative (2003)¹</td>
<td>2,028</td>
<td>II–IV and ≤40</td>
<td>Candesartan 32 mg once daily</td>
<td>BB</td>
<td>2.8</td>
<td>CV death or unplanned hospital admission for HF</td>
</tr>
<tr>
<td>VALIANT (2003)</td>
<td>14,703</td>
<td>≤35 and post-MI</td>
<td>Valsartan 160 mg BID vs. 80 mg valsartan BID+ 50 mg captopril TID vs. 50 mg captopril TID</td>
<td>BB</td>
<td>2.05</td>
<td>Death</td>
</tr>
<tr>
<td>HEAAL (2009)¹</td>
<td>3,846</td>
<td>II–IV and ≤40</td>
<td>150 mg losartan vs. 50 mg losartan daily</td>
<td>BB</td>
<td>4.7</td>
<td>Death or admission for HF</td>
</tr>
</tbody>
</table>

*At least 50% of patients enrolled in the study had these drug groups as baseline therapy.

¹All patients intolerant to ACEI.

**Table 2. ARBs in Systolic HF: Randomized Trials**

<table>
<thead>
<tr>
<th>Treatment, trial by year</th>
<th>n</th>
<th>Disease severity</th>
<th>Intervention</th>
<th>Baseline therapy*</th>
<th>Trial duration (years)</th>
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</tr>
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</table>

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¹All patients intolerant to ACEI.
Current Pharmacological Targets of Systolic HF

Table 3. Aldosterone Blockers in Systolic HF: Randomized Trials

<table>
<thead>
<tr>
<th>Treatment, trial by year</th>
<th>n</th>
<th>Disease severity</th>
<th>Intervention</th>
<th>Baseline therapy</th>
<th>Trial duration (years)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES (1999)</td>
<td>1,663</td>
<td>III–IV and ≤35</td>
<td>Spironolactone 25–50 mg once daily</td>
<td>ACEI</td>
<td>2</td>
<td>Death</td>
</tr>
<tr>
<td>EPHESUS (2003)</td>
<td>6,642</td>
<td>≤40 and post-MI</td>
<td>Eplerenone 25–50 mg once daily</td>
<td>ACEI/ARB, and BB</td>
<td>1.3</td>
<td>Death</td>
</tr>
<tr>
<td>EMPHASIS-HF (2010)</td>
<td>2,737</td>
<td>II and ≤30</td>
<td>Eplerenone 25–50 mg once daily</td>
<td>ACEI/ARB, and BB</td>
<td>1.75**</td>
<td>Composite</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment, trial by year</th>
<th>Estimated mortality in placebo or control group in 1st year (%)</th>
<th>Overall mortality during entire study period in control/placebo (%)</th>
<th>Relative risk reduction in primary endpoint (%)</th>
<th>P value for primary endpoint</th>
<th>HR in experimental group</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES (1999)</td>
<td>25</td>
<td>46</td>
<td>30</td>
<td>&lt;0.001</td>
<td>1.3</td>
</tr>
<tr>
<td>EPHESUS (2003)</td>
<td>13.6</td>
<td>16.7</td>
<td>15</td>
<td>0.008</td>
<td>0.66</td>
</tr>
<tr>
<td>EMPHASIS-HF (2010)</td>
<td>–</td>
<td>13.5</td>
<td>29</td>
<td>&lt;0.001</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*At least 50% of patients enrolled in the study had these drug groups as baseline therapy.
**Early termination because of demonstrated benefit in the experimental group.

