

## Section 7: Heart Failure in Patients With Reduced Ejection Fraction

### Overview

There are 3 primary issues that must be considered when treating heart failure (HF) patients with reduced left ventricular ejection fraction (LVEF): (1) improving symptoms and quality of life, (2) slowing the progression or reversing cardiac and peripheral dysfunction, and (3) reducing mortality. General measures, such as salt restriction, weight loss, lipid control, and other nonpharmacologic measures are addressed in Section 6. Pharmacologic approaches to symptom control, including diuretics, vasodilators, intravenous inotropic drugs, anticoagulants, and antiplatelet agents are discussed at the end of this section.

Two classes of agents have become the recommended cornerstone of therapy to delay or halt progression of cardiac dysfunction and improve mortality: angiotensin-converting enzyme (ACE) inhibitors and beta blockers. Even while these agents are underused in the treatment of HF, new classes of agents have been added that show an impact on mortality, complicating decisions about optimal pharmacologic therapy. These include angiotensin receptor blockers (ARBs), aldosterone antagonists, and the combination of hydralazine and an oral nitrate, all of which are considered in the following recommendations.

### ACE Inhibitors

#### Recommendation

**7.1 ACE inhibitors are recommended for routine administration to symptomatic and asymptomatic patients with LVEF  $\leq$  40%. (Strength of Evidence = A)**

**ACE inhibitors should be titrated to doses used in clinical trials, as tolerated during concomitant up-titration of beta blockers. (Strength of Evidence = C).**

#### Background

There is compelling evidence that ACE inhibitors should be used to inhibit the renin-angiotensin-aldosterone system (RAAS) in all HF patients with reduced LVEF, whether or not they are symptomatic (Table 7.1). A number of large clinical trials have demonstrated improvement in morbidity and mortality in HF patients with reduced LVEF, both chronically and post-myocardial infarction (MI).<sup>1-3</sup> The mortality benefit is strongest across New York Heart Association (NYHA) class II-IV HF, but appears present in patients who are NYHA class I as well.<sup>4</sup>

The major side effects of ACE inhibitors in patients with HF are hypotension and azotemia. Both are usually well tolerated and do not indicate the need to lower the dose

or discontinue the ACE inhibitor. The azotemia commonly is related to a relative volume-depleted state caused by diuretic therapy and may be improved by a reduction in diuretic dose. Moderate renal insufficiency should not be considered a contraindication to the use of ACE-inhibitors, although careful attention to serum potassium and creatinine levels is imperative.<sup>5</sup> The major symptomatic side effect is a dry cough that usually does not require discontinuation of the drug. Care should be taken to distinguish between a cough that is ACE inhibitor-related and one that is due to worsening pulmonary congestion. If the cough impairs the patient's quality of life, alternative therapy, such as an ARB, is recommended.<sup>6</sup>

### Recommendations

**7.2 It is recommended that other therapy be substituted for ACE inhibitors in the following circumstances:**

- **In patients who cannot tolerate ACE inhibitors due to cough, ARBs are recommended. (Strength of Evidence = A)**
- **The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. (Strength of Evidence = C)**
- **Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. (Strength of Evidence = C)**

**7.3 ARBs are recommended for routine administration to symptomatic and asymptomatic patients with an LVEF  $\leq$  40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. (Strength of Evidence = A)**

**7.4 ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. (Strength of Evidence = B)**

**The combination of hydralazine and oral nitrates may be considered in this setting in patients who do not tolerate ARB therapy. (Strength of Evidence = C)**

#### Background

Both ACE inhibitors and ARBs inhibit the RAAS, but by different mechanisms. ACE inhibitors block an enzyme responsible for converting angiotensin I to angiotensin II and for degrading various kinins. However, during chronic therapy, angiotensin II levels are not completely suppressed by ACE inhibitors for at least 2 reasons. Instituting an ACE inhibitor increases renin levels, resulting in higher levels of angiotensin I, which will tend by mass action to produce greater angiotensin II levels. Production of angiotensin II may also occur through non-ACE enzyme systems not blocked by

**Table 7.1.** ACE-inhibitor, Angiotensin Receptor Blocker, and Beta-Blocker Therapy in HF with Low LVEF

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose Achieved in Clinical Trials
<b>ACE-inhibitors</b>				
Captopril	Capoten	6.25 mg tid	50 mg tid	122.7 mg/day <sup>171</sup>
Enalapril	Vasotec	2.5 mg bid	10 mg bid	16.6 mg/day <sup>3</sup>
Fosinopril	Monopril	5-10 mg qd	80 mg qd	n/a
Lisinopril	Zestril, Prinivil	2.5-5 mg qd	20 mg qd	*4.5 mg/day (low dose ATLAS) 33.2 mg/day (high dose ATLAS) <sup>172</sup>
Quinapril	Accupril	5 mg bid	80 mg qd	n/a
Ramipril	Altace	1.25-2.5 mg qd	10 mg qd	n/a
Trandolapril	Mavik	1 mg qd	4 mg qd	n/a
<b>Angiotensin Receptor Blockers</b>				
Candesartan	Atacand	4-8 mg qd	32 mg qd	24 mg/day <sup>173</sup>
Losartan	Cozaar	12.5-25 mg qd	150 mg qd	129 mg/day <sup>174</sup>
Valsartan	Diovan	40 mg bid	160 mg bid	254 mg/day <sup>15</sup>
<b>Beta-blockers</b>				
Bisoprolol	Zebeta	1.25 mg qd	10 mg qd	8.6 mg/day <sup>24</sup>
Carvedilol	Coreg	3.125 mg bid	25 mg bid	37 mg/day <sup>43</sup>
Carvedilol	Coreg CR	10 mg qd	80 mg qd	
Metoprolol succinate CR/XL	Toprol XL	12.5-25 mg qd	200 mg qd	159 mg/day <sup>25</sup>
<b>Aldosterone Antagonists</b>				
Spironolactone	Aldactone	12.5 to 25 mg qd	25 mg qd	26 mg/day <sup>68</sup>
Eplerenone	Inspra	25 mg qd	50 mg qd	42.6 mg/day <sup>69</sup>
<b>Other Vasodilators</b>				
Fixed dose Hydralazine/ Isosorbide dinitrate	BiDil	37.5 mg hydralazine/20 mg isosorbide dinitrate tid	75 mg hydralazine/40 mg isosorbide dinitrate tid	142.5 mg hydralazine/76 mg isosorbide dinitrate/day <sup>81</sup>
Hydralazine	Apresoline	37.5 mg qid	75 mg qid	270 mg/day <sup>79</sup>
Isosorbide dinitrate	Isordil	20 mg qid	40 mg qid	136 mg/day <sup>79</sup>

\*No difference in mortality between high and low dose groups, but 12% lower risk of death or hospitalization in high dose group vs. low dose group.

inhibitors of this enzyme.<sup>7,8</sup> Thus, despite treatment with ACE inhibitors in patients with chronic HF, angiotensin II levels may remain elevated and increase over time.<sup>9,10</sup>

ARBs block the effects of angiotensin II on the ATI receptor, independent of the source of angiotensin II production. Coupled with angiotensin II “escape,” this led to the hypothesis that ARBs might be superior to ACE inhibitors in HF and that the addition of ARBs to ACE inhibitors in patients with chronic HF might provide additional blockade of the RAAS and greater therapeutic benefit. ACE inhibitors reduce the degradation of kinins, which may lead to important therapeutic benefits not provided by ARBs, making the potential combination of the two agents more attractive.<sup>11,12</sup> Recommendations 7.13, 7.21, and 7.22 and the accompanying background discusses combination ACE-inhibitor and ARB therapy.

ACE inhibitors can have some troublesome side effects, including cough and angioedema, which may limit therapy with these agents. ARBs have been demonstrated to be well tolerated in randomized trials of patients judged to be intolerant of ACE inhibitors.<sup>13,14</sup> Both drugs have similar effects on blood pressure, renal function, and potassium.<sup>13</sup> The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Alternative trial prospectively tested the effect of an ARB in an ACE inhibitor intolerant population of patients with chronic HF and an LVEF < 40%. The addition of candesartan in these patients resulted in a reduction in the composite endpoint of cardiovascular death or hospital admission for HF from 40% in the control group to 33% in the candesartan group over a mean follow-up of 34 months with

a trend toward decreased all-cause mortality.<sup>13</sup> Post-hoc subgroup analysis of a small number of patients in the Valsartan in Heart Failure Trial (Val-HeFT) also found that patients intolerant to ACE inhibitors had fewer HF hospitalizations and a trend toward improved mortality with the addition of valsartan.<sup>15</sup> These data suggest that an ARB should be used in ACE inhibitor intolerant patients with chronic HF and LVEF < 40%. ARBs should be titrated as tolerated, in conjunction with beta blocker therapy, to target doses used in clinical trials (Table 7.1). ARBs should be considered instead of ACE inhibitors primarily in patients who are intolerant of ACE inhibitors because of intractable cough or angioedema. ARBs appear as likely as ACE inhibitors to produce hypotension, worsening renal function, and hyperkalemia. See background to Recommendations 7.19–7.20 for information about isosorbide dinitrate/hydralazine as an alternative to ACE-inhibitor therapy in intolerant patients.

**Angioedema and ARBs.** Nearly three-quarters of patients in CHARM-Alternative were intolerant to ACE inhibitors primarily because of cough, but intolerance was also reported in 13% from symptomatic hypotension, 12% from renal dysfunction, and 4% from angioedema/anaphylaxis.<sup>13</sup> In that study, 3 patients taking candesartan and none taking placebo had angioedema. None of the episodes were life-threatening and only 1 of the 3 patients discontinued candesartan. The 3 cases of angioedema all occurred in the 39 patients intolerant to ACE inhibitors because of angioedema. Thus, the risk of recurrent angioedema with ARBs in patients with angioedema

from ACE inhibition appears to be acceptable, assuming careful instructions and patient monitoring.

## Recommendation

### 7.5 Individual ARBs may be considered as initial therapy rather than ACE inhibitors for patients with the following conditions:

- HF Post-MI (Strength of Evidence = A)
- Chronic HF and reduced LVEF (Strength of Evidence = B)

## Background

Support for the use of the ARB, valsartan, in patients post-MI is provided by The Valsartan in Acute Myocardial Infarction Trial (VALIANT), which randomized 14,703 patients 0.5 to 10 days post-MI to valsartan, valsartan plus captopril, or captopril alone. Patients enrolled had clinical or radiologic signs of HF, evidence of reduced LVEF, or both.<sup>16</sup> The primary end point was all-cause mortality. There were no statistical differences among the 3 groups at a mean follow-up of 24.7 months. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group, and cough, rash, and taste disturbance were more common in the captopril group. The authors concluded that monotherapy with valsartan was equivalent to monotherapy with captopril. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) study randomized 5477 patient with HF or reduced LVEF post-MI to captopril or losartan.<sup>17</sup> The primary endpoint was all-cause mortality. There were 946 deaths during a mean follow-up of 2.7 years: 499 (18%) in the losartan group and 447 (16%) in the captopril group (relative risk 1.13 [95% CI 0.99–1.28],  $P = .07$ ). Thus valsartan appears equivalent to captopril in patients with HF or reduced LVEF post-MI, but the data do not clearly support equivalence of losartan to captopril in these patients.

In patients with chronic HF and reduced LVEF, 2 reviews have addressed the equivalence of ARBs and ACE inhibitors.<sup>18,19</sup> One meta-analysis concluded that ARBs should be considered “suitable alternatives” to ACE inhibitors. The Centers for Medicare and Medicaid Services has used this review to consider both ARBs and ACE inhibitors as acceptable to satisfy performance standards in patients with HF.<sup>20</sup> A second review suggested that ACE-inhibitors remain first line therapy, whereas ARBs were recommended for ACE-intolerant patients.<sup>18</sup>

### Beta Adrenergic Receptor Blockers (Table 7.1)

## Recommendation

### 7.6 Beta blockers shown to be effective in clinical trials of patients with HF are recommended for patients with an LVEF $\leq$ 40%. (Strength of Evidence = A)

## Background

Beta blocker therapy, advocated for HF by some investigators since the 1970s,<sup>21</sup> remains a major advance in the

treatment of patients with HF and reduced LVEF. Several large-scale clinical trials, involving more than 10,000 patients, have provided unequivocal evidence of important reductions in both mortality and morbidity.<sup>22–28</sup> The marked beneficial effects of beta blockade has been well demonstrated in large-scale clinical trials of symptomatic patients with NYHA class II-IV HF and reduced LVEF using carvedilol, bisoprolol, and metoprolol controlled release/extended release (CR/XL) (Table 7.1).<sup>24–28</sup> These trials added beta blockade to background therapy that included ACE inhibitors and diuretics in more than 90% of patients. The trial results support benefit from both  $\beta_1$  selective and nonselective beta blockers, whether ancillary properties are present or not. Beta blocking agents with intrinsic sympathomimetic activity are likely to worsen survival and should be avoided in patients with HF.<sup>29</sup> The beta blockers that have been shown to be effective in clinical trials and their corresponding doses are shown in Table 7.1. Whenever possible, beta blockers proven to be efficacious in clinical trials should be used. A general summary of recommendations for the successful administration of beta blockers are provided in Table 7.2.

