

Narrative Review: Pharmacotherapy for Chronic Heart Failure: Evidence from Recent Clinical Trials

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Heart failure is an important cause of morbidity and mortality. Clinical trials over the past 2 decades have revolutionized the care of patients with systolic heart failure, and substantial data support the use of angiotensin-converting enzyme inhibitors, β -blockers, angiotensin-receptor blockers, and aldosterone blockers in the management of this serious condition. This article reviews the

evidence on the pharmacologic treatment of heart failure, with a focus on recent clinical trials.

Ann Intern Med. 2005;142:132-145.

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Heart failure is a leading cause of death and hospitalization in the developed world (1), and its prevalence is expected to increase as the population ages (2). The goals of treatment of heart failure are to prolong survival, relieve symptoms and improve quality of life, and prevent hospitalization and progression of disease.

Several landmark randomized clinical trials were recently completed. Our objective is to provide a concise, up-to-date summary of the available evidence for the busy clinician caring for patients with heart failure. Although other novel treatments have demonstrated efficacy (3–9), we focus on pharmacologic therapy for chronic systolic heart failure. Recent excellent reviews have been published on management of diastolic heart failure (10, 11) and acute decompensated heart failure (12). Of note, heart failure is a chronic and progressive disorder that can be conceptually classified into various stages (13). Thus, patients who have structural heart disease but have not yet manifested symptoms of heart failure should be considered as having the disease in an early stage (13). Clinical trials have established the efficacy of certain pharmacologic therapies among these asymptomatic patients.

METHODS

We searched the MEDLINE database by using the Medical Subject Heading term *heart failure, congestive*, with the subheading *drug therapy*. We limited the search to English-language articles on human research that were published between 1990 and August 2004. The search yielded 4007 citations. Additional sources of information were bibliographies of identified articles, consensus guidelines (13–15), Cochrane databases, and Internet searches. Whenever possible, we gathered data from large-scale randomized trials with clinically important end points (death and hospitalization) because these studies have the most rigorous designs and provide the most useful information.

DIURETICS

Strong clinical consensus (13–15) indicates that diuretics should be used to treat volume overload. A meta-

analysis of several small trials also suggests that use of diuretics reduces the risk for death and worsening heart failure (16). However, the use of non-potassium-sparing diuretics was independently associated with worse outcomes, possibly owing to electrolyte depletion (17). Diuretics should not be used alone to manage heart failure (13–15). The dose should be carefully tailored to the individual patient to control fluid retention but avoid hypotension and renal failure.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The renin-angiotensin-aldosterone system is activated in chronic heart failure, and its degree of activation correlates with prognosis (18). In addition to causing increases in preload and afterload, angiotensin II has direct mitogenic effects on cardiac myocytes and endothelial cells that lead to adverse ventricular remodeling.

Overwhelming evidence supports the use of angiotensin-converting enzyme (ACE) inhibitors in treating and preventing heart failure (19–24). A meta-analysis of 32 trials completed before 1995 that involved 7105 patients with heart failure concluded that ACE inhibitors reduced the total mortality rate by 23% (95% CI, 12% to 34%; $P < 0.001$) and the combined end point of death from or hospitalization for heart failure by 35% (CI, 26% to 43%; $P < 0.001$) (25). **Table 1** summarizes the results of 6 major trials that examined mortality as the primary outcome. When patients from the latter 5 trials (12 763 patients) are pooled, the groups that received an ACE inhibitor had a significantly lower risk for death (hazard ratio, 0.80 [CI, 0.74 to 0.87]; $P < 0.001$) or hospitalization for heart failure (hazard ratio, 0.67 [CI, 0.61 to 0.74]; $P < 0.001$) than

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Table 1. Major Randomized, Double-Blind, Controlled Trials of Angiotensin-Converting Enzyme Inhibitors in the Treatment of Heart Failure*