Abbreviations see in Tables 1, 2.

spironolactone, thus emphasizing the need for judicious use of aldosterone antagonists among patients, particularly the elderly, already on ACE inhibitors.34

The benefits of mineralocorticoid-receptor antagonists were demonstrated in the EMPHASIS-HF trial among patients with an EF <30% or EF between 30% and 35% with a prolonged QRS >130 ms and mild HF symptoms (NYHA class II).35 Treatment with eplerenone (titrated from 25 mg to 50 mg daily), a selective mineralocorticoid antagonist, resulted in a 29% reduction in the combined endpoint of death from cardiovascular causes or HF admissions compared with placebo. A significant reduction in mortality was observed in patients receiving eplerenone vs. placebo (12.5 vs. 15.5; hazard ratio (HR) 0.76; 95% CI 0.62–0.93). These benefits were seen with excellent background therapy with ACE inhibitors or ARB (94% use) and β-blocker (87% use).

In addition to their utility in chronic HF with mild to severe symptoms, mineralocorticoid receptors antagonists have also demonstrated benefit in patients with myocardial dysfunction following acute MI. The EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival) study randomized patients 3–14 days within MI and an EF <40% and HF symptoms or diabetes mellitus to either eplerenone (25 mg initially, titrated to 50 mg daily) or placebo.36 At 16 months, treatment with eplerenone resulted in a significant reduction in the primary endpoint, which was death from any cause, death from cardiovascular cause or hospitalization for HF, acute MI, stroke or ventricular arrhythmias. The reduction in mortality was driven by a decrease in cardiovascular mortality (12.3% with eplerenone vs. 14.6% with placebo).

Direct Renin Inhibitors

Despite the use of ACE inhibitors and ARBs, perpetual renin release because of the loss of negative feedback inhibition can lead to an increase downstream products of the RAA system. Direct renin inhibition thus may have a substantial role in the treatment of chronic systolic HF. The Aliskiren Observation of Heart Failure Treatment (ALOFT) study randomized patients with NYHA class II–IV HF, history of hypertension and elevated plasma BNP concentrations (>100 pg/ml) on a background therapy of ACE inhibitors or ARBs and β-blockers to the direct renin antagonist, aliskiren, or placebo. After a follow-up period of 3 months, there was a significant reduction in N-terminal pro-BNP with aliskiren.37 Both the ASTRONAUT study and the ATMOSPHERE study will evaluate the benefits the aliskiren in the prevention of cardiovascular events, including death and HF admissions. ASTRONAUT will enroll patients on standard HF medication with an LV EF <40% and an estimated glomerular filtration rate ≥40 ml·min⁻¹·1.73 m⁻² who have been hospitalized with decompensated HF to aliskerin or placebo.38 ATMOSPHERE will test whether aliskerin, an ACE inhibitor or both will be effective in delaying the first occurrence of cardiovascular death or HF hospitalization. Patients with chronic systolic HF, NYHA class II–IV symptoms, and elevated plasma levels of BNP will be randomized to aliskeren, enalapril or both, and the study will evaluate whether combination therapy is superior to enalapril alone and if aliskerin monotherapy is superior or non-inferior to enalapril monotherapy.39 Although there is promise in its effects on reducing HF symptoms as demonstrated by the ALOFT study, a study comparing aliskerin’s effects on the regression of LV hypertrophy was equivalent but not additive to that of losartan.40 The exact role of aliskerin in the treatment of chronic HF will be clarified by further, larger clinical trials.

Sympathetic Nervous System Activation

Beta-Blocker Therapy

Heightened sympathetic activity is central to the pathogenesis of systolic HF and elevated levels of norepinephrine correlate with poor prognosis in chronic HF patients.41 There is decrease in β-receptor density because of chronic sympathetic stimulation, which can be reversed with β-blockers and thereby improve myocardial inotropic and chronotropic responses.42 Treatment with β-blockers has also been demonstrated to produce improvements in LV systolic function and positive re-
modeling with reductions in end-systolic and end-diastolic volumes. Studies from Sweden dating back to the 1970s demonstrate efficacy of β-blockers in HF. Larger trials have demonstrated the utility of extended-release metoprolol, carvedilol and bisoprolol in HF (Table 4). The varying profiles and selectivity of β-blockers have yielded different results across trials.