Nebivolol is a  $\beta_1$  selective beta blocker that is currently only approved for the treatment of hypertension in the United States (U.S.), but it does not have a Food and Drug Administration (FDA) approved indication for HF. Outcomes with nebivolol have recently been reported in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial. The study was a randomized trial in 2128 patients  $\geq$ 70 years with a history of HF (a hospitalization for HF in the last year or an LVEF  $\leq$ 35%). The primary endpoint of all-cause mortality or cardiovascular hospitalizations was reduced with nebivolol from 35.3% to 31.1% (HR 0.86, 95% CI 0.74–0.99,  $p = 0.039$ ).<sup>28</sup> In contrast to other beta blocker trials, nebivolol did not significantly reduce all-cause mortality (HR 0.88, 95% CI 0.71–1.08,  $P=0.21$ ).<sup>28</sup>

The randomized controlled trials of beta blockers were conducted in addition to ACE-inhibitor therapy. Thus, ACE-inhibitors have generally been initiated first, followed by beta-blockade. The Cardiac Insufficiency Bisoprolol Study III (CIBIS III) trial evaluated the effect of either bisoprolol or enalapril monotherapy for 6 months, followed by combination therapy on mortality and hospitalization.<sup>30</sup> The findings of this study suggested that the safety and efficacy of either approach (beta blocker initiation first or ACE-inhibitor initiation first) was similar.<sup>30</sup>

## Recommendation

### 7.7 The combination of a beta blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF $\leq$ 40%

- Post-MI (Strength of Evidence = B)
- Non Post-MI (Strength of Evidence = C)

**Table 7.2.** Summary of Recommendations for the Administration of Beta Blocker Therapy

<b>General</b>	<ul style="list-style-type: none"> <li>● Initiate at low doses</li> <li>● Uptitrate gradually, generally no sooner than at 2-week intervals</li> <li>● Use target doses shown to be effective in clinical trials</li> <li>● Aim to achieve target dose in 8-12 weeks</li> <li>● Maintain at maximum tolerated dose</li> </ul>
<b>Considerations if symptoms worsen or other side effects appear</b>	<ul style="list-style-type: none"> <li>● Adjust dose of diuretic or other concomitant vasoactive medication</li> <li>● Continue titration to target dose after symptoms return to baseline</li> <li>● Considerations if uptitration continues to be difficult               <ul style="list-style-type: none"> <li>○ Prolong titration interval</li> <li>○ Reduce target dose</li> <li>○ Consider referral to a HF specialist</li> </ul> </li> </ul>
<b>If an acute exacerbation of chronic HF occurs</b>	<ul style="list-style-type: none"> <li>● Maintain therapy if possible</li> <li>● Reduce dosage if necessary</li> <li>● Avoid abrupt discontinuation</li> <li>● If discontinued or reduced, reinstate gradually before discharge</li> </ul>

See Recommendations 7.10–7.11 and accompanying text for specific recommendations

## Background

Randomized controlled data support the efficacy of ACE inhibitors in reducing both the likelihood of developing HF and the need for treatment or hospitalization in asymptomatic patients with an LVEF  $\leq 35\%$ .<sup>31</sup> Similar data are not available to support the use of beta blocker therapy in asymptomatic patients with reduced LVEF. Nevertheless, a number of arguments support the routine use of beta blockade in these patients. Guidance is provided by studies indicating the effectiveness of beta blocker therapy in patients following MI with good symptomatic and functional recovery, yet reduced LVEF.<sup>31–33</sup> These studies enrolled a number of patients without clinical HF. The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study demonstrated a reduction in all cause mortality, cardiovascular mortality, and recurrent non-fatal MI for patients with post-MI reduced LVEF randomized to carvedilol.<sup>34</sup> Multiple studies suggest myocardial remodeling following beta blocker therapy in patients with symptomatic HF as well.<sup>35–38</sup>

## Recommendation

**7.8 Beta blocker therapy is recommended for patients with a recent decompensation of HF after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive agents, including inotropic support. Whenever possible, beta blocker therapy should be initiated in the hospital setting at a low dose prior to discharge in stable patients. (Strength of Evidence = B)**

## Background

Ongoing clinical experience and current trial data indicate that beginning beta blockade at low dose in the hospital is possible in patients with improved congestion and other symptoms.<sup>39,40</sup> Initiation of therapies in hospital is known to result in better utilization and the attainment of more optimal doses of a variety of cardiovascular drugs.<sup>41,42</sup>

Beta blocker therapy should not be initiated in patients with acute decompensated heart failure (ADHF) with persistent symptoms and congestion. However, many patients hospitalized for HF are NYHA functional class IV from volume overload, and will improve sufficiently with standard therapy to allow introduction of beta blockade. The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) provides strong evidence in a prospective, randomized trial that patients with advanced HF, treated aggressively to reduce congestion and improve symptoms, benefit substantially from the introduction of beta blockade.<sup>43</sup>

## Recommendations

**7.9 Beta blocker therapy is recommended in the great majority of patients with HF and reduced LVEF, even if there is concomitant diabetes, chronic obstructive lung disease, or peripheral vascular disease. Beta blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, with asthma, or with resting limb ischemia. Considerable caution should be used if beta blockers are initiated in patients with marked bradycardia (<55 beats/min) or marked hypotension (systolic blood pressure <80 mm Hg). Beta blockers are not recommended in patients with asthma with active bronchospasm. (Strength of Evidence = C)**

**7.10 It is recommended that beta blockade be initiated at low doses and uptitrated gradually, typically at 2-week intervals in patients with reduced LVEF, and after 3-10 day intervals in patients with reduced LVEF following newly diagnosed MI. (Strength of Evidence = B)**

**7.11 It is recommended that beta blocker therapy be continued in most patients experiencing a symptomatic exacerbation of HF during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload, or symptomatic bradycardia (Strength of Evidence = C)**

A temporary reduction of dose (generally by one-half) in this setting may be considered. Abrupt discontinuation in patients with symptomatic exacerbation should be avoided, unless the situation is life-threatening. (Strength of Evidence = C)

If discontinued or reduced, beta blockers should be reinstated before the patient is discharged. In

**general, doses should be uptitrated to the previous well-tolerated dose as soon as safely possible (Strength of Evidence =B)**

## Background

The beta blockers studied in clinical trials are now established as routine therapy in patients with reduced LVEF. This therapy is well tolerated by a large majority of patients with HF, even those with comorbid conditions like diabetes mellitus,<sup>44,45</sup> chronic obstructive lung disease<sup>46</sup> and peripheral vascular disease.<sup>47</sup>

Clinical trials of beta blockers in HF have been conducted by uptitrating beta blockers to a maximum tolerated dose rather than titrating to a reduction in heart rate. Recent meta-analyses of previous trials suggest that the magnitude of benefit of beta blockers may be related to the reduction in heart rate rather than the dose of beta blocker.<sup>48–51</sup> However, until further data are available the current recommendation to uptitrate to doses of beta blockers used in randomized clinical trials will remain unchanged. In trials of chronic HF with reduced LVEF, beta blockers were initiated at low doses and uptitrated gradually, typically at 2-week intervals.<sup>24–27</sup> In patients with reduced LVEF following newly diagnosed MI, beta blockers were initiated at low disease and uptitrated after 3–10 day intervals.<sup>34</sup> Doses found to be effective in HF trials are generally achieved in 8 to 12 weeks. Patients developing worsening HF symptoms or other side effects during titration may require a dosage adjustment of diuretic or concomitant vasoactive medications. If side effects resolve with medication adjustment, patients can subsequently be titrated to target or maximally tolerated doses. Some patients may require a more prolonged interval during uptitration, a temporary reduction in beta blocker dose, or, in rare cases, withdrawal of therapy. If switching from a non-evidence based beta blocker to an evidence-based beta blocker, wait 24 hours from the last dose of a once-daily agent or wait 12 hours from the last dose of a twice-daily agent before beginning an evidence-based beta blocker.<sup>52</sup> The dose of the evidence-based beta blocker should be the equivalent of one-half the non evidence-based dose for most patients, although lower initial doses may be clinically appropriate for some patients; then uptitrate to target dose at 2-week intervals.<sup>52</sup>

Clinical deterioration during stable maintenance therapy with beta blockers rarely is related to administration of these agents. Nonadherence to medications, progression of underlying LV dysfunction and the adverse influence of a number of comorbid factors, including the occurrence of ischemia, hemodynamic instability from arrhythmia, and pulmonary complications such as pneumonia, are much more likely to be responsible for clinical deterioration. The best course is to use standard therapy to relieve congestion and treat exacerbating factors, rather than reduce or discontinue beta blockade. A retrospective review of patients enrolled in the Outcomes of a Prospective Trial

of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial of patients hospitalized with ADHF, found that continuation of beta blockade did not interfere with symptomatic improvement during admission,<sup>53</sup> supporting the continuation of beta blockade in patients hospitalized with an episode of decompensation. This same observation was made in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial.<sup>54</sup> In the Carvedilol or Metoprolol European Trial (COMET), patients whose beta blocker was discontinued or the dose reduced during a HF hospitalization had a higher mortality at 1 and 2 years as compared to patients whose therapy was continued.<sup>55</sup> Data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry also demonstrated an association between lower post-discharge mortality risk and continuation of beta blocker therapy during a HF hospitalization, even after adjustment for other prognostic factors.<sup>56</sup>

The Beta-blocker Continuation Versus Interruption in Patients with Congestive Heart Failure Hospitalized for a Decompensation Episode (B-CONVINCED) study was a randomized, controlled, open label trial of beta-blockade continuation versus discontinuation in 169 patients with acutely decompensated HF and LVEF <40%.<sup>57</sup> There was no difference between groups in general well-being or dyspnea at either day 3 or day 8 after randomization. Length of hospital stay was not different between groups, and there was no difference in in-hospital mortality or death or rehospitalization at 3 months. The proportion of patients receiving beta blockade at 3 months was higher for patients who were maintained on beta blockade during the hospitalization (90% vs. 76%,  $P=0.04$ ).<sup>57</sup>

Abrupt withdrawal of beta blockade should be avoided, especially in patients with coronary artery disease. Studies of the withdrawal of beta blockade in patients with reduced LVEF, but improved and stable clinical HF, have revealed a substantial risk of worsening HF and early death after beta blocker discontinuation.<sup>58,59</sup>

In certain patients, frequent return visits for dose titration may be difficult to accommodate in a busy clinical practice. Trained personnel, including nurse practitioners, physician assistants, and pharmacists, with physician supervision, may more efficiently perform patient education and reevaluation during uptitration. HF specialty programs are more likely to have the resources to provide this follow-up and education.<sup>60</sup> Patients should be aware that symptomatic deterioration is possible early in therapy and that symptomatic improvement may be delayed weeks to months.

Referral to clinicians with HF expertise may be helpful for patients who do not have contraindications to beta blockade (such as symptomatic bradycardia), but who have difficulty initiating, uptitrating or maintaining beta blocker therapy. Several factors may contribute to difficulty in using beta blocker therapy, including recent or multiple

HF hospitalizations; HF associated with ischemia, uncontrolled hypertension, moderate–severe valvular disease, syncope, or renal dysfunction; other multiple, active comorbidities, including asthma and chronic obstructive pulmonary disease; intolerance to other recommended HF drug therapies; persistent poor adherence to the HF plan of care; low output state; and persistent NYHA class III or IV symptoms.

### **Implantation of Cardiac Pacemakers in Patients With Baseline Bradycardia: An Unresolved Issue**

Given the strength of evidence supporting beta blocker therapy in patients with symptomatic HF, some physicians would consider pacemaker implantation when symptomatic bradycardia or heart block occurs during the initiation of this therapy. No clinical trial data are available to support this practice. Data from a decision analysis/cost-effectiveness modeling study suggested that prophylactic pacemaker insertion to allow beta blocker treatment in patients with bradycardia may be associated with clinical benefits, and may be cost-effective.<sup>14</sup> However, this approach cannot be recommended in the absence of clinical data.<sup>6,14</sup> It should be recognized that right ventricular (RV) pacing alone may result in deterioration of ventricular function, negating any potential benefit from beta blockade.<sup>61</sup> Consideration should be given to the withdrawal of other drugs that may have bradycardic effects.

### **Angiotensin Receptor Blockers (Table 7.1)**

See recommendation 7.2-7.5 and the accompanying background for a discussion of the role of ARBs as an alternative to ACE-inhibitors.

#### **Recommendations**

- 7.12** The routine administration of an ARB is not recommended in addition to ACE inhibitor and beta blocker therapy in patients with a recent acute MI and reduced LVEF. (Strength of Evidence = A)
- 7.13** The addition of an ARB should be considered in patients with HF due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. (Strength of Evidence = A)

#### **Background**

**Post-MI Studies.** The VALIANT trial evaluated the clinical effectiveness of ACE inhibitors and ARBs in patients with a recent MI (0.5-14 days), an LVEF  $\leq 40\%$  and clinical or radiographic signs of HF.<sup>16</sup> The addition of valsartan to captopril did not result in a significant improvement in total mortality or cardiovascular mortality compared to captopril alone, and there were more drug-related adverse events in the valsartan-captopril group.

The Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) was designed to prove that losartan would be superior or not inferior to captopril in decreasing all-cause mortality in patients with MI complicated by reduced LVEF.<sup>17</sup> There was a trend toward decreased all-cause mortality in the captopril group compared with losartan, and fewer captopril-treated patients experienced sudden death or a resuscitated cardiac arrest.<sup>17</sup> The addition of losartan to captopril did not result in a significant improvement in total mortality or cardiovascular mortality compared with captopril alone, and there were more drug-related adverse events in the losartan-captopril group.

The results of VALIANT cannot be directly compared with those of Val-HeFT and CHARM, because VALIANT was conducted in patients with recent MI and both an ACE inhibitor and ARB were added, rather than adding the ARB to a stable patient on chronic ACE inhibitor therapy. These data suggest that an ARB may be beneficial when added to an ACE inhibitor and beta blocker in patients with chronic HF, but not in those with HF because of a recent MI. See Recommendations 7.21 and 7.22 and accompanying background for more information on the optimal use of multi-drug therapy.