Study (Reference)	Eligibility Criteria	Patients, n	Drug Regimen†	Duration of Follow-up, mo	Primary Outcome	Main Results and Comments
Cooperative North Scandinavian Enalapril Survival Study (19)	NYHA class IV heart failure, cardiomegaly	253	Enalapril, 20 mg twice daily, vs. placebo	6	All-cause mortality	Trial terminated early; 40% reduction in overall mortality rate ($P = 0.002$), largely because of less progressive heart failure; significant improvement in functional class
Studies of Left Ventricular Dysfunction-Treatment (20)	NYHA class I-IV heart failure, LVEF ≤ 0.35	2569	Enalapril, 10 mg twice daily, vs. placebo	41	All-cause mortality	16% reduction in mortality rate (95% CI, 5%–26%; $P = 0.0036$) and fewer hospitalizations for worsening heart failure; most patients had NYHA class II or III heart failure
Studies of Left Ventricular Dysfunction-Prevention (21)	Asymptomatic left ventricular dysfunction (LVEF ≤ 0.35)	4228	Enalapril, 10 mg twice daily, vs. placebo	37	All-cause mortality	No significant difference in overall mortality; trend toward lower rate of death from cardiovascular causes in enalapril group; secondary end points were lower incidence of heart failure ($P < 0.001$) and fewer hospitalizations for heart failure ($P < 0.001$)
Survival and Ventricular Enlargement (22)‡	Acute MI within 3–16 d, LVEF ≤ 0.40 , no overt heart failure	2231	Captopril, 50 mg 3 times daily, vs. placebo	42	All-cause mortality, cardiovascular mortality and morbidity	19% reduction in overall mortality rate (95% CI, 3%–32%; $P = 0.019$); significant reduction in death from cardiovascular causes, development of heart failure, hospitalization for heart failure, and recurrent MI
Acute Infarction Ramipril Efficacy (23)‡	Acute MI within 3–10 d, clinical evidence of heart failure	2006	Ramipril, 5 mg twice daily, vs. placebo	15	All-cause mortality	27% reduction in overall mortality rate (95% CI, 11%–40%; $P = 0.002$); significant reduction in the incidence of severe heart failure, MI, and stroke
Trandolapril Cardiac Evaluation (24)‡	Acute MI within 3–7 d, LVEF ≤ 0.35	2606	Trandolapril, 4 mg once daily, vs. placebo	36	All-cause mortality	22% reduction in overall mortality rate (95% CI, 9%–33%; $P = 0.001$); lower risk for cardiovascular death, sudden death, and severe heart failure

* LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association.

† Target dose.

‡ Studies included patients with left ventricular dysfunction after MI.

did patients who received placebo (26). These benefits were seen in all subgroups, although they were greater in patients with more severe heart failure. Furthermore, long-term follow-up of these studies suggests that these benefits are sustained over many years (27–29).

Despite their proven efficacy, ACE inhibitors are often underprescribed or used in low doses (30, 31). The Assessment of Treatment with Lisinopril and Survival randomized trial showed that high doses of lisinopril (compared with low doses) significantly reduced the risk for death from or hospitalization for heart failure (32). Whenever possible, the doses prescribed should be carefully titrated upward to those used in clinical trials (Table 2) or the maximum tolerated. Angiotensin-converting enzyme inhibitors should not be given to patients with symptomatic hypotension, hyperkalemia, worsening renal failure, or bilateral renal artery stenoses. Cough, a well-known side effect of ACE inhibitors, may also be caused by uncontrolled heart failure, which requires intensification rather than withdrawal of therapy.

β -ADRENERGIC RECEPTOR BLOCKERS

Because of their negative inotropic effects, β -blockers were once thought to be absolutely contraindicated in heart failure. Activation of the sympathetic nervous system initially acts as a compensatory mechanism to maintain cardiac function, but sustained activation has detrimental consequences, including increased myocardial demand for oxygen, renal retention of sodium, and cardiac preload and afterload (18). High plasma levels of norepinephrine are correlated with worse clinical outcomes in patients with heart failure (33). In the failing heart, the β -adrenergic system is desensitized through downregulation of β -receptors and uncoupling of their signaling pathways (34). Catecholamines are directly cardiotoxic by triggering cardiomyocyte necrosis and apoptosis; β -blockade attenuates these effects (35). Furthermore, in patients with heart failure, treatment with β -blockers resulted in reverse cardiac remodeling, as indicated by significant decreases in systolic and diastolic volumes and increases in left ventricular ejection fraction (36–38).