The benefits of carvedilol, a non-selective β-blocker with additional α-1 receptor blockade, were demonstrated in patients with mild to severe HF, as well as in patients with myocardial dysfunction after MI. Carvedilol has antioxidant and antiproliferative properties that provide additional benefit. When compared with metoprolol, carvedilol has tended to produce greater improvements in LVEF and stroke work and increased reductions in norepinephine levels. Carvedilol has demonstrated significant reductions in morbidity and mortality among patients with mild to moderate HF through the United States Carvedilol Heart Program. Pooled data from the 4 component trials demonstrated that carvedilol produced a 65% lower risk of mortality, including a significant decrease in the risk of death from progressive HF as well as in the risk of sudden death, over an average follow-up period of 6.5 months. The short follow-up time was secondary to the design of the program, which evaluated the safety and tolerability of carvedilol. Each of the individual protocols was designed to evaluate primarily a nonfatal endpoint with mortality a prespecified outcome. The COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) study later demonstrated benefits in morbidity and mortality among patients with more advanced (NYHA class III–IV) HF. Among the carvedilol group, there was 35% reduction in death and a 24% reduction in the combined endpoint of death and hospitalization. Benefits with carvedilol were also apparent in patients with LV dysfunction (LVEF ≤40%) following acute MI in the CAPRICORN trial. There was a 20% reduction in all-cause mortality with carvedilol, although no difference was seen in the combined primary endpoint of all-cause mortality or hospital admissions for cardiovascular causes.

Metoprolol has demonstrated efficacy in smaller trials prior to the larger MERIT-HF trial. In the Metoprolol in Dilated Cardiomyopathy trial, patients randomized to metoprolol tarrate demonstrated improvement in EF and exercise capacity, as well as a tendency towards improved mortality over the course of 1 year. Survival benefit of metoprolol succinate was established by the MERIT-HF trial, in which there was a 34% reduction in mortality, including sudden cardiac death and death from progressive HF, over a mean follow-up of 1 year. Metoprolol XL, at a target dose of 200 mg/day, was well tolerated and led to overall functional improvements and decreased hospitalizations.

Carvedilol may be arguably superior to metoprolol based on the results of the COMET trial, in which carvedilol (25 mg twice daily) was compared with short-acting metoprolol tarrate (50 mg twice daily). Carvedilol was superior to metoprol-

| Table 4. BBs in Systolic HF: Randomized Trials |
| Treatment, trial by year | n | Disease severity | Intervention | Baseline therapy* | Trial duration (years) |
| BBs | | | | | |
| U.S. Carvedilol Heart Failure Study Group (1996) | 1,094 | ≤35 | Carvedilol 25–50 mg BID | ACEI | 0.54** |
| CIBIS-II (1999) | 2,647 | III–IV and ≤35 | Bisoprolol 10 mg once daily | ACEI | 1.3** |
| MERIT-HF (1999) | 3,991 | III–IV and ≤40 | Metoprolol CR/XL 200 mg once daily | ACE-I | 1** |
| COMET (2003) | 3,029 | II–IV and ≤35 | Metoprolol 200 mg once daily | ACEI | 4.83 |