### **Aldosterone Antagonists (Table 7.1)**

#### **Recommendations**

- 7.14** Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF ( $< 35\%$ ) while receiving standard therapy, including diuretics. (Strength of Evidence = A)
- 7.15** Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical HF signs and symptoms or history of diabetes mellitus, and an LVEF  $< 40\%$ . Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a beta blocker. (Strength of Evidence = A)
- 7.16** Aldosterone antagonists are not recommended when creatinine is  $> 2.5$  mg/dL (or creatinine clearance is  $< 30$  ml/min) or serum potassium is  $> 5.0$  mmol/L or in conjunction with other potassium-sparing diuretics. (Strength of Evidence = A)
- 7.17** It is recommended that serum potassium concentration be monitored frequently following initiation or change in an aldosterone antagonist. Monitoring should reflect protocols followed in clinical trials. (Strength of Evidence = A)
- 7.18** In the absence of persistent hypokalemia ( $< 4.0$  mmol/L), supplemental potassium is not recommended in patients taking an aldosterone antagonist. (Strength of Evidence = A)

## Background

Sustained activation of aldosterone appears to play an important role in the pathophysiology of HF.<sup>62</sup> Increased renin and angiotensin II levels contribute to the stimulation of aldosterone secretion. Elevated circulating levels of this hormone enhance sodium retention and potassium and magnesium loss. Aldosterone upsets autonomic balance by increasing sympathetic activation and parasympathetic inhibition and promotes cardiac and vascular structural remodeling through collagen synthesis.<sup>63–65</sup>

Although ACE inhibition may transiently decrease aldosterone secretion, there are diverse stimuli other than angiotensin II for the production of this hormone.<sup>66</sup> Studies suggest a rapid return of aldosterone to levels similar to those before ACE inhibition.<sup>67</sup> The potential pathophysiologic role of aldosterone and the results of a pilot study that suggested low doses of spironolactone were tolerated in HF, led to additional investigation of these agents in severe HF and subsequently in post-MI HF.<sup>68,69</sup>

The Randomized Aldactone Evaluation Study (RALES) was designed to determine the effect of low-dose spironolactone on survival in severely symptomatic (recent or current NYHA class IV) HF patients treated with an ACE inhibitor, loop diuretic, and, in many cases, digoxin.<sup>68</sup> The study enrolled a total of 1663 patients with reduced LVEF (LVEF  $\leq$  35%) resulting from ischemic and nonischemic etiologies. All-cause mortality was the prespecified primary endpoint. There were 386 (46%) deaths in the placebo group compared with 284 (35%) in the spironolactone group. The risks of sudden death or of death from progressive HF were both reduced. The frequency of hospitalization for HF was 35% lower in patients treated with spironolactone compared with placebo. Greater improvement was noted in NYHA functional class in those receiving spironolactone. Because deaths in class III patients were designated as a worsening in NYHA class, this functional improvement likely reflects the mortality benefit of the drug.

The inclusion and exclusion criteria for the RALES trial are important to consider when applying the study results to clinical practice. The yearly mortality rate in the placebo group was high, reflecting the advanced HF of study participants. The potential benefit of aldosterone antagonists in patients with milder HF and lower risk cannot be determined from RALES data. It should be noted that only 10% of placebo and 11% of spironolactone patients in the RALES trial were treated with beta blocker therapy. Patients with potassium levels  $>$  5.0 mmol/L were excluded, as were patients with abnormal renal function, defined as a creatinine  $>$  2.5 mg/dL. Patients recruited into the trial met the potassium inclusion criteria despite the frequent concomitant use of potassium supplementation at baseline (28%). Adhering to these patient characteristics may be necessary to avoid excessive hyperkalemia during spironolactone treatment. In clinical practice, a more conservative approach to serum creatinine may be warranted. The

recommended serum creatinine cutoff of 2.5 mg/dL in this guideline is consistent with the eligibility criteria for the RALES trial. However, the majority of patients enrolled in RALES had a serum creatinine below this level. In addition, several groups including women, the elderly, or patients with low muscle mass may have a lower creatinine clearance for a given level of serum creatinine. For these patients, it may be reasonable to calculate an estimated creatinine clearance rather than relying solely on the serum creatinine value. Aldosterone antagonists are not recommended in patients with creatinine clearance  $<$  30 ml/min.

Spironolactone should be used in conjunction with standard therapy, including ACE inhibitors, digoxin, diuretics, and beta blockers. It should be initiated at a dose of 12.5 to 25 mg per day. Spironolactone can be titrated to 37.5 mg or 50 mg with careful monitoring in patients with refractory HF or persistent hypokalemia. Serum potassium and creatinine should be monitored closely in the first few weeks of therapy. If the serum potassium exceeds 5.0 mmol/L, then the dose of spironolactone should be decreased to 25 mg every other day and medications that could contribute to hyperkalemia should be adjusted. The risk of hyperkalemia with aldosterone antagonism is increased in patients with older age, diabetes, higher serum creatinine levels, and higher ACE inhibitor doses. In community settings the risk is far higher than documented during careful monitoring in trial settings, and may be as high as 20%.<sup>70</sup> This risk should be taken into careful consideration when treating with an aldosterone antagonist, and remains present even after successful initiation of this therapy. Patients should continue to be monitored carefully and should be instructed not to take the aldosterone antagonist during any circumstances of volume loss such as gastroenteritis.

In addition to hyperkalemia, gynecomastia or breast pain may be important side effects of spironolactone, but not eplerenone. They were reported in 10% of the men randomized to spironolactone versus 1% of the males in the placebo group in the RALES trial. These side effects were more frequent in patients taking digoxin.

Clinical studies with the selective aldosterone antagonist, eplerenone, have demonstrated favorable results in patients with HF after acute MI. A multicenter, randomized, double-blind, placebo-controlled trial, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), tested the effect of eplerenone versus placebo in 6642 patients.<sup>69</sup> Patients were enrolled after an acute MI if they had an LVEF  $\leq$  40% and HF documented by signs and symptoms. HF signs and symptoms were not required if patients had diabetes. Exclusion criteria for the study included creatinine  $>$  2.5 mg/dL and serum potassium  $>$  5.0 mmol/L. Patients were generally receiving agents shown to be effective in reducing risk in patients after acute MI, including beta blockers, ACE inhibitors, aspirin and cholesterol-lowering agents. The hypothesis was that eplerenone would reduce overall mortality and cardiovascular mortality or hospitalization.

The results, after an average follow-up 16 months, revealed a statistically significant reduction in cardiovascular mortality or hospitalization and all-cause mortality and hospitalization in the group receiving eplerenone.<sup>69</sup> The reduction in all-cause mortality was observed as early as 30 days after randomization.<sup>71</sup> There was also a significant reduction in sudden cardiac death favoring eplerenone treatment.

Adverse reactions to eplerenone were uncommon. As with spironolactone, serious hyperkalemia was more prevalent with eplerenone treatment. It should be noted that baseline serum potassium concentration in both the eplerenone and placebo groups was 4.3 mmol/L. As outlined in the recommendation for use, it is important to monitor electrolytes, especially potassium. The major predictors of hyperkalemia in EPHEUS were estimated glomerular filtration rate (eGFR) <60 ml/min, baseline serum potassium above the median (4.3 mEq/L), diabetes mellitus, and prior use of antiarrhythmic drugs. The effect of eplerenone on all-cause mortality was not affected by baseline serum potassium or the change in serum potassium from baseline.<sup>72</sup> Post-hoc analyses suggested that patients who were not on ACE inhibitors or ARBs and beta blockers had less benefit from the addition of eplerenone than those on these neurohormonal antagonists.<sup>69</sup> A recent systematic review of post-MI and HF studies in subjects with reduced LVEF using the aldosterone antagonists spironolactone, eplerenone, and canrenoate confirmed benefits in all-cause mortality, hospitalizations, and LVEF.<sup>73</sup>

**Remodeling Post MI** Another study randomized 134 patients post-anterior MI after revascularization to spironolactone versus placebo.<sup>74</sup> All patients were on ACE inhibitors. After 1 month, LVEF was improved, end-diastolic dimension was reduced, and markers of collagen synthesis were reduced in the spironolactone group, indicating an improvement in LV remodeling after MI. One of the limitations of this study was that only 31% of patients were on beta blockers. A substudy of EPHEUS demonstrated lower levels of collagen biomarkers among patients randomized to eplerenone, suggesting that it suppresses post-MI remodeling.<sup>75</sup>

**Aldosterone Antagonists in Mild to Moderate HF.** Patients enrolled in RALES had chronic severe HF (NYHA IV at enrollment or in the past). EPHEUS studied patients who were post-MI. Aldosterone antagonists have not been proven effective in patients with mild to moderate HF in the absence of recent MI or in patients with HF and preserved LV systolic function.

**Selective Versus Nonselective Aldosterone Antagonists.** The efficacy of selective and nonselective aldosterone antagonists is generally considered to be equivalent. The potential advantage of a selective aldosterone blocker that blocks only the mineralocorticoid receptor is a reduction in side effects. A nonselective blocker, such as spironolactone, blocks the mineralocorticoid, glucocorticoid,

androgen, and progesterone receptors, resulting in potential gynecomastia and sexual dysfunction. The incidence of gynecomastia with eplerenone in EPHEUS was 0.5%, whereas it was 10% with spironolactone in RALES.<sup>68,69</sup>

**Hyperkalemia.** Hyperkalemia is a life-threatening complication of aldosterone antagonists and is much more likely to occur in patients with diabetes or renal insufficiency or in those taking ACE inhibitors or ARBs. When more than one of these risk factors is present, the likelihood of hyperkalemia increases. In RALES and EPHEUS, aldosterone antagonists were not initiated if the creatinine was >2.5 mg/dL or serum potassium was >5.0 mmol/L. In RALES, the potassium was monitored every 4 weeks for 12 weeks, every 3 months up to a year, and every 6 months after the first year. In the EPHEUS trial, in which patients were taking a larger number of concomitant medications, potassium was measured at 48 hours, at 4-5 weeks, and then every 3 months. Potassium was measured 1 week after a dose increase of an aldosterone antagonist. Although patients with creatinine <2.5 mg/dL were enrolled in the clinical trials, very few patients actually had a creatinine >1.7 mg/dL. Thus additional monitoring should be considered in these patients.

Few patients will tolerate an aldosterone antagonist in the absence of concomitant therapy with a potassium-wasting diuretic. Potassium supplements and potassium-containing salt supplements should be reduced or, if possible, discontinued. Serum potassium monitoring should be at least as rigorous as in RALES and EPHEUS and more rigorous in patients with multiple risk factors. Nonsteroidal anti-inflammatory agents, including cyclooxygenase-2 inhibitors, should be avoided because they may worsen renal insufficiency, increasing the risk of hyperkalemia.

## Renin Inhibitors

Aliskiren is an orally active renin inhibitor that appears to suppress the RAAS to a similar degree as ACE-inhibitors.<sup>76</sup> The Aliskiren Observation of Heart Failure Treatment (ALOFT) study evaluated aliskiren in addition to an ACE-inhibitor in patients with NYHA class II-IV HF. The primary endpoint was the change from baseline to 3 months in N-terminal prohormone brain natriuretic peptide (NT-proBNP). NT-proBNP was lower for patients randomized to aliskiren, whereas it was higher for patients randomized to placebo ( $P=0.01$ ).<sup>77,78</sup> Phase 3 trials to evaluate the effects of aliskiren on mortality and morbidity are ongoing.

## Oral Nitrates and Hydralazine

### Recommendations

**7.19 A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to beta blockers and ACE inhibitors**

**for African Americans with HF and reduced LVEF.**

- **NYHA III or IV HF (Strength of Evidence = A)**
- **NYHA II HF (Strength of Evidence = B) (See Section 15: Special Populations)**

**7.20 A combination of hydralazine and isosorbide dinitrate may be considered in non-African-American patients with HF and reduced LVEF who remain symptomatic despite optimized standard therapy. (Strength of Evidence = C)**

## Background

The Vasodilator Heart Failure Trial (V-HeFT) was the first major randomized HF trial and was conducted in Veterans Administration hospitals throughout the US. Patients who remained symptomatic with mild to severe symptoms of HF despite treatment with diuretics and digoxin were randomized to a combination of hydralazine and isosorbide dinitrate or prazosin or placebo. The combination of hydralazine and isosorbide dinitrate was associated with a reduction in all-cause mortality compared to both placebo and prazosin that was of borderline statistical significance ( $P = .053$ ).<sup>79</sup> In V-HeFT II, the combination of hydralazine and isosorbide dinitrate was compared with enalapril in a population similar to V-HeFT I.<sup>80</sup> All-cause mortality was 28% lower with enalapril than with the hydralazine isosorbide dinitrate combination. However, quality of life and peak exercise capacity as measured by peak oxygen consumption were better with hydralazine-isosorbide dinitrate.

The African-American Heart Failure Trial (A-HeFT) enrolled 1050 self-identified African-American patients who had NYHA class III or IV HF with dilated ventricles and reduced LVEF.<sup>81</sup> In this placebo-controlled, blinded, and randomized trial, subjects were randomly assigned to receive a fixed combination of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for HF. 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 because of a significantly higher mortality rate in the placebo group than in the group given the fixed combination of isosorbide dinitrate plus hydralazine (10.2% vs 6.2%,  $P = .02$ ). The mean primary composite score was significantly better in the group given isosorbide dinitrate plus hydralazine than in the placebo group, as were its individual components: 43% reduction in the rate of death from any cause, 33% relative reduction in the rate of first hospitalization for HF, and an improvement in the quality of life. These results taken together constitute a strong recommendation for the addition of the fixed combination of isosorbide dinitrate/hydralazine to the standard medical regimen for HF in African Americans. Data cannot exclude a benefit of the isosorbide dinitrate/hydralazine combination in

non-African Americans when added to the standard medical regimen for HF.

## Optimal Use of Multi-Drug Therapy

### Recommendations

**7.21 Additional pharmacologic therapy should be considered in patients with HF and reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure, and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. (Strength of Evidence = C)**

- **Addition of an ARB. (Strength of Evidence = A)**
- **Addition of an aldosterone antagonist:**
  - **for severe HF (Strength of Evidence = A)**
  - **for moderate HF (Strength of Evidence = C)**
  - **for post-MI HF (Strength of Evidence = A)**
- **Addition of the combination of hydralazine/isosorbide dinitrate:**
  - **for African Americans (Strength of Evidence = A)**
  - **for others (Strength of Evidence = C)**

**7.22 Additional pharmacological therapy should be considered in patients with HF and reduced LVEF who are unable to tolerate a beta blocker and have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor. The choice of specific agent will be influenced by clinical considerations, including renal function status, chronic serum potassium concentration, blood pressure and volume status. The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended due to the high risk of hyperkalemia. (Strength of Evidence = C)**

- **Addition of an ARB. (Strength of Evidence = C)**
- **Addition of an aldosterone antagonist:**
  - **for severe HF (Strength of Evidence = C)**
  - **for moderate HF (Strength of Evidence = C)**
- **Addition of the combination of hydralazine/isosorbide dinitrate:**
  - **for African Americans (Strength of Evidence = C)**
  - **for others (Strength of Evidence = C)**

## Background

Multi-drug therapy is required for optimal management to slow progression and improve outcome in patients with HF and reduced LVEF. An ACE inhibitor plus a beta blocker is standard background therapy. An ARB can be substituted for an ACE inhibitor if clinically indicated. An ARB can be added to an ACE inhibitor in individuals in whom beta blocker is contraindicated or not tolerated. The optimal choice of additional drug therapy to further improve outcome in patients already treated with 2 of these 3 drugs is not firmly established. An aldosterone inhibitor, an ARB (if the patient is already on an ACE inhibitor) and the combination of isosorbide dinitrate and hydralazine have all been shown to exert further benefit in controlled trials, but have not been the subject of comparative trials. The choice among these agents may be influenced by the patient's age, renal function, serum potassium, racial background, and severity of the clinical syndrome. Certain combinations would require careful monitoring. For example, if an ARB or aldosterone antagonist were combined with an ACE inhibitor, with or without beta blocker therapy, elderly patients would require close monitoring of serum potassium, especially those with diabetes or renal insufficiency.