Over the past 2 decades, multiple clinical trials have

Table 2. Drugs with Proven Efficacy in Clinical Trials*

Drug	Class	Starting Dosage	Target Dosage in Clinical Trials
Captopril	ACE inhibitor	6.25–12.5 mg 3 times daily	50 mg 3 times daily
Enalapril	ACE inhibitor	2.5–5 mg twice daily	10–20 mg twice daily
Ramipril	ACE inhibitor	2.5 mg twice daily	5 mg twice daily
Trandolapril	ACE inhibitor	1 mg/d	4 mg/d
Bisoprolol	Selective β_1 -blocker	1.25 mg/d	10 mg/d
Carvedilol	α_1 , nonselective β -blocker with antioxidant properties	3.125 mg twice daily	25 mg twice daily (50 mg twice daily for patients with body weight > 85 kg [>187 lb])
Metoprolol succinate	Selective β_1 -blocker	12.5–25 mg/d	200 mg/d
Candesartan	Angiotensin-receptor blocker	4–8 mg/d	32 mg/d
Losartan	Angiotensin-receptor blocker	12.5 mg/d	50 mg/d†
Valsartan	Angiotensin-receptor blocker	20 mg twice daily	160 mg twice daily
Eplerenone	Selective aldosterone-receptor blocker	25 mg/d	50 mg/d
Spironolactone	Aldosterone-receptor blocker	25 mg/d	25–50 mg/d‡

* ACE = angiotensin-converting enzyme.

† Consider using 50 mg twice daily if tolerated.

‡ After 8 weeks, the dose can be increased to 50 mg/d if patients showed symptoms and signs of progressive heart failure without hyperkalemia.

evaluated the effects of β -blockers in more than 10 000 patients with heart failure. Meta-analyses of early small studies showed that use of β -blockers reduced the all-cause mortality rate by approximately 32%, regardless of the cause of heart failure (39–41). Use of β -blockers also reduced the incidence of hospitalizations for heart failure and improved functional class and left ventricular ejection fraction. Subsequently, several large mortality trials have been completed (42–49). Table 3 summarizes the results of these major trials. Overall, the estimated number needed to treat for benefit to prevent 1 death in the first year is 26, even though most patients are already receiving background therapy with an ACE inhibitor (52). β -Blockers are also safe and effective in patients with advanced heart failure (53, 54). Although no clinical trial has specifically assessed the effect of β -blockers in asymptomatic patients with left ventricular systolic dysfunction, the recent Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction, which included patients without clinical heart failure who had had myocardial infarction, showed that carvedilol reduced the all-cause mortality rate by 23% (50). Therefore, current guidelines recommend that asymptomatic patients with left ventricular dysfunction be treated with β -blockers (13).

Contraindications to β -blockers include severe bronchospasm, advanced heart block, bradycardia, and hypotension. As in clinical trials, treatment with a β -blocker should be initiated at low doses, followed by gradual increases over weeks to target doses, and patients should be closely monitored (Table 3). In general, patients with recent decompensated heart failure and clear volume overload should not begin therapy with β -blockers until their volume status is optimized. Adverse effects include fatigue, worsening of heart failure, bradycardia, and hypotension. Of note, severe systolic dysfunction is frequently associated with low blood pressure. Although no universally accepted cutoff value has been established, asymptomatic but “low” blood pressure is not a contraindication to therapy with a β -blocker (or