*At least 50% of patients enrolled in the study had these drug groups as baseline therapy. **Early termination because of demonstrated benefit in the experimental group. Abbreviations see in Tables 1, 2.
Ivabradine, a selective β-1 receptor blocker, also has proven efficacy in the treatment of chronic systolic HF. After initial demonstration of hemodynamic benefit, the CIBIS II trial demonstrated a 32% reduction in mortality with bisoprolol treatment in patients with an LVEF <35% and NYHA class III–IV symptoms.\(^\text{66}\) Despite the positive results of the aforementioned trial, different profiles of β-blockers have accounted for varying degrees of efficacy in the treatment of HF. Carvedilol was thought to impart some of its benefits through its vasodilator properties, although the long-term benefits cannot be entirely attributed to α-adrenergic blockade.\(^\text{67}\) Other β-blockers with significant vasodilating properties have not yielded the same results. In the SENIORS trial, nebivolol, a β-1 selective blocker with NO-mediated vasodilating properties, demonstrated a reduction in cardiovascular mortality and HF admissions in elderly (>70 years) patients with HF and both preserved and reduced systolic function. However, this reduction was not as substantial as with other β-blockers, which led the US Food and Drug Administration to not approve the drug for the treatment of HF. Bucindolol, a non-selective β-blocker with additional weak α-blocking properties and some intrinsic sympathomimetic activity, was not shown to have survival benefit in a diverse population of patients with NYHA class III–IV chronic HF in the BEST trial.\(^\text{68}\) These results may be partially attributed to the intrinsic sympathomimetic activity of bucindolol, which at higher dose can stimulate β-1 and β-2 receptors.\(^\text{69,70}\) Additionally, race-specific difference in the β-adrenergic pathway could account for the varying benefits of β-blockers. Prespecified subgroup analysis demonstrated that bucindolol showed no benefit in black patients, but there was a trend towards survival benefit in nonblack patients with LVEF >20% and nonischemic cardiomyopathy.\(^\text{71}\)

Genetic variations in cardiac adrenergic stimulation may influence the effects of β-blockers and progression of HF. Black patients who are homozygous for the α-2C receptor polymorphism (α2CDe1322–325) were demonstrated in one study to have a higher risk of HF.\(^\text{72}\) On the other hand, black patients with mutations in a G protein-coupled receptor kinase (GRK5-Leu41 polymorphism) were found to have decreased HF death and progression secondary to enhanced β-adrenergic receptor desensitization of excess catecholamine signaling.\(^\text{73}\)

### Heart Rate Modulation

The benefits of β-blockers have not always correlated with the degree of chronotropic suppression, although resting tachycardia has been correlated with adverse events in HF.\(^\text{74}\) The Systolic Heart Failure trial treatment with the I  inhibitor ivabradine (SHIFT) Trial was designed to ascertain whether heart rate control alone would yield benefits in HF. Ivabradine, a selective inhibitor of the hyperpolarization-activated cyclic-nucleotide-gated funny current (If) involved in sinoatrial node responsiveness, was used to produce heart-rate reduction alone without other cardiovascular effects. Over a 23-month follow-up period, ivabradine resulted in a significant reduction in the primary endpoint of cardiovascular death or hospitalizations for HF.\(^\text{75}\) There was direct association between the heart rate achieved and outcomes.\(^\text{76}\) However, patients receiving 50% or more of the target β-blocker doses had no significant benefit from ivabradine for the primary outcome, thus raising the possibility again of underdosing of β-blockers altering outcomes. Furthermore, there was no significant reduction in all-cause cardiovascular mortality, which raises the question as to the drug’s place among other HF medications.

### Sympathetic Blockade: Theoretic Treatment for HF

In theory, additional blockade of the sympathetic system could further attenuate the progression of HF when there is ongoing sympathetic activation despite maximization of standard HF medications. The Systolic HTN-2 Trial demonstrated the effectiveness of catheter-based renal sympathetic denervation in the treatment of drug-resistant hypertensive patients.\(^\text{77}\) Activation of the renal sympathetic nerves can lead to the release of renin from the juxtaglomerular apparatus and activation of the RAAs system, volume expansion through sodium retention and renal vasoconstriction.\(^\text{78}\) Theoretical benefits of catheter-based renal sympathetic denervation in HF are derived from animal models. In a study of rats that underwent MI, renal denervation attenuated LV remodeling and reduced filling pressures compared with controls.\(^\text{79}\) Furthermore, exaggerated renal sympathetic nerve activity has been shown to promote congestion through a decrease in renal excretory responses to atrial peptides.\(^\text{80}\) Whether renal denervation is a potential treatment modality in HF remains to be seen and may be worth clinical evaluation.