The use of 4 or more of these drugs in combination cannot be recommended on the basis of clinical trial evidence for additional efficacy, but such combinations have been used in subsets of patients enrolled in clinical trials. In the CHARM-Added trial, an ARB was safely administered to patients receiving an ACE inhibitor, beta blocker and aldosterone inhibitor, when patients were closely monitored for hyperkalemia and worsening renal function.<sup>82</sup> Non-significant increases in serum creatinine and serum potassium have been observed in clinical trials, and clinicians must closely monitor patients for these adverse effects when using these drugs in combination. In the A-HeFT study, black patients were given isosorbide dinitrate-hydralazine in addition to an ACE inhibitor, an ARB, and an aldosterone inhibitor with no apparent adverse effect.<sup>81</sup> Nonetheless, the use of combinations of 4 or more of these drugs would not be based on evidence for further efficacy and should mandate close monitoring of blood pressure, renal function, and serum potassium.

As discussed previously in this section, ARBs, aldosterone antagonists, and hydralazine/isosorbide dinitrate all have been shown to be beneficial in patients with chronic HF with or without beta blocker therapy. However, no study has specifically evaluated patients who are intolerant to beta blockers. Those who are intolerant due to hypotension or worsening HF are likely to have more severe HF and to be at higher risk of hypotension, worsening renal function, or hypokalemia with additional medical therapy. Thus closer clinical and laboratory monitoring is important.

## Diuretic Therapy

### Recommendation

**7.23 Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms (orthopnea, edema, and shortness of breath), or signs of elevated filling pressures (jugular venous distention, peripheral edema, pulsatile hepatomegaly, and, less commonly, rales). (Strength of Evidence = A) Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with HF. (Strength of Evidence = B)**

### Background

Loop and distal tubular diuretics are necessary adjuncts in the medical therapy for HF when symptoms are the result of sodium and water retention. Diuretics reduce congestive symptoms and signs and can be titrated as needed to restore euvolemia and to reach an estimated "dry" weight goal for the patient.

Relief of signs and symptoms must be achieved without causing side effects, particularly symptomatic hypotension or worsening renal function. Underutilization of diuretic therapy is common, but excessive diuresis is also problematic, limiting ventricular preload and producing excessive lowering of blood pressure, especially in conjunction with antihypertensive drugs such as ACE inhibitors, ARBs, and beta blockers. Diuretic administration should be accompanied by a recommendation for dietary sodium restriction to between 2000 and 3000 mg daily for the typical patient with HF (see Section 6). Fluid restriction is best reserved for the patient refractory to diuretics with a high oral fluid intake or symptomatic hyponatremia.

Although some retrospective analyses have generated concern about the long-term safety of diuretics,<sup>83,84</sup> this concern is not supported by any controlled data. There are few controlled studies of diuretics because few symptomatic patients can be managed without them. Still, there are data to support the safety and efficacy of diuretics.<sup>85</sup> A trial in which patients with stable and relatively mild HF without evidence of significant volume overload were randomized to substitution of an ACE inhibitor or continued diuretic showed that the large majority of patients required reinstatement of diuretic therapy.<sup>86</sup> Very small trials suggest that in patients with reduced LVEF with or without HF, ACE inhibitor therapy may prevent remodeling more than diuretics, but that diuretics may be superior for symptom improvement.<sup>87,88</sup> However, there are no controlled clinical trial data prospectively evaluating the overall impact of diuretic therapy on mortality in patients with HF.

Diuretics may cause activation of the RAAS, potentiate hypotensive effects of ACE inhibitors,<sup>89,90</sup> and may decrease cardiac output, especially in patients with diastolic LV dysfunction. Diuretics also may induce hypokalemia and hypomagnesemia.

**Loop Diuretics.** Loop diuretics, which act on the ascending limb of the renal medullary loop of Henle, are considered the diuretic class of choice for the treatment of HF. These drugs produce a greater fractional excretion of filtered sodium than is induced by thiazide-type diuretics. The onset of action with intravenous administration is within minutes, making this route of administration preferable for the acutely symptomatic or hospitalized patient (see Section 12).

**Thiazide Diuretics.** Thiazide diuretics, which inhibit sodium reabsorption in the distal renal tubule, may be effective as monotherapy in HF patients with mild volume overload and preserved renal function. They are generally superior to loop diuretics as antihypertensive agents. They are delivered to their site of action by filtration and are ineffective when the glomerular filtration rate falls below 30 mL/min.

**Potassium-Sparing Diuretics.** Potassium-sparing diuretics, other than aldosterone antagonists, have no direct diuretic activity. Several are formulated in combination with thiazides for the treatment of hypertension, but are not generally useful in HF. For patients with excessive potassium losses on loop diuretics, coincident administration of these agents can be helpful. However, because of their beneficial effects on prognosis and ability to facilitate diuresis, aldosterone antagonists are preferred for this purpose. The use of these agents for purposes other than as a diuretic is discussed earlier in this section. [Table 7.3](#) and [Table 7.4](#) provide dosage and other information about loop diuretics, thiazides, and potassium-sparing diuretics.<sup>6,91,92</sup>

## Recommendation

**7.24 The initial dose of diuretic may be increased as necessary to relieve congestion. Restoration of normal volume status may require multiple adjustments over many days and occasionally weeks in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with short-acting loop diuretics, increasing administration frequency to twice or even 3 times per day will provide more diuresis with less physiologic perturbation than larger single doses. (Strength of Evidence = B)**

**Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided HF and refractory fluid**

**retention despite high doses of other loop diuretics. (Strength of Evidence = C)**

**Intravenous administration of diuretics may be necessary to relieve congestion. (Strength of Evidence = A)**

**Diuretic refractoriness may represent patient non-adherence, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.**

## Background

HF can adversely affect the pharmacokinetics of diuretics in a number of ways. Delayed absorption, resulting from gut edema from high central venous pressure, can reduce peak serum concentration. The volume of distribution is variable in the setting of chronic HF. Relative hypotension or reduced cardiac output producing a limitation in renal blood flow reduces the delivery of diuretic to the kidney. In general, these limitations can be overcome by successively increasing the dose administered.

## Recommendation

**7.25 Addition of chlorothiazides or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high-dose loop diuretic therapy. But chronic daily use, especially of metolazone, should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer-acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. (Strength of Evidence = C)**

## Background

Thiazide-type diuretics can be used in combination with loop diuretics to augment natriuresis when high doses of loop diuretic are ineffective at restoring euvolemia. Improved natriuresis from the combination of these 2 classes of diuretics is expected as they act at different sites in the kidney to produce sodium loss. In addition, resistance to loop diuretics can occur, partially due to progressive hypertrophy of distal renal tubular endothelial cells. This results in greater distal tubular reabsorption of sodium, which in turn reduces the net natriuretic effect of loop diuretics. Combining a thiazide-type diuretic with a loop diuretic typically will overcome this compensatory hypertrophy and result in a significantly greater diuretic effect. Metolazone is a thiazide-like diuretic with better oral availability than loop diuretics. It has a half-life of approximately 14 hours.

**Table 7.3.** Loop Diuretics

Agent	Initial Daily Dose (mg)	Maximum Total Daily Dose (mg)	Elimination	Duration of Action (hr)
Furosemide*	20–40 mg qd or bid	600 mg	65%R 35%M	4–6
Bumetanide*	0.5–1.0 mg qd or bid	10 mg	62%R 38%M	6–8
Torsemide*	10–20mg qd	200 mg	20%R 80%M	12–16
Ethacrynic acid* <sup>+</sup>	25–50 mg qd or bid	200 mg	67%R 33%M	6

Equivalent doses: furosemide 40 mg = bumetanide 1 mg = torsemide 20 mg = ethacrynic acid 50 mg.

R = renal; M = metabolic; B = excreted into bile; U = unknown.

\*Available for oral or intravenous administration (no dosage adjustments).

<sup>+</sup>Non-sulfa containing, may be used in sulfa-allergic patients.

**Table 7.4.** Other Diuretics

Agent	Initial Daily Dose (mg)	Maximum Total Daily Dose (mg)	Elimination	Duration of Action (hr)
<b>Thiazides</b>				
Chlorothiazide*	250–500 qd or bid	1000 mg	R	6–12
Chlorthalidone	12.5–25 mg qd	100 mg	65%R 10%B 25%U	24–72
Hydrochlorothiazide	25 mg qd or bid	200 mg	R	6–12
Metolazone	2.5 mg qd	20 mg	80%R 10%B 10%U	12–24
Idapamide	2.5 mg qd	5 mg	M	36
*May be given IV in doses of 250–1000 mg.				
<b>Potassium-Sparing</b>				
Spironolactone*	12.5–25 qd	50 mg*	M	48–72
Eplerenone* <sup>+</sup>	25–50 qd	100 mg*	R, M	
Amiloride	5 qd	20 mg	R	24
Triamterene	50–75 bid	200 mg	M	7–9

R = renal; M = metabolic; B = excreted into bile; U = unknown.

\*Higher doses have been used to control volume retention or hyperkalemia but close monitoring is mandatory.

<sup>+</sup>Do not use if creatinine clearance is  $\leq 30$  mL/min or with cytochrome 3A4 inhibitors.

The diuretic effects of metolazone are preserved even in patients with reduced GFR ( $< 20$  ml/min) because it does not decrease GFR or renal plasma flow; in contrast, thiazide diuretics can decrease GFR which contribute to their lower efficacy in patients with renal impairment.

## Recommendation

**7.26 Careful observation for the development of side effects, including electrolyte abnormalities, symptomatic hypotension, renal dysfunction, or worsening renal function, is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = B)**

## Background

Hypokalemia from excessive potassium wasting is common during loop diuretic therapy, especially during the reversal of significant volume overload. Thiazide-type diuretics also contribute to potassium wasting. Serum potassium concentration should be monitored when diuretics are used, particularly during initiation and uptitration of therapy, with supplements given as needed. Other electrolyte disturbances associated with chronic diuretic use include hypomagnesemia and hypocalcemia.

Excessive diuresis may lead to volume depletion during treatment. Symptoms may include fatigue and shortness of breath, rather than the more predictable symptoms of lightheadedness. Hyperkalemia may accompany mild volume depletion and is more likely to occur in patients receiving ACE inhibitors, ARBs, and/or aldosterone blockers, especially in patients with diabetes or those taking potassium supplements or ingesting foods with high potassium content.

Use of loop and distal tubular diuretics in combination may be necessary to relieve symptoms, but may result in excessive volume loss and electrolyte disturbance. Distal tubular diuretics should be introduced cautiously when they are combined with loop diuretics, and patients should be monitored closely for side effects. Initially, only single low doses (eg, metolazone 2.5 mg) should be administered to determine the magnitude of response. If necessary, higher doses may be used subsequently, but this should be done cautiously with close monitoring of electrolytes and volume status. Twice-daily dosing of distal agents is generally not helpful because they have a long duration of action. In most cases, the frequency of use can be cut back to every other day, once or twice weekly, or as needed based on a weight threshold.

Worsening renal function is common with excessive diuresis, especially when patients are receiving ACE inhibitors or ARBs. Fortunately, reduction in diuretic dose and restoration of euvolemia will return renal function to

baseline levels in almost all cases unless hypovolemia has been prolonged or worsening renal function is due to another cause (eg, nephrotoxic drugs, post-obstructive uropathy). Intensification of diuretic therapy in these patients may be accompanied by a worsening of renal function reflected by modest elevations in blood urea nitrogen and serum creatinine concentration. Some reduction in renal function may be a necessary tradeoff for symptom relief in this setting. While there is an association between worsening renal function and adverse outcomes in HF, causality remains unproven.

The occurrence of reduced renal function should prompt a review of the patient's current medications to avoid concomitant administration of nephrotoxic drugs or drugs that reversibly affect renal function (eg, nonsteroidal anti-inflammatory drugs, antibiotics) and to determine if dose reduction in medications dependent on renal clearance (eg, digoxin) is warranted. It is essential to recognize progressive renal insufficiency from decreasing renal perfusion that will require adjustment of diuretic therapy. Worsening renal function can also result from inadequate diuresis and volume overload leading to renal venous or intraabdominal hypertension.

Loop diuretics may be associated with a variety of other side effects that may require additional treatment to correct. Rapid intravenous administration of high-dose loop diuretics should be avoided whenever possible, because hearing loss to the point of deafness can result from middle ear toxicity. Skin reactions from photosensitivity to rashes are not uncommon, and other hypersensitivity reactions including interstitial nephritis may occur. High doses of loop diuretics can worsen glucose tolerance and may result in hyperuricemia and symptoms of gout, prompted by increased uric acid reabsorption. Thiazide diuretics share most of the side effects seen with loop diuretics, although an association with pancreatitis appears to be unique to loop diuretics.

## Recommendation

**7.27 Patients requiring diuretic therapy to treat fluid retention associated with HF generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. (Strength of Evidence = C)**

## Background

Reduced diuretic requirement is not uncommon during the course of HF treatment. The initiation of more effective

therapies, such as ACE inhibitors and beta blockers, may result in substantial improvement in underlying LV dysfunction and in neurohormonal abnormalities that result in sodium and water retention. Improvement in adherence to dietary sodium restrictions is not unusual during chronic therapy for HF and may substantially reduce the need for diuretic therapy. Reevaluation of diuretic dose and frequency should occur over the course of initiation and titration of therapy.