ACE inhibitor). For example, a post hoc analysis of the Carvedilol Prospective Randomized Cumulative Survival study demonstrated that tolerance and benefit of carvedilol therapy were similar in patients with the lowest pretreatment systolic blood pressure (85 to 95 mm Hg) and those with higher blood pressure (P for interaction > 0.10) (55). Because low blood pressure identifies patients with worse outcome, the absolute benefit of treatment is also greater among these patients. Of note, clinical responses are often not apparent in the first 2 to 3 months of treatment, and transient clinical deterioration may occur in this period. No good evidence exists to guide management of decompensated heart failure in patients receiving long-term therapy with a β -blocker. Options include increasing the dose of diuretic and temporarily reducing the dose of β -blocker. If therapy with a positive inotropic agent is required, a phosphodiesterase inhibitor may be preferred (56, 57). Once the patient's condition stabilizes, therapy with the β -blocker should be reintroduced carefully, at graduated doses. It is not entirely clear whether the benefits of β -blockers represent a class effect (58–60). For example, the Beta-Blocker Evaluation of Survival Trial (48) found no benefit of therapy with bucindolol. Although therapy with carvedilol was superior to metoprolol tartrate in reducing the overall mortality rate in the Carvedilol Or Metoprolol European Trial (51), it remains controversial whether this finding was related to the dosing regimens used (short-acting metoprolol tartrate and comparative efficacies of β -blockade at the dosages given) (61–63) or differences in mechanisms of action (effect of additional α -blockade and nonselective β -blockade by carvedilol) (64). Only agents whose efficacy has been proven in mortality trials are recommended at this time (Table 2).

ANGIOTENSIN-RECEPTOR BLOCKERS

Angiotensin-receptor blockers specifically block angiotensin II type 1 receptors, which are thought to mediate

Table 3. Major Randomized, Double-Blind, Controlled Trials of β -Blockers in the Treatment of Heart Failure*

Study (Reference)	Eligibility Criteria	Patients, <i>n</i>	Drug Regimen†	Duration of Follow-up, <i>mo</i>	Primary Outcome	Main Results and Comments
Metoprolol in Dilated Cardiomyopathy (42)	Idiopathic dilated cardiomyopathy, LVEF \leq 0.40	383	Metoprolol, 100–150 mg daily (divided into twice daily or 3 times daily), vs. placebo	12–18	Death or need for heart transplantation	34% reduction in primary composite end point ($P = 0.058$) due to reduced need for heart transplantation ($P < 0.001$); 94% of patients were in NYHA class II or III
Cardiac Insufficiency Bisoprolol Study (43)	NYHA class III or IV, LVEF \leq 0.40	641	Bisoprolol, 5 mg/d, vs. placebo	23	All-cause mortality	Trend toward reduced mortality (hazard ratio, 0.80 [95% CI, 0.56–1.15]; $P > 0.2$); power was reduced because of lower than expected mortality rate and patient enrollment; bisoprolol significantly improved functional status and reduced the rate of hospitalization for heart failure
U.S. Carvedilol Heart Failure Study Group (44)	NYHA class II–IV, LVEF \leq 0.35	1094	Carvedilol, 25–50 mg twice daily, vs. placebo	6	All-cause mortality, exercise tolerance, quality of life	Trial terminated early because of significant reduction in mortality rate (hazard ratio, 0.65 [95% CI, 0.39–0.80]; $P < 0.001$); lower risk for hospitalization for cardiovascular causes
Australia/New Zealand Heart Failure Research Collaborative Group study (45)	Stable heart failure due to ischemic heart disease, current NYHA class I–III (or previous NYHA II–IV), LVEF \leq 0.45	415	Carvedilol, 25 mg twice daily, vs. placebo	12	Changes in LVEF, duration of treadmill exercise	Significant increase in LVEF and decrease in left ventricular dimensions; lower rate of death or hospital admission; no difference in functional status
Cardiac Insufficiency Bisoprolol Study–II (46)	Stable NYHA class III–IV, LVEF \leq 0.35	2647	Bisoprolol, 10 mg/d, vs. placebo	16	All-cause mortality	Trial terminated early because of significant mortality benefit (hazard ratio, 0.66 [95% CI, 0.54–0.81]; $P < 0.001$); fewer sudden deaths and hospital admissions
Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (47)	Stable NYHA class II–IV, LVEF \leq 0.40	3991	Metoprolol succinate, 200 mg/d, vs. placebo	12	All-cause mortality	Trial stopped early because of significant mortality benefit (hazard ratio, 0.66 [95% CI, 0.53–0.81]; $P = 0.0062$); fewer sudden deaths and deaths from worsening heart failure
β -Blocker Evaluation of Survival Trial (48)	Stable NYHA class III or IV, LVEF \leq 0.35	2708	Bucindolol, 50–100 mg twice daily, vs. placebo	24	All-cause mortality	Trial stopped because of no significant difference in mortality ($P = 0.16$); fewer deaths from cardiovascular causes with bucindolol; survival benefit only in nonblack patients
Carvedilol Prospective Randomized Cumulative Survival (49)	NYHA class III or IV, LVEF \leq 0.25	2289	Carvedilol, 25 mg twice daily, vs. placebo	10.4	All-cause mortality	Trial stopped early because of significant mortality benefit (hazard ratio, 0.65 [95% CI, 0.52–0.81]; $P = 0.0014$); 24% reduction in combined risk for death or hospitalization
Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (50)‡	Acute myocardial infarction within 3 to 21 days, LVEF \leq 0.40	1959	Carvedilol, 25 mg twice daily, vs. placebo	16	All-cause mortality or admissions for cardiovascular reasons	No difference in primary composite end point but significant reduction in mortality (hazard ratio, 0.77 [95% CI, 0.60–0.98]; $P = 0.03$); absolute risk reduction, 3%
Carvedilol Or Metoprolol European Trial (51)	NYHA class II–IV, LVEF \leq 0.35, \geq 1 admission for cardiovascular reasons within 2 y	3029	Carvedilol, 25 mg twice daily, vs. metoprolol tartrate, 50 mg twice daily	58	All-cause mortality	Hazard ratio, 0.83 (95% CI, 0.74–0.93; $P = 0.0017$) in favor of carvedilol; absolute risk reduction, 6%; no difference in the composite end point of all-cause mortality and hospital admissions