### NO Mediators

#### Vasodilators

The combination of hydralazine and nitrates has the potential for both arterial and venous dilation. In addition, nitrates serve as NO donors and hydralazine prevents NO degradation, which can lead to the accumulation of reactive oxygen species. The therapeutic effect of this combined treatment is thus in part because of enhanced NO availability and antioxidant effects. Endothelial NO synthase (eNOS3) is the primary source of vascular NO, and polymorphisms of the NO3 locus account for much of the variability in NO levels. Black subjects are more likely to have functional NO3 genomic variants, specifically Glu298, −786 T, and intron 4a alleles, compared with white subjects. These polymorphisms may not only influence overall prognosis but also response to medications.\(^\text{81,82}\)

The combination of hydralazine and isosorbide dinitrate (H-ISDN) was formulated to be an oral equivalent to sodium nitroprusside, which had proven benefits in the treatment of elevated peripheral vascular resistance, a sine qua non of acute heart decompensated HF.\(^\text{83,84}\) H-ISDN was initially shown to be of benefit in the V-HeFT I study in which patients with HF were randomized to placebo, prazosin (α1-receptor blocker) or H-ISDN (Table 5). The combination produced significant mortality reductions over a 3-year period whereas prazosin demonstrated no benefit.\(^\text{85}\) Additionally, there was a significant improvement in EF at 1 year (4.2% vs. −0.1%; P<0.001). Although enalapril proved superior to H-ISDN in the V-HeFT II study as detailed above, it is interesting to note that H-ISDN produced a significantly greater improvement in EF vs. enalapril (3.3% vs. 2.1%, respectively). There was also an improve-
In patients with HF and preserved EF, sildenafil improved pulmonary pressures and right ventricular function, lowered wedge pressures, and improved lung interstitial fluid balance when compared with placebo. Its use in systolic HF therefore, appears to be for patients with concomitant significant diastolic dysfunction and secondary pulmonary hypertension after failure of standard HF therapy, including H-ISDN and diuretics.

### Inflammatory Mediators

Advanced chronic HF is a catabolic state characterized by inflammation and cachexia. Circulating proinflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), IL-6, and C-reactive protein, may be elevated in patients with chronic HF. These cytokines can lead to protein loss, leukocyte and endothelial cell activation (partially mediated through upregulated xanthine oxidase via free radical release), and anemia through abnormal iron metabolism and hematopoiesis.

N-3 polyunsaturated fatty acids (PUFA) can have favorable effects on inflammation by reducing cytokine production and enhancing endothelial function. Furthermore, they have shown favorable effects on atherothrombosis and ventricular arrhythmias. For these reasons, n-3 PUFAs were studied in patients with symptomatic HF (NYHA class II–IV), regardless of etiology or EF, in the GISSI-HF trial. Treatment with n-3 PUFA (850–882 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the ratio of 1:1.2) resulted in a small, yet significant improvement in mortality and hospital admissions for cardiovascular causes. Over a median follow-up of 3.9 years, there was a 7% reduction in mortality (27% n-3 PUFA vs. 29% placebo) and a 3% reduction in hospital admissions with minimal medication side-effects.

Anemia is common in HF patients and correlates with outcomes. Inflammation plays a direct role in the anemia of HF, as TNF-α and IL-6 can inhibit erythropoietin production and suppress bone marrow erythroid progenitor cell proliferation. IL-6 also stimulates hepatic production of hepcidin, which inhibits duodenal iron absorption and decreases ferroprotein production, leading to impaired release of stored iron.

### Table 5. Hydralazine and Nitrates in Systolic HF: Randomized Trials

<table>
<thead>
<tr>
<th>Treatment, trial by year</th>
<th>Disease severity</th>
<th>Intervention</th>
<th>Baseline therapy*</th>
<th>Trial duration (years)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydralazine and isosorbide dinitrate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-HeFT (1986)</td>
<td>&lt;45</td>
<td>Hydralazine 75mg TID/QID and isosorbide dinitrate 40mg TID</td>
<td>–</td>
<td>2.3</td>
<td>Death</td>
</tr>
<tr>
<td>A-HeFT (2004)*</td>
<td>III–IV</td>
<td>Hydralazine 75mg TID and isosorbide dinitrate 40mg TID</td>
<td>ACEI and BB</td>
<td>0.83**</td>
<td>Composite</td>
</tr>
</tbody>
</table>