## Recommendation

**7.28 It is recommended that patients and caregivers be given education that will enable them to demonstrate understanding of the early signs of fluid retention and the plan for initial therapy. (Strength of Evidence = C)**

**Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload (typically short-term weight gain of 2 to 4 lb). (Strength of Evidence = C) (See Section 6 for more information on this topic)**

## Background

Episodic increases in sodium intake over weeks and months of follow-up are expected, given the natural variation in diet common in the daily lives of patients with HF. If untreated, this excessive dietary sodium intake may result in development or recurrence of congestive symptoms. The ability to recognize early signs and symptoms of volume overload is an important aspect of self-care for these patients. Intervention early in the development of fluid overload may allow restoration of volume status without hospitalization.

A strategy effective in many patients involves adjustment of the diuretic dose according to increases in daily weight. Some patients find it effective to increase diuretic empirically when dietary sodium indiscretion occurs. In some patients with advanced HF, monitoring of renal function and potassium is necessary before or during these periods.

## Digoxin

## Recommendation

**7.29 Digoxin may be considered to improve symptoms in patients with reduced LVEF (LVEF  $\leq$ 40%) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers:**

- NYHA class II-III (Strength of Evidence = B)
- NYHA class IV (Strength of Evidence = C)

## Background

Although little controversy exists as to the benefit of digoxin in patients with symptomatic HF with reduced LVEF

and concomitant atrial fibrillation, the debate continues over its current role in similar patients with normal sinus rhythm. Information regarding digoxin's mechanism of action and ongoing analyses of clinical data from the Digitalis Investigation Group (DIG) trial and the combined databases of several other large trials provide evidence of digoxin's efficacy.<sup>93–99</sup> Digoxin, a drug that is inexpensive and can be given once daily, represents the only oral agent with positive inotropic effects approved for the management of HF, although as discussed below, in the low doses currently used, digoxin may work more by neurohormonal modulation than inotropy. Digoxin has an important therapeutic role in symptomatic patients with HF from reduced LVEF.

The efficacy of digoxin in HF with reduced LVEF has traditionally been attributed to its relatively weak positive inotropic action arising from inhibition of sodium-potassium ATPase and the resulting increase in cardiac myocyte intracellular calcium. However, digitalis has additional actions that may contribute significantly to its beneficial effects in patients with HF. Digoxin has important neurohormonal modulating effects that cannot be ascribed to its inotropic action, and it ameliorates autonomic dysfunction as shown by studies of heart rate variability, which indicate increased parasympathetic and baroreceptor sensitivity during therapy.<sup>100–103</sup>

The DIG trial provides important data concerning the efficacy of digoxin in patients with HF from reduced LVEF.<sup>97</sup> In the main part of this trial, 6800 patients with LVEF  $\leq 45\%$  were randomized to digoxin or placebo in addition to diuretics and ACE inhibitors. The primary end point of all-cause mortality was not significantly different between the placebo and the digoxin groups. The need for hospitalization and cointervention (defined as increasing the dose of diuretics and ACE inhibitors or adding new therapies for worsening HF) was significantly lower in the digoxin group, even in those patients who were not previously taking digoxin. Twenty-eight percent fewer patients on digoxin compared with placebo were hospitalized for worsening HF. Digoxin has not been studied prospectively in patients on current neurohormonal blockade including both ACE-inhibitors and beta blockers, and retrospective studies suggest it may not provide benefit in these patients. A prospective, randomized trial evaluating the benefits of digoxin would be valuable.<sup>104,105</sup>

Results from the DIG study showed a neutral effect on the primary study endpoint, mortality from any cause, during an average follow-up of approximately 3 years. These long-term data are consistent with recent results obtained from an analysis of the combined Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED) and Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme) RADIANCE study databases.<sup>99</sup> In this analysis, patients who continued digoxin as part of triple therapy with diuretics and an ACE inhibitor were much less likely to develop worsening HF (4.7%) than those treated with a diuretic alone (39%,  $P < .001$ ), diuretic plus digoxin (19%,  $P = .009$ ),

or diuretic plus an ACE inhibitor (25%,  $P = .001$ ). The DIG trial was conducted prior to the widespread use of beta blockers, and no large trial of digoxin in addition to therapy with both ACE-inhibitors and beta blockers is available.

Although the number of patients in the DIG trial with NYHA functional class IV HF was limited, retrospective analysis of this subgroup found clear evidence of clinical benefit of digoxin.<sup>106</sup> Other results from this trial confirm that digoxin works to improve symptoms across the spectrum of HF with reduced LVEF. A prespecified subgroup analysis of patients with evidence of severe HF, as manifested by LVEF  $< 25\%$  or cardiothoracic ratio (CTR)  $> 0.55$ , showed the benefit of digoxin.<sup>100,106</sup> The following reductions in the combined endpoint of all-cause mortality or hospitalization were seen on digoxin compared with placebo: 16% reduction (95% CI 7–24%) in patients with an LVEF  $< 25\%$ , and a 15% reduction (95% CI 6–23%) in patients with a CTR  $> 0.55$ . Reductions in the risk of the combined endpoint of HF-related mortality or hospitalization were even more striking: 39% for patients with LVEF  $< 25\%$  and 35% for patients with a CTR  $> 0.55$ .

Evidence for the efficacy of digoxin in patients with mild symptoms of HF has been provided by a second retrospective cohort analysis of the combined PROVED and RADIANCE databases.<sup>107</sup> The outcome of patients in these trials randomized to digoxin withdrawal or continuation was categorized using a prospectively obtained HF score based on clinical signs and symptoms. Patients in the mild HF group who were randomized to digoxin withdrawal were at increased risk of treatment failure and had deterioration of exercise capacity and LVEF compared with patients who continued digoxin (all  $P < .01$ ).

## Recommendation

**7.30 It is recommended that the dose of digoxin, which should be based on lean body mass, renal function, and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be  $< 1.0$  ng/mL, generally 0.7–0.9 ng/mL. (Strength of Evidence = B)**

## Background

Recent data suggest that the target dose (and serum concentration) of digoxin therapy should be lower than traditionally assumed. Although higher doses may be necessary for maximal hemodynamic effects,<sup>94</sup> beneficial neurohormonal and functional effects appear to be achieved at relatively low serum digoxin concentrations (SDC) typically associated with daily doses of 0.125 to 0.25 mg.<sup>94,103,108</sup> A retrospective analysis of the relationship of SDC to outcomes in the DIG trial demonstrated a strong direct relationship between the risk of death and SDC, with concentrations  $> 1.2$  ng/mL being associated with harm, whereas concentrations  $< 1.0$  ng/mL were associated with

favorable outcomes.<sup>109</sup> These findings supporting the efficacy of low SDC are reinforced by a retrospective cohort analysis of the combined PROVED and RADIANCE databases indicating that patients with a low SDC (<0.9 ng/mL) were no more likely to experience worsening symptoms of HF on maintenance digoxin than those with a moderate (0.9–1.2 ng/mL) or high (>1.2 ng/mL) SDC.<sup>93,109</sup> All SDC groups were significantly less likely to deteriorate during follow-up compared with patients withdrawn from digoxin.

Therefore, patients with reduced LVEF and normal sinus rhythm should be started on a maintenance dose of digoxin (no loading dose) of 0.125 or 0.25 mg once daily based on ideal body weight, age, and renal function. For young patients with normal renal function, a dose of 0.25 mg/day will be typical. Most patients with HF are older and have reduced renal function and should begin at 0.125 mg daily. Patients with a baseline conduction abnormality, or who are small in stature or elderly, should be started at 0.125 mg/day, which can be up-titrated if necessary. Updated dosing nomograms have been published in light of the recognized benefits of digoxin at lower serum concentrations, and they may be useful to clinicians in selecting appropriate an appropriate digoxin dose.<sup>110</sup> After dosing has continued for a sufficient period for serum concentration to reach steady state (typically 5 daily doses), some clinicians consider the measurement of a SDC, especially in elderly patients or those with impaired renal function where the digoxin dose often is not predictive of SDC. SDC measurements may be considered when (1) a significant change in renal function occurs; (2) a potentially interacting drug (amiodarone, quinidine, verapamil, itraconazole, erythromycin, clarithromycin, ritonavir, propafenone, or cyclosporine, and others) is added or discontinued; or (3) confirmation of suspected digoxin toxicity is necessary in a patient with signs/symptoms or electrocardiogram changes consistent with this diagnosis. Samples for trough SDC should be drawn more than 6 hours after dosing; otherwise, the result is difficult to interpret because the drug may not be fully distributed into tissues.

## Recommendations

- 7.31 Digoxin should be considered for achieving adequate control of the ventricular response to atrial fibrillation in patients with HF. (Strength of Evidence = B)**
- 7.32 High doses of digoxin (maintenance dose >0.25 mg daily) for the purpose of rate control are not recommended. (Strength of Evidence = C)**

## Background

Adequate ventricular rate control is important in patients with atrial fibrillation. During chronic therapy, the recommendations followed in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) trial

are a reasonable starting point.<sup>111</sup> These recommendations include: a resting heart rate  $\leq 80$  bpm, an average heart rate by Holter monitor of  $\leq 100$  bpm, and no heart rate  $>110\%$  of the age-predicated maximum or a heart rate  $\leq 110$  bpm during a 6-minute walk test. Digoxin alone is often inadequate to control ventricular response in patients with atrial fibrillation. Digoxin slows ventricular response to atrial fibrillation through enhancement of vagal tone. However, with exertion or other increases in sympathetic activity, vagal tone may diminish and ventricular rate accelerate. Addition of a beta blocker complements the pharmacologic action of digoxin and improves rate control. When beta-adrenergic blockers cannot be used, amiodarone has been used by some physicians, but chronic use has potentially significant risks, including thyroid disease and lung toxicity. If amiodarone is added, the dose of digoxin should be reduced by half and the SDC should be monitored to maintain the serum concentration in the desired range. Short-term, intravenous administration of diltiazem or amiodarone has been used for the acute treatment of patients with very rapid ventricular response, especially if the rapid rate is felt to be contributing to hemodynamic compromise. The negative inotropic effects of nondihydropyridine calcium channel blockers (diltiazem and verapamil) must be considered if these agents are used. Digoxin does not lower blood pressure; thus, it may be particularly valuable when hypotension from other agents is a concern.

Although digoxin continues to play a role in some patients with HF and atrial fibrillation, the traditional practice of arbitrarily increasing the dose and SDC of digoxin until ventricular response is controlled should be abandoned, because the risk of digoxin toxicity increases as well.

## Anticoagulation and Antiplatelet Drugs

### Recommendation

- 7.33 Treatment with warfarin (goal international normalized ratio [INR] 2.0-3.0) is recommended for all patients with HF and chronic or documented paroxysmal, persistent, or long-standing atrial fibrillation (Strength of Evidence = A) or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack (Strength of Evidence = C), unless contraindicated.**

### Background

Patients with HF are recognized to be at increased risk for arterial or venous thromboembolic events. In addition to atrial fibrillation and poor ventricular function, which promote stasis and increase the risk of thrombus formation, patients with HF have other manifestations of hypercoagulability. Evidence of heightened platelet activation, increased plasma and blood viscosity, and increased plasma levels of fibrinopeptide A, beta-thromboglobulin, D-dimer, and von Willebrand factor have been found in many patients.<sup>112–114</sup> Despite a predisposition, estimates

regarding the incidence of thromboemboli in patients with HF vary substantially between 1.4% and 4.2% per 100 patient years.<sup>115–117</sup> Although variability in the reported incidence likely results from differences in the populations studied and the methodology used to identify these events, the consensus is that pulmonary and systemic emboli are not common in HF patients in sinus rhythm. Traditionally, discussion of anticoagulation in patients with HF has centered on warfarin. Antiplatelet agents are often used in patients with HF from ischemic heart disease.

Previous guidelines have recommended warfarin anticoagulation in patients with HF complicated by atrial fibrillation or prior thromboembolic events.<sup>118</sup> Warfarin anticoagulation was specifically not recommended in patients with HF in the absence of these indications.

Recommendations regarding warfarin use, in the absence of atrial fibrillation or clinically overt systemic or pulmonary thromboemboli, must be made on the basis of cohort data and expert opinion. The likely incidence of thromboembolic events and the possibility of averting them with warfarin are important considerations for any guideline recommendation. In addition, the potential beneficial effects of warfarin on coronary thrombotic events, independent of embolic phenomena, must be taken into account. The substantial clinical trial data reflecting the beneficial effects of antiplatelet therapy in patients with ischemic heart disease suggest that the role of this therapy in patients with reduced LVEF should be addressed.

Previous guideline recommendations have been positive concerning warfarin therapy in patients with HF complicated by atrial fibrillation, a common clinical presentation. The benefit of warfarin anticoagulation in this setting is well established through several randomized trials.<sup>119</sup> Warfarin anticoagulation should be implemented in these patients unless clear contraindications exist.

## Recommendation

**7.34 It is recommended that patients with symptomatic or asymptomatic ischemic cardiomyopathy and documented recent large anterior MI or recent MI with documented LV thrombus be treated with warfarin (goal INR 2.0-3.0) for the initial 3 months post-MI (Strength of Evidence = B) unless contraindicated.**

**Other patients with ischemic or nonischemic cardiomyopathy and LV thrombus should be considered for chronic anticoagulation, depending on the characteristics of the thrombus, such as its size, mobility, and degree of calcification. (Strength of Evidence = C)**

## Background

LV thrombus is a frequent finding in patients with dilated dysfunctional ventricles, especially in patients who have

suffered a large anterior MI, although the incidence appears to be declining with modern therapies.<sup>120–122</sup> LV thrombus is associated with thromboembolism, especially cerebral embolism.<sup>123–125</sup> Two-thirds of these embolic events occur in the first week after MI.<sup>124,125</sup> When LV mural thrombus is present, anticoagulation does appear to reduce the incidence of subsequent embolic events.<sup>123</sup> There are no randomized trials of anticoagulation for LV thrombus, but the data presented have led to a recommendation for short-term (3 months) anticoagulation in patients with a large anterior MI and wall motion abnormality or in patients with LV thrombus.<sup>126</sup>

## Background

Cohort analyses examining the relationship between warfarin use and noncoronary thromboembolism in patients with HF have not yielded consistently positive findings.<sup>115,117,127–130</sup> It is possible that the lack of consistent benefit was related to the low incidence of identifiable embolic events in these populations. Other retrospective evaluations of the use of anticoagulation in patients with HF have also yielded conflicting results.<sup>131–133</sup> Thromboembolic events were not different in HF patients who were taking warfarin as compared to those who were not in several retrospective analyses.<sup>117,134,135</sup> Warfarin was associated with a reduction in cardiovascular events and death in a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) studies,<sup>136</sup> whereas no difference in antiplatelet or anticoagulant therapy were observed in another analysis.<sup>137</sup>

A recent review suggested that anticoagulation with warfarin in patients with HF reduced death and cardiovascular events but that the data were insufficient to recommend routine use.<sup>138</sup> Two prospective randomized trials of anticoagulation have been published since that review but both were underpowered. The Warfarin/Aspirin Study in Heart Failure (WASH) randomized 279 patients with HF to warfarin (INR target 2.5), 300 mg aspirin, or no treatment.<sup>139</sup> There were no differences in the combined primary outcomes of death, MI, or stroke. However, significantly more patients randomized to aspirin were hospitalized for ADHF or serious adverse gastrointestinal events.