* CR/XL = controlled released, extended release; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

† Target dose.

‡ Study of patients with left ventricular dysfunction after myocardial infarction.

most of the detrimental effects of angiotensin II in heart failure (18). Angiotensin-receptor blockers may offer additional advantages over ACE inhibitors by direct blockade of angiotensin II that is generated through the alternative (non-ACE) pathway. Furthermore, ACE inhibitors incompletely suppress angiotensin II production in the long term and can produce a bothersome dry cough by inhibiting kininase II, which degrades bradykinin. However, at least some of the beneficial effects of ACE inhibitors are related to accumulation of bradykinins. Early studies showed that combined treatment with ACE inhibitors and angiotensin-receptor blockers led to improved exercise tolerance and favorable left ventricular remodeling (65–67).

A meta-analysis pooled the results of 17 randomized, controlled trials that compared angiotensin-receptor blockers with placebo or ACE inhibitors in 12 469 patients with heart failure (68). Compared with placebo, angiotensin-receptor blockers nonsignificantly reduced the rate of death and hospitalization among patients not taking ACE inhibitors. Subsequently, the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity-Alternative trial, which specifically enrolled patients with heart failure who could not tolerate ACE inhibitors, showed that therapy with candesartan significantly decreased the risk for death from cardiovascular causes or hospitalization for heart failure compared with placebo (69).

Several trials have compared angiotensin-receptor blockers with ACE inhibitors. The unexpected benefit to mortality in favor of losartan observed in the pilot Evaluation of Losartan in the Elderly study (70) was not confirmed in the larger Evaluation of Losartan in the Elderly II study, which showed a trend toward a lower mortality rate in patients who received captopril and failed to establish the noninferiority of losartan (71). The Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan compared captopril with losartan in 5477 patients with acute myocardial infarction and left ventricular systolic dysfunction (72). After a mean follow-up of 2.7 years, there was a trend toward an increased all-cause mortality rate, and the rate of death from cardiovascular causes was significantly higher among patients who received losartan. However, in all 3 studies, fewer patients had to discontinue therapy with losartan because of adverse effects (70–72). The largest study of an angiotensin-receptor blocker to date is the Valsartan in Acute Myocardial Infarction trial, which enrolled 14 703 patients with acute myocardial infarction complicated by heart failure (73). It was powered for superior and noninferior comparisons of monotherapy with valsartan versus captopril, and of valsartan plus captopril versus captopril alone, in reducing overall mortality. Valsartan was found to be noninferior to captopril ($P = 0.002$ for a prespecified hazard ratio < 1.13 in the per protocol analysis).