### Table 6. Relative Risk Reduction of Primary Endpoint

<table>
<thead>
<tr>
<th>Treatment, trial by year</th>
<th>Estimated mortality in placebo or control group in 1st year (%)</th>
<th>Overall mortality during entire study period in control/placebo (%)</th>
<th>Relative risk reduction in primary endpoint (%)</th>
<th>P value for primary endpoint</th>
<th>HR in experimental group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydralazine and isosorbide dinitrate</strong></td>
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<tr>
<td>V-HeFT (1986)</td>
<td>26.4</td>
<td>44</td>
<td>34</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>A-HeFT (2004)*</td>
<td>9</td>
<td>10.2</td>
<td>–</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

*At least 50% of patients enrolled in the study had these drug groups as baseline therapy.
**Early termination because of demonstrated benefit in the experimental group.
†All patients had to self-identify as black.
QID, 4 times daily. Other abbreviations see in Tables 1,2.
deficiency is a strong, independent predictor of adverse outcomes in HF. The FAIR-HF trial, the treatment of iron deficiency with intravenous ferric carboxymaltose in patients with chronic HF resulted in improvements in symptoms, functional capacity and quality of life. The RED-HF (The Reduction of Events with Darbepoetin alfa in Heart Failure) trial will determine whether treatment of anemia with darbepoetin alfa will result in a mortality benefit or reduction in hospital admissions for HF.

Gene and Cell-Based Therapy

Gene therapy for the treatment of HF has focused on exogenous delivery of genes that may have impaired endogenous expression secondary to myocardial damage and mutations. Calcium metabolism, enhanced ionotropy and angiogenesis have been primary targets for the genetic manipulation of HF. Methods to alter cardiac homeostasis have targeted the sarcoplasmic reticulum calcium ATPase (SERCA2a) pump and an inhibitor of the pump, phospholamban. SERCA2a activity is decreased in HF, resulting in contractile dysfunction secondary to impaired calcium regulation. Upregulation of SERCA2a has been demonstrated to provide benefits in cardiac lusitropy, inotropy and energetics. In rodent models of HF created through aortic banding, adenovirus vectors carrying the SERCA2a gene led to improved phosphocreatine/ATP ratios, decreased LV volumes and an overall survival advantage when compared with controls. The application of adenovirus-associated virus type 1/SERCA2a vectors in humans subjects with HF is currently underway through the CUPID (Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease) Investigators. Safety of the vector has already been demonstrated in a phase 2 trial and overall efficacy will need to be evaluated in larger confirmatory trials.

Although the prospect of stem cell therapy has generated enthusiasm over the past decade, the results of clinical trials have been mixed, despite the use of several cell lines. The use of cardiac stem cell (CSC) therapy demonstrated promise in the SCIPIO trial. In post-MI patients, intracoronary infusion of autologous CSCs at the time of cardiac bypass led to an improvement in LV systolic function and a reduction in infarct size. Again, larger trials will be necessary to confirm efficacy in a broader population.

Conclusion

Through the past 3 decades, treatment options for HF have advanced beyond diuretics and digoxin to include therapies that alter the course of disease and promote reverse remodeling, improvement in functional status and ultimately an improvement in survival. After mortality benefits were established with vasodilator therapy, modulation of neurohormonal responses, suppression of the RAAS axis and attenuation of sympathetic activation have become the fundamental focus of modern HF treatment. Despite these therapeutic advancements and the use of device therapies, including implantable cardioverter defibrillators and cardiac resynchronization therapy, the mortality associated with advanced HF remains high. Future directions in the management of HF include cell-based therapy, gene therapy and potential refinement of current therapy based on genetic variations. Ultimately, further understanding of additional mechanisms leading to the progression of HF will enable its prevention to advanced stages.

References