In the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, patients with symptomatic HF and reduced LVEF were randomized to aspirin 162 mg/day, clopidogrel 75 mg/day, or open-label warfarin to achieve an INR of 2.5 to 3.<sup>140</sup> The primary endpoint of the study was the composite of all-cause mortality, non-fatal MI, and non-fatal stroke. The majority of patients had an ischemic etiology of HF, although the study population was not limited to patients with coronary artery disease. There were no statistically significant differences in the primary endpoint for warfarin versus aspirin, for clopidogrel versus aspirin, or for warfarin versus clopidogrel.<sup>140</sup> However, as in WASH, fewer patients randomized to warfarin were hospitalized for HF. A recent retrospective

analysis of 290 patients with HF and LVEF <35% and idiopathic dilated cardiomyopathy reported an odds ratio of 3.4 ( $P = .027$ ) for stroke in those with LV thrombus but no difference in mortality.<sup>141</sup> In the absence of strong data, the decision to anticoagulate must be an individual one. There are insufficient data for or against the use of warfarin in patients with dilated cardiomyopathy and LVEF  $\leq 35\%$ .

The analysis of the SOLVD population mentioned above focused on the relation between warfarin use and the risk of all-cause mortality rather than risk for embolic events.<sup>136</sup> After adjustment for baseline differences, patients treated with warfarin at baseline had a 24% lower risk of mortality during follow-up. Warfarin use also was associated with an 18% reduction in the combined endpoint of death or hospitalization for HF. In the SOLVD population, the benefit associated with warfarin use was not significantly influenced by (1) presence or absence of symptoms, (2) randomization to enalapril or placebo, (3) gender, (4) presence or absence of atrial fibrillation, (5) age, (6) LVEF, (7) NYHA class, or (8) etiology.

The benefit associated with warfarin use in the cohort analysis of the SOLVD population was related to a reduction in cardiac mortality. Specifically, there was a significant reduction among warfarin users in deaths that were identified as sudden, in deaths associated with HF, and in fatal MI. There was no significant difference in deaths considered cardiovascular but non-cardiac, including pulmonary embolism and fatal stroke. Some caution is needed related to this finding as the number of cardiovascular deaths that were non-cardiac was far smaller than the number of cardiac deaths.

Reduction in ischemic events is one potential explanation for the apparent benefit from warfarin in the SOLVD study. Warfarin users showed a reduced rate of hospitalization for unstable angina or nonfatal MI. Prior investigations in patients following acute MI showed that warfarin anticoagulation, when begun within 4 weeks, reduced the incidence of fatal and non-fatal coronary events, as well as pulmonary emboli and strokes.<sup>139</sup>

As with other post-hoc cohort analyses, it is possible that the findings from the SOLVD study may result from unidentified differences between the treatment groups, for which statistical correction could not adequately adjust. For this reason, evidence from any cohort study must be considered less powerful than that derived from randomized, controlled trials.

## Recommendations

**7.35 Long-term treatment with an antiplatelet agent, generally aspirin in doses of 75 to 81 mg, is recommended for patients with HF due to ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors. (Strength of Evidence = B)**

**Warfarin (goal INR 2.0-3.0) and clopidogrel (75 mg) also have prevented vascular events in post-**

**MI patients and may be considered as alternatives to aspirin. (Strength of Evidence = B)**

**7.36 Routine use of aspirin is not recommended in patients with HF without atherosclerotic vascular disease. (Strength of Evidence = C)**

## Background

**Combined Use of Aspirin and an ACE Inhibitor.** Strong evidence supports the clinical benefit of both aspirin and ACE inhibitors in ischemic heart disease and atherosclerosis.<sup>142-145</sup> However, post-hoc analyses of large randomized trials involving ACE inhibitors in HF and post-MI have raised the possibility of an adverse drug interaction between aspirin and ACE inhibitors.<sup>146</sup>

It is critical to understand the possible nature of the adverse interaction raised by these retrospective analyses. Because both aspirin and ACE inhibitors are beneficial in ischemic heart disease, patients taking both agents might be expected to do better than patients on either agent alone. However, if the 2 drugs have similar mechanisms of action, then additive benefit would not be expected. Another possibility is that one drug might antagonize the effects of the other, resulting in reduced benefit from the combination.

**Post-MI.** Early work concerning the nature of the interaction in ischemic heart disease, using data from the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) studies in post-MI patients, suggested not only lack of additive benefit, but also the possibility of a negative effect on mortality from the combination of aspirin and ACE inhibition. A large-scale meta-analysis of patients after acute MI failed to confirm an adverse interaction, with evidence of significant benefit from ACE inhibition in patients taking and not taking aspirin.<sup>147</sup> However, the point estimate for the reduction in mortality in patients taking the combination of aspirin and ACE inhibition, whereas not statistically less than for aspirin alone, was lower, providing no support for additive benefit from the 2 drugs.

**Heart Failure.** A retrospective cohort analysis of the SOLVD study found that patients on antiplatelet therapy (assumed to be aspirin in the great majority of cases) derived no additional survival benefit from the addition of enalapril.<sup>146</sup> Other studies have shown no clear evidence of harm from the combination of aspirin and ACE inhibitors in patients with HF.<sup>148</sup>

**Relationship to Dose.** There is also some evidence that the potential interaction between aspirin and ACE inhibitor may be dose-related. A meta-analysis of all hypertension and HF patients who have received both aspirin and ACE inhibitors suggests that aspirin at doses  $\leq 100$  mg did not interact with ACE inhibitors.<sup>149</sup> Any interaction, if

observed, occurred at higher doses of aspirin. A more recent meta-analysis could not confirm or exclude a modest effect of aspirin on the benefits of ACE inhibitors.<sup>147</sup>

A potential mechanism for the hypothesized adverse interaction between aspirin and ACE inhibitors in patients with HF involves prostaglandin synthesis. ACE inhibition is felt to augment bradykinin, which in turn stimulates the synthesis of various prostaglandins that may contribute vasodilatory and other salutary effects. In the presence of aspirin, the bradykinin-induced increase in prostaglandins should be attenuated or blocked, potentially reducing the benefits of ACE inhibition. Invasive hemodynamic monitoring has demonstrated that the acute hemodynamic effect of enalapril is blunted by concomitant administration of aspirin.<sup>150</sup> Another possibility is that aspirin and ACE inhibitors act in a similar fashion in HF so that no added benefit is gained from the combination. ACE inhibitors appear to reduce ischemic events in HF patients possibly through antithrombotic effects, which could mimic those of antiplatelet agents. Recent study results suggesting that aspirin may have independent beneficial action on ventricular remodeling support the hypothesis of similar mechanisms of action for ACE inhibitors and aspirin.<sup>151</sup>

Development of the adenosine diphosphate antagonists, ticlopidine and clopidogrel, provide alternative therapy for platelet inhibition that does not appear to influence prostaglandin synthesis.<sup>152</sup> In direct comparison with aspirin, large-scale clinical trial results have established the efficacy of clopidogrel in the prevention of vascular events in patients with arteriosclerotic disease.<sup>153</sup> In WATCH, there were no statistically significant differences in death, MI, or stroke for warfarin versus aspirin, for clopidogrel versus aspirin, or for warfarin versus clopidogrel.<sup>140</sup> A hemodynamic study found a similar reduction in systemic vascular resistance in HF patients treated with the combination of ACE inhibitor and ticlopidine versus ACE inhibitor alone, suggesting no adverse hemodynamic interaction between ACE inhibition and this type of antiplatelet compound.<sup>154</sup> Definitive resolution of the therapeutic implications of the aspirin-ACE inhibitor interaction and determination of alternative therapy, if any, in HF awaits the results of additional studies.

## Amiodarone Therapy

### Recommendation

**7.37 Antiarrhythmic agents, including amiodarone, are not recommended for the primary prevention of sudden death in patients with HF. (Strength of Evidence = A)**

### Background

Ventricular arrhythmias are common in HF patients, and sudden cardiac death continues to account for a significant proportion of the mortality in this syndrome. Sudden death

in HF may arise from a variety of causes, including bradyarrhythmias, conduction disturbances, electromechanical dissociation, acute MI, or pulmonary embolus. However, the majority of these deaths are thought to be due to ventricular tachyarrhythmias. Therefore, there has been considerable interest in the potential role of antiarrhythmic drug therapy in patients with HF.<sup>155</sup> Randomized, placebo controlled trials of antiarrhythmic drug therapy for ventricular arrhythmias or atrial fibrillation has not been shown to improve survival in HF.<sup>5,155–157</sup> The frequency of ambient ventricular ectopic activity is a marker for disease severity. Suppression of ventricular ectopy with amiodarone does not improve survival.<sup>155,157</sup> Many antiarrhythmic drugs have adverse hemodynamic effects sufficient to have negative consequences in patients with HF. Patients with HF are at higher risk for proarrhythmic effects of antiarrhythmic agents. The major role for the use of these agents in HF is to reduce recurrences of symptomatic arrhythmias, usually in patients who have an implanted cardioverter defibrillator (ICD).<sup>158</sup>

Amiodarone blocks multiple cardiac ionic currents and has activity against ventricular and atrial arrhythmias, as well as slowing the sinus rate and the ventricular response to atrial fibrillation. Bradycardia is the major proarrhythmic effect, but the potential for multiple noncardiac toxicities (pulmonary, thyroid, liver, neurologic) require ongoing monitoring, and multiple potential drug interactions often require consideration. Amiodarone therapy has not been shown to improve mortality in randomized placebo controlled trials.<sup>155,157</sup> The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) tested the hypothesis that either amiodarone or an ICD, or both, improve survival compared with placebo in patients with NYHA Class II or III HF and LVEF <35% of ischemic or nonischemic etiology.<sup>155</sup> A total of 2521 patients were randomly assigned to ICD, amiodarone, or placebo. The patients were well treated: 87% were on ACE inhibitors or ARBs and 78% were on beta blockers at last follow-up. ICD, but not amiodarone improved mortality compared to placebo (Section 9).

Amiodarone was compared to placebo in a smaller double-blind, randomized trial that enrolled 674 patients with a mean age of 66 years. The majority (56%) had NYHA class II symptoms, and their mean LVEF = 26%.<sup>157</sup> No differences were observed in all-cause or cardiac mortality or sudden death rates between the amiodarone and placebo groups. Another small randomized trial did suggest a beneficial effect of amiodarone, but there were significant limitations in the design and conduct of this trial. Treatment assignment was randomized, but not double-blind or placebo-controlled. The trial was discontinued prematurely when a 28% reduction was observed in all-cause mortality, the primary endpoint. Although not strictly involving HF patients, 2 post-MI trials found no benefit of amiodarone on mortality.<sup>159,160</sup>

A retrospective analysis of the COMET trial evaluated mortality among patients receiving amiodarone at baseline.<sup>161</sup> Patients who were treated with amiodarone at baseline had a higher risk of death due to circulatory failure

during follow-up than those who did not receive amiodarone, irrespective of functional class (HR 2.4, 95% CI 1.9–3.1,  $P < .001$ ). Amiodarone was not associated with an increased risk of sudden death in this analysis.<sup>161</sup>

Amiodarone has significant long term toxicities, including lung, liver, and thyroid toxicity such that periodic monitoring is required during long term therapy. The most common cardiac adverse effect is bradycardia which can be potentiated by beta-adrenergic blockers. Bradycardia may also increase RV pacing from defibrillators which may have an adverse hemodynamic effect in some patients. Whether these effects contributed to the increased mortality observed in the subgroup of patients with more severe (NYHA Class III) HF in SCD-HeFT is not known.

Therapy with Vaughn Williams Class I drugs (quinidine, disopyramide, mexiletine, flecainide, propafenone) should be avoided. Flecainide has been shown to increase mortality when administered to patients with prior MI.<sup>162</sup> These agents have been linked to increased mortality in HF patients with atrial fibrillation.<sup>163</sup> Potential adverse effects can include a negative inotropic effect of sodium channel blockade and proarrhythmic effects. The Class III potassium channel blocking agents sotalol and dofetilide have not been shown to improve mortality in HF and are associated with a risk of proarrhythmia (most often the polymorphic ventricular tachycardia torsade de pointes, associated with QT prolongation). Impaired renal function that reduces excretion of these drugs and diuretic induced hypokalemia increase the proarrhythmia risk. The d-isomer of sotalol (d-sotalol) increased mortality in survivors of MI.<sup>164</sup> A randomized trial of dofetilide in patients with ventricular dysfunction found no benefit on mortality, although hospitalizations were reduced, possibly due to decreased atrial fibrillation.<sup>165</sup> A significant incidence of torsade de points was noted, despite precautions to exclude patients with renal insufficiency and other risk factors for QT prolongation.

Dronedarone blocks multiple cardiac ionic currents, and it has been shown to have activity to reduce atrial fibrillation and to reduce the ventricular response in atrial fibrillation when it recurs. Efficacy appears to be less than for amiodarone.<sup>166</sup> It reduces tubular secretion of creatinine, increasing serum creatinine. A study in patients with HF and LVEF  $< 35\%$  was terminated early due to a two fold increased mortality in patients treated with dronedarone.<sup>167</sup> The FDA approval states that dronedarone is contraindicated in patients with Class IV HF or those with Class II or III HF who have had a recent HF decompensation.

## Recommendations

- 7.38 In patients with HF and an ICD, amiodarone may be considered to reduce the frequency of recurrent symptomatic arrhythmias causing ICD shocks. (Strength of Evidence = C)**
- 7.39 It is recommended that when amiodarone therapy is initiated, the potential for interactions with other**

**drugs be reviewed. The maintenance doses of digoxin, warfarin, and some statins should be reduced when amiodarone is initiated and then carefully monitored. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended. (Strength of Evidence = A)**

- 7.40 Routine use of amiodarone therapy for asymptomatic arrhythmias that are not felt to contribute to HF or ventricular dysfunction is not recommended. (Strength of Evidence = B)**

## Background

Amiodarone therapy modifies the pharmacokinetics of a number of drugs commonly used in patients with HF. In particular, it may substantially enhance the actions of digoxin and warfarin, with the definite potential of adverse clinical consequences. In general, the digoxin dose should be reduced by half, but follow-up determination of SDC is desirable to ensure a concentration of 0.5-0.9 ng/mL. The warfarin dose should be adjusted to maintain the INR target for the individual patient. Even after amiodarone is discontinued, these pharmacokinetic interactions can persist for months due to its long half-life. Since amiodarone also has beta-blocking properties, substantial bradycardia may occur with this combination of drugs. Amiodarone is not recommended for asymptomatic arrhythmias or those not causing HF due to the multiple drug-drug interactions and the serious side effect profile.

## Polyunsaturated Fatty Acids

### Recommendation

- 7.41 n-3 polyunsaturated fatty acids (PUFA) may be considered to reduce mortality in HF patients with NYHA class II-IV symptoms and reduced LVEF. (Strength of Evidence = B)**

### Background

n-3 polyunsaturated fatty acids (PUFA) have been associated with lower mortality after MI, primarily from a reduction in sudden cardiac death.<sup>168</sup> In the GISSI-Prevenzione trial, 3-year treatment with low-dose n-3 PUFA was associated with a significant reduction of total mortality (21%) in patients who survived a recent MI. In the published design paper for the subsequent GISSI-HF trial, the authors described the results of an unpublished, post-hoc analysis of the GISSI-Prevenzione trial, showing that in nearly 2000 post-infarction patients with LV dysfunction enrolled in the trial, the effects of n-3 PUFA on all-cause and sudden mortality were similar to those observed in the overall trial population.<sup>169</sup> A single randomized controlled trial, the Italian GISSI-HF trial, has been conducted with n-3 PUFA in the HF population.<sup>170</sup> Patients with NYHA Class II–IV symptoms and LVEF  $< 40\%$  were

enrolled. Patients with LVEF  $\geq 40\%$  were also eligible, provided they had been hospitalized for HF at least once in the preceding year (accounted for 9% of the total population). Patients were randomized to either 1 g/day of PUFA (850–882 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the average ratio of 1:1.2) or matching placebo. The primary endpoints were time to death, and time to death or cardiovascular hospitalization. A total of 3494 patients were enrolled in the n-3 PUFA group and 3481 in the placebo group. All cause mortality was 27% in the n-3 PUFA group and 29% in the placebo group (adjusted HR 0.91, 95.5% CI 0.833–0.998,  $P=0.041$ ). All-cause death or cardiovascular hospitalization occurred in 57% of the n-3 PUFA treated patients and 59% of the placebo group (adjusted HR 0.92, 99% CI 0.849–0.999,  $P=0.009$ ). Patients were receiving standard medical therapy for HF, with 93% on ACE-inhibitors or ARBs, 65% on beta blockers, and approximately 40% on spironolactone. N-3 PUFA was generally well tolerated, with gastrointestinal complaints being the most commonly reported adverse effect in both groups.<sup>170</sup> The therapy is not widely adopted, but it may be considered as an adjunctive therapy in patients with chronic HF.

## References

- Packer M, Cohn J. Consensus recommendations for the management of chronic heart failure. On behalf of the membership of the advisory council to improve outcomes nationwide in heart failure. *Am J Cardiol* 1999;83:1A–38A.
- The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429–35.
- The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302.
- Konstam MA, Kronenberg MW, Rousseau MF, Udelson JE, Melin J, Stewart D, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. *Circulation* 1993;88:2277–83.
- Frances CD, Noguchi H, Massie BM, Browner WS, McClellan M. Are we inhibited? Renal insufficiency should not preclude the use of ACE inhibitors for patients with myocardial infarction and depressed left ventricular function. *Arch Intern Med* 2000;160:2645–50.
- Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009; 53:e1–e90.
- Petrie MC, Padmanabhan N, McDonald JE, Hillier C, Connell JM, McMurray JJ. Angiotensin converting enzyme (ACE) and non-ACE dependent angiotensin II generation in resistance arteries from patients with heart failure and coronary heart disease. *J Am Coll Cardiol* 2001;37:1056–61.
- Wolny A, Clozel JP, Rein J, Mory P, Vogt P, Turino M, et al. Functional and biochemical analysis of angiotensin II-forming pathways in the human heart. *Circ Res* 1997;80:219–27.
- Jorde UP, Ennezat PV, Lisker J, Suryadevara V, Infeld J, Cukon S, et al. Maximally recommended doses of angiotensin-converting enzyme (ACE) inhibitors do not completely prevent ACE-mediated formation of angiotensin II in chronic heart failure. *Circulation* 2000; 101:844–6.
- Kawamura M, Imanashi M, Matsushima Y, Ito K, Hiramori K. Circulating angiotensin II levels under repeated administration of lisinopril in normal subjects. *Clin Exp Pharmacol Physiol* 1992;19: 547–53.
- Wetherow FN, Helmy A, Webb DJ, Fox KA, Newby DE. Bradykinin contributes to the vasodilator effects of chronic angiotensin-converting enzyme inhibition in patients with heart failure. *Circulation* 2001;104:2177–81.
- Wetherow FN, Dawson P, Ludlam CA, Fox KA, Newby DE. Marked bradykinin-induced tissue plasminogen activator release in patients with heart failure maintained on long-term angiotensin-converting enzyme inhibitor therapy. *J Am Coll Cardiol* 2002;40:961–6.
- Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;362:772–6.
- Stecker EC, Fendrick AM, Knight BP, Aaronson KD. Prophylactic pacemaker use to allow beta-blocker therapy in patients with chronic heart failure with bradycardia. *Am Heart J* 2006;151:820–8.
- Cohn JN, Tognoni G. Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *New England Journal of Medicine* 2001;345: 1667–75.
- Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *New England Journal of Medicine* 2003;349:1893–906.
- Dickstein K, Kjekshus J. OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan*. *Lancet* 2002;360:752–60.
- Gring CN, Francis GS. A hard look at angiotensin receptor blockers in heart failure. *J Am Coll Cardiol* 2004;44:1841–6.
- Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SR. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Intern Med* 2004;141:693–704.
- McClellan MB, Loeb JM, Clancy CM, Francis GS, Jacobs AK, Kizer KW, et al. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers in chronic heart failure. *Ann Intern Med* 2005;142:386–7.
- Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet* 1993;342:1441–6.
- Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 1997;30:27–34.
- Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;98:1184–91.
- CIBIS II Investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9–13.
- MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001–7.

26. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;334:1349–55.
27. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;106:2194–9.
28. Flather MD, Shibata MC, Coats AJ, van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;26:215–25.
29. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet* 1990;336:1–6.
30. Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation* 2005;112:2426–35.
31. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685–91.
32. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986;73:503–10.
33. Vantrimpont P, Rouleau JL, Wun CC, Ciampi A, Klein M, Sussex B, et al. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. SAVE Investigators. *J Am Coll Cardiol* 1997;29:229–36.
34. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;357:1385–90.
35. Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *J Am Coll Cardiol* 1995;25:1154–61.
36. Lowes BD, Gill EA, Abraham WT, Larrain JR, Robertson AD, Bristow MR, et al. Effects of carvedilol on left ventricular mass, chamber geometry, and mitral regurgitation in chronic heart failure. *Am J Cardiol* 1999;83:1201–5.
37. Waagstein F, Stromblad O, Andersson B, Bohm M, Darius M, Delius W, et al. Increased exercise ejection fraction and reversed remodeling after long-term treatment with metoprolol in congestive heart failure: a randomized, stratified, double-blind, placebo-controlled trial in mild to moderate heart failure due to ischemic or idiopathic dilated cardiomyopathy. *Eur J Heart Fail* 2003;5:679–91.
38. Dubach P, Myers J, Bonetti P, Schertler T, Froelicher V, Wagner D, et al. Effects of bisoprolol fumarate on left ventricular size, function, and exercise capacity in patients with heart failure: analysis with magnetic resonance myocardial tagging. *Am Heart J* 2002;143:676–83.
39. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *J Am Coll Cardiol* 2004;43:1534–41.
40. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Carvedilol use at discharge in patients hospitalized for heart failure is associated with improved survival: an analysis from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2007;153. 82.e1–82.e11.
41. Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *Am J Cardiol* 2001;87:819–22.
42. Lappe JM, Muhlestein JB, Lappe DL, Badger RS, Bair TL, Brockman R, et al. Improvements in 1-year cardiovascular clinical outcomes associated with a hospital-based discharge medication program. *Ann Intern Med* 2004;141:446–53.
43. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651–8.
44. Deedwania PC, Giles TD, Klibaner M, Ghali JK, Herlitz J, Hildebrandt P, et al. Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J* 2005;149:159–67.
45. Nodari S, Metra M, Dei CA, Dei CL. Efficacy and tolerability of the long-term administration of carvedilol in patients with chronic heart failure with and without concomitant diabetes mellitus. *Eur J Heart Fail* 2003;5:803–9.
46. Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007;49:171–80.
47. Paravastu SC, Mendonca D, Da SA. Beta blockers for peripheral arterial disease. *Cochrane Database Syst Rev* 2008;. CD005508.
48. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet* 2008;372:817–21.
49. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. *Am J Cardiol* 2008;101:865–9.
50. Cucherat M. Quantitative relationship between resting heart rate reduction and magnitude of clinical benefits in post-myocardial infarction: a meta-regression of randomized clinical trials. *Eur Heart J* 2007;28:3012–9.
51. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 2009;150:784–94.
52. Abraham WT, Iyengar S. Practical considerations for switching beta-blockers in heart failure patients. *Rev Cardiovasc Med* 2004;5(Suppl 1):S36–44.
53. Gattis WA, O'Connor CM, Leimberger JD, Felker GM, Adams KF, Gheorghiade M. Clinical outcomes in patients on beta-blocker therapy admitted with worsening chronic heart failure. *Am J Cardiol* 2003;91:169–74.
54. Butler J, Young JB, Abraham WT, Bourge RC, Adams KF Jr, Clare R, et al. Beta-blocker use and outcomes among hospitalized heart failure patients. *J Am Coll Cardiol* 2006;47:2462–9.
55. Metra M, Torp-Pedersen C, Cleland JG, Di LA, Komajda M, Remme WJ, et al. Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. *Eur J Heart Fail* 2007;9:901–9.
56. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. *J Am Coll Cardiol* 2008;52:190–9.
57. Jondeau G, Neuder Y, Eicher JC, Jourdain P, Fauveau E, Galinier M, et al. B-CONVINCED: Beta-blocker CONTinuation Vs. INTerruption in patients with Congestive heart failure hospitalized for a decompensation episode. *Eur Heart J* 2009;30:2186–92.
58. Morimoto S, Shimizu K, Yamada K, Hiramitsu S, Hishida H. Can beta-blocker therapy be withdrawn from patients with dilated cardiomyopathy? *Am Heart J* 1999;138:456–9.
59. Waagstein F, Caidahl K, Wallentin I, Bergh CH, Hjalmarson A. Long-term beta-blockade in dilated cardiomyopathy. Effects of short- and long-term metoprolol treatment followed by withdrawal and re-administration of metoprolol. *Circulation* 1989;80:551–63.

60. Uretsky BF, Pina I, Quigg RJ, Brill JV, MacInerney EJ, Mintzer R, et al. Beyond drug therapy: nonpharmacologic care of the patient with advanced heart failure. *Am Heart J* 1998;135:S264–84.
61. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;288:3115–23.
62. Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. *Circulation* 1981;63:645–51.
63. Duprez DA, De Buyzere ML, Rietzschel ER, Taes Y, Clement DL, Morgan D, et al. Inverse relationship between aldosterone and large artery compliance in chronically treated heart failure patients. *Eur Heart J* 1998;19:1371–6.
64. Wang W. Chronic administration of aldosterone depresses baroreceptor reflex function in the dog. *Hypertension* 1994;24:571–5.
65. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991;83:1849–65.
66. Okubo S, Niimura F, Nishimura H, Takemoto F, Fogo A, Matsusaka T, et al. Angiotensin-independent mechanism for aldosterone synthesis during chronic extracellular fluid volume depletion. *J Clin Invest* 1997;99:855–60.
67. Struthers AD. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. *J Card Fail* 1996;2:47–54.
68. Pitt B, Zannad F, Remme WJ. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709–17.
69. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–21.
70. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;351:543–51.
71. Pitt B, White H, Nicolau J, Martinez F, Gheorghide M, Aschermann M, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005;46:425–31.
72. Pitt B, Bakris G, Ruilope LM, DiCarlo L, Mukherjee R. Serum potassium and clinical outcomes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). *Circulation* 2008;118:1643–50.
73. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. *Eur Heart J* 2009;30:469–77.
74. Hayashi M, Tsutamoto T, Wada A, Tsutsui T, Ishii C, Ohno K, et al. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. *Circulation* 2003;107:2559–65.
75. Iraqi W, Rossignol P, Angioi M, Fay R, Nuee J, Ketelslegers JM, et al. Extracellular cardiac matrix biomarkers in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study. *Circulation* 2009;119:2471–9.
76. Seed A, Gardner R, McMurray J, Hillier C, Murdoch D, MacFadyen R, et al. Neurohumoral effects of the new orally active renin inhibitor, aliskiren, in chronic heart failure. *Eur J Heart Fail* 2007;9:1120–7.
77. Recio-Mayoral A, Kaski JC, McMurray JJ, Horowitz J, van Veldhuisen DJ, Remme WJ. Clinical trials update from the European Society of Cardiology Congress in Vienna, 2007: PROSPECT, EVEREST, ARISE, ALOFT, FINESSE, Prague-8, CARESS in MI and ACUITY. *Cardiovasc Drugs Ther* 2007;21:459–65.
78. Cleland JG, Abdellah AT, Khaleva O, Coletta AP, Clark AL. Clinical trials update from the European Society of Cardiology Congress 2007: 3CPO, ALOFT, PROSPECT and statins for heart failure. *Eur J Heart Fail* 2007;9:1070–3.
79. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;314:1547–52.
80. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303–10.
81. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;351:2049–57.
82. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767–71.
83. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. *Circulation* 1999;100:1311–5.
84. Domanski M, Norman J, Pitt B. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 2003;42:705–8.
85. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002;82:149–58.
86. Grinstead WC, Francis MJ, Marks GF, Tawa CB, Zoghbi WA, Young JB. Discontinuation of chronic diuretic therapy in stable congestive heart failure secondary to coronary artery disease or to idiopathic dilated cardiomyopathy. *Am J Cardiol* 1994;73:881–6.
87. Boccellini A, Zachara E, Liberatore SM, Carboni GP, Prati PL. Addition of captopril versus increasing diuretics in moderate but deteriorating heart failure: a double-blind comparative trial. *Postgrad Med J* 1986;62(Suppl. 1):184–7.
88. Richardson A, Bayliss J, Scriven AJ, Parameshwar J, Poole-Wilson PA, Sutton GC. Double-blind comparison of captopril alone against frusemide plus amiloride in mild heart failure. *Lancet* 1987;2:709–11.
89. Packer M, Lee WH, Medina N, Yushak M, Kessler PD. Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. *Ann Intern Med* 1987;106:346–54.
90. Cody RJ, Franklin KW, Laragh JH. Postural hypotension during tilt with chronic captopril and diuretic therapy of severe congestive heart failure. *Am Heart J* 1982;103:480–4.
91. Brater DC. Diuretic therapy. *N Engl J Med* 1998;339:387–95.
92. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;29:2388–442.
93. Adams KF Jr, Gheorghide M, Uretsky BF, Patterson JH, Schwartz TA, Young JB. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002;39:946–53.
94. Gheorghide M, Hall VB, Jacobsen G, Alam M, Rosman H, Goldstein S. Effects of increasing maintenance dose of digoxin on left ventricular function and neurohormones in patients with chronic heart failure treated with diuretics and angiotensin-converting enzyme inhibitors. *Circulation* 1995;92:1801–7.
95. Gheorghide M, Pitt B. Digitalis Investigation Group (DIG) trial: a stimulus for further research. *Am Heart J* 1997;134:3–12.

96. Packer M, Gheorghide M, Young JB, Costantini PJ, Adams KF, Cody RJ, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med* 1993;329:1–7.
97. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525–33.
98. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol* 1993;22:955–62.
99. Young JB, Gheorghide M, Uretsky BF, Patterson JH, Adams KF Jr. Superiority of "triple" drug therapy in heart failure: insights from the PROVED and RADIANCE trials. Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin. Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme. *J Am Coll Cardiol* 1998;32:686–92.
100. Gheorghide M, Ferguson D. Digoxin. A neurohormonal modulator in heart failure? *Circulation* 1991;84:2181–6.
101. Krum H, Bigger JT Jr, Goldsmith RL, Packer M. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. *J Am Coll Cardiol* 1995;25:289–94.
102. Ferguson DW, Berg WJ, Sanders JS, Roach PJ, Kempf JS, Kienzle MG. Sympathoinhibitory responses to digitalis glycosides in heart failure patients. Direct evidence from sympathetic neural recordings. *Circulation* 1989;80:65–77.
103. Newton GE, Tong JH, Schofield AM, Baines AD, Floras JS, Parker JD. Digoxin reduces cardiac sympathetic activity in severe congestive heart failure. *J Am Coll Cardiol* 1996;28:155–61.
104. Dhaliwal AS, Bredikis A, Habib G, Carabello BA, Ramasubbu K, Bozkurt B. Digoxin and clinical outcomes in systolic heart failure patients on contemporary background heart failure therapy. *Am J Cardiol* 2008;102:1356–60.
105. van Veldhuisen DJ, de Boer RA. Low-dose digoxin in heart failure. *Int J Cardiol* 2009;136:90–1.
106. Adams KF Jr, Patterson J, Gattis WA, O'Connor C, Schwartz T, Gheorghide M. Favorable effects of digoxin on mortality and morbidity in patients with class IV congestive heart failure due to systolic dysfunction: retrospective analysis of the DIG study [abstract]. *J Am Coll Cardiol* 2003;41:164A.
107. Adams KF Jr, Gheorghide M, Uretsky BF, Young JB, Ahmed S, Tomasko L, et al. Patients with mild heart failure worsen during withdrawal from digoxin therapy. *J Am Coll Cardiol* 1997;30:42–8.
108. Slatton ML, Irani WN, Hall SA, Marcoux LG, Page RL, Grayburn PA, et al. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? *J Am Coll Cardiol* 1997;29:1206–13.
109. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003;289:871–8.
110. Bauman JL, DiDomenico RJ, Viana M, Fitch M. A method of determining the dose of digoxin for heart failure in the modern era. *Arch Intern Med* 2006;166:2539–45.
111. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825–33.
112. Yamamoto K, Ikeda U, Furuhashi K, Irokawa M, Nakayama T, Shimada K. The coagulation system is activated in idiopathic cardiomyopathy. *J Am Coll Cardiol* 1995;25:1634–40.
113. Sbarouni E, Bradshaw A, Andreotti F, Tuddenham E, Oakley CM, Cleland JG. Relationship between hemostatic abnormalities and neuroendocrine activity in heart failure. *Am Heart J* 1994;127:607–12.
114. Jafri SM, Ozawa T, Mammen E, Levine TB, Johnson C, Goldstein S. Platelet function, thrombin and fibrinolytic activity in patients with heart failure. *Eur Heart J* 1993;14:205–12.
115. Kyrle PA, Korninger C, Gossinger H, Glogar D, Lechner K, Niessner H, et al. Prevention of arterial and pulmonary embolism by oral anticoagulants in patients with dilated cardiomyopathy. *Thromb Haemost* 1985;54:521–3.
116. Ciaccheri M, Castelli G, Cecchi F, Nannini M, Santoro G, Troiani V, et al. Lack of correlation between intracavitary thrombosis detected by cross sectional echocardiography and systemic emboli in patients with dilated cardiomyopathy. *Br Heart J* 1989;62:26–9.
117. Dunkman WB, Johnson GR, Carson PE, Bhat G, Farrell L, Cohn JN. Incidence of thromboembolic events in congestive heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;87:VI94–101.
118. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Guidelines for the evaluation and management of heart failure. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). *Circulation* 1995;92:2764–84.
119. Laupacis A, Albers G, Dalen J, Dunn MI, Jacobson AK, Singer DE. Antithrombotic therapy in atrial fibrillation. *Chest* 1998;114:579S–89S.
120. Chiarella F, Santoro E, Domenicucci S, Maggioni A, Vecchio C. Pre-discharge two-dimensional echocardiographic evaluation of left ventricular thrombosis after acute myocardial infarction in the GISSI-3 study. *Am J Cardiol* 1998;81:822–7.
121. Greaves SC, Zhi G, Lee RT, Solomon SD, MacFadyen J, Rapaport E, et al. Incidence and natural history of left ventricular thrombus following anterior wall acute myocardial infarction. *Am J Cardiol* 1997;80:442–8.
122. Van Dantzig JM, Delemarre BJ, Bot H, Koster RW, Visser CA. Doppler left ventricular flow pattern versus conventional predictors of left ventricular thrombus after acute myocardial infarction. *J Am Coll Cardiol* 1995;25:1341–6.
123. Vaitkus PT, Barnathan ES. Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: a meta-analysis. *J Am Coll Cardiol* 1993;22:1004–9.
124. Behar S, Tanne D, Abinader E, Agmon J, Barzilai J, Friedman Y, et al. Cerebrovascular accident complicating acute myocardial infarction: incidence, clinical significance and short- and long-term mortality rates. The SPRINT Study Group. *Am J Med* 1991;91:45–50.
125. Komrad MS, Coffey CE, Coffey KS, McKinnis R, Massey EW, Califf RM. Myocardial infarction and stroke. *Neurology* 1984;34:1403–9.
126. Harrington RA, Becker RC, Ezekowitz M, Meade TW, O'Connor CM, Vorchheimer DA, et al. Antithrombotic therapy for coronary artery disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:513S–48S.
127. Dries DL, Rosenberg YD, Waclawiw MA, Domanski MJ. Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence for gender differences in the studies of left ventricular dysfunction trials. *J Am Coll Cardiol* 1997;29:1074–80.
128. Loh E, Sutton MS, Wun CC, Rouleau JL, Flaker GC, Gottlieb SS, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med* 1997;336:251–7.
129. Natterson PD, Stevenson WG, Saxon LA, Middlekauff HR, Stevenson LW. Risk of arterial embolization in 224 patients awaiting cardiac transplantation. *Am Heart J* 1995;129:564–70.
130. Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981;47:525–31.
131. de Boer RA, Hillege HL, Tjeerdsma G, Verheugt FW, van Veldhuisen DJ. Both antiplatelet and anticoagulant therapy may favorably affect outcome in patients with advanced heart failure. A retrospective analysis of the PRIME-II trial. *Thromb Res* 2005;116:279–85.
132. Echemann M, Alla F, Briancon S, Juilliere Y, Virion JM, Mertes PM, et al. Antithrombotic therapy is associated with better survival in patients with severe heart failure and left ventricular systolic dysfunction (EPICAL study). *Eur J Heart Fail* 2002;4:647–54.

133. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669–77.
134. Cioffi G, Pozzoli M, Forni G, Franchini M, Opasich C, Cobelli F, et al. Systemic thromboembolism in chronic heart failure. A prospective study in 406 patients. *Eur Heart J* 1996;17:1381–9.
135. Baker DW, Wright RF. Management of heart failure. IV. Anticoagulation for patients with heart failure due to left ventricular systolic dysfunction. *JAMA* 1994;272:1614–8.
136. Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Warfarin anticoagulation and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol* 1998;31:749–53.
137. Dries DL, Domanski MJ, Waclawiw MA, Gersh BJ. Effect of antithrombotic therapy on risk of sudden coronary death in patients with congestive heart failure. *Am J Cardiol* 1997;79:909–13.
138. Lip GY, Gibbs CR. Antiplatelet agents versus control or anticoagulation for heart failure in sinus rhythm: a Cochrane systematic review. *QJM* 2002;95:461–8.
139. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004;148:157–64.
140. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation* 2009;119:1616–24.
141. Crawford TC, Smith WT, Velazquez EJ, Taylor SM, Jollis JG, Kisslo J. Prognostic usefulness of left ventricular thrombus by echocardiography in dilated cardiomyopathy in predicting stroke, transient ischemic attack, and death. *Am J Cardiol* 2004;93:500–3.
142. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;2:349–60.
143. Collaborative overview of randomised trials of antiplatelet therapy— I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994;308:81–106.
144. Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, Holder DA, et al. Aspirin, sulfipyrazone, or both in unstable angina. Results of a Canadian multicenter trial. *N Engl J Med* 1985;313:1369–75.
145. Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. *N Engl J Med* 1997;336:847–60.
146. Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Antiplatelet agents and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trial. *J Am Coll Cardiol* 1998;31:419–25.
147. Teo KK, Yusuf S, Pfeffer M, Torp-Pedersen C, Kober L, Hall A, et al. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet* 2002;360:1037–43.
148. McAlister FA, Ghali WA, Gong Y, Fang J, Armstrong PW, Tu JV. Aspirin use and outcomes in a community-based cohort of 7352 patients discharged after first hospitalization for heart failure. *Circulation* 2006;113:2572–8.
149. Nawarskas JJ, Spinler SA. Does aspirin interfere with the therapeutic efficacy of angiotensin-converting enzyme inhibitors in hypertension or congestive heart failure? *Pharmacotherapy* 1998;18:1041–52.
150. Hall D, Zeitler H, Rudolph W. Counteraction of the vasodilator effects of enalapril by aspirin in severe heart failure. *J Am Coll Cardiol* 1992;20:1549–55.
151. Oosterga M, Anthonio RL, de Kam PJ, Kingma JH, Crijs HJ, van Gilst WH. Effects of aspirin on angiotensin-converting enzyme inhibition and left ventricular dilation one year after acute myocardial infarction. *Am J Cardiol* 1998;81:1178–81.
152. Sharis PJ, Cannon CP, Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998;129:394–405.
153. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348:1329–39.
154. Spaulding C, Charbonnier B, Cohen-Solal A, Juilliere Y, Kromer EP, Benhamda K, et al. Acute hemodynamic interaction of aspirin and ticlopidine with enalapril: results of a double-blind, randomized comparative trial. *Circulation* 1998;98:757–65.
155. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.
156. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;358:2667–77.
157. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995;333:77–82.
158. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA* 2006;295:165–71.
159. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. *Lancet* 1997;349:675–82.
160. Julian DG, Camm AJ, Frangin G, Janse MJ, Munoz A, Schwartz PJ, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarction Amiodarone Trial Investigators. *Lancet* 1997;349:667–74.
161. Torp-Pedersen C, Metra M, Spark P, Lukas MA, Moullet C, Scherhag A, et al. The safety of amiodarone in patients with heart failure. *J Card Fail* 2007;13:340–5.
162. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406–12.
163. Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 1992;20:527–32.
164. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. *Lancet* 1996;348:7–12.
165. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, Kober L, Sandoe E, Egstrup K, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med* 1999;341:857–65.
166. Piccini JP, Hasselblad V, Peterson ED, Washam JB, Califf RM, Kong DF. Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol* 2009;54:1089–95.
167. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijs H, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;358:2678–87.
168. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty

- acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. [erratum appears in *Lancet* 2001;357:642]. *Lancet* 1999;354:447–455.
169. Tavazzi L, Tognoni G, Franzosi MG, Latini R, Maggioni AP, Marchioli R, et al. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. *Eur J Heart Fail* 2004;6:635–41.
  170. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372:1223–30.
  171. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747–52.
  172. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999;100:2312–8.
  173. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;362:759–66.
  174. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009;374:1840–8.