Studies have also compared combination therapy with angiotensin-receptor blockers and ACE inhibitors and treatment with ACE inhibitors alone. In the Valsartan

Heart Failure Trial, which was randomized, double-blind, and placebo-controlled, treatment with valsartan significantly reduced the number of hospitalizations by 24% and improved symptoms, quality of life, and left ventricular ejection fraction. However, the mortality rate was similar in both groups (74). Similarly, in the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity-Added trial, addition of therapy with candesartan to treatment with an ACE inhibitor led to a significant reduction in the composite end point of cardiovascular death or hospitalization for heart failure (75). In contrast to the Valsartan Heart Failure Trial and the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Added, Valsartan in Acute Myocardial Infarction showed no incremental benefit of combination treatment, and adverse events were more common (73). The differences in study samples (patients who had recently had myocardial infarction versus those with chronic heart failure of various causes), drug titration (add-on therapy vs. concurrent up-titration), and dosages used may explain this discrepancy (76).

Table 4 summarizes the results of major randomized clinical trials of angiotensin-receptor blockers. As do ACE inhibitors, angiotensin-receptor blockers may produce hypotension, hyperkalemia, and renal dysfunction, conditions that require careful monitoring. The dose should be adjusted as tolerated to those used in clinical trials (Table 2). However, it has been suggested that the dose of losartan used in the Evaluation of Losartan in the Elderly Study II and the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (50 mg/d) might be inadequate and may have in part accounted for the trend toward a higher mortality rate compared with captopril (50 mg three times daily) (77). Although a post hoc analysis of a small subgroup in the Valsartan Heart Failure Trial showed that triple therapy with an ACE inhibitor, angiotensin-receptor blocker, and β -blocker was associated with a higher mortality rate, the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Added and the Valsartan in Acute Myocardial Infarction studies did not confirm this adverse interaction.

Given the more extensive clinical experience with ACE inhibitors and the lower cost of available generic formulations, these agents remain the logical first-line therapy (77). Angiotensin-receptor blockers are a safe and effective alternative in patients who cannot tolerate ACE inhibitors.

ALDOSTERONE ANTAGONISTS

Plasma aldosterone levels may be elevated by 20-fold in patients with heart failure (78). This effect is due to increased production by the adrenal glands, which are stimulated by high plasma angiotensin concentrations, and to decreased hepatic aldosterone clearance secondary to hepatic hypoperfusion. Aldosterone is also produced in the heart and blood vessels and may have important paracrine effects. Aldosterone regulates urinary retention of sodium,

Table 4. Major Randomized, Double-Blind, Controlled Trials of Angiotensin-Receptor Blockers in the Treatment of Heart Failure*

Study (Reference)	Eligibility Criteria	Patients, n	Drug Regimen	Duration of Follow-up, mo	Primary Outcome	Main Results and Comments
Evaluation of Losartan in the Elderly (70)	Age \geq 65 y, NYHA class II–IV, LVEF \leq 0.40	722	Losartan, 50 mg/d, vs. captopril, 50 mg 3 times daily	48	Persistent increase in serum creatinine concentration of \geq 26.5 μ mol/L (\geq 0.3 mg/dL)	Similar frequency of increased creatinine concentration in both groups; lower all-cause mortality rate in the losartan group (hazard ratio, 0.54; $P = 0.035$); fewer patients receiving losartan discontinued treatment
Evaluation of Losartan in the Elderly II (71)	Age \geq 60 y, NYHA class II–IV, LVEF \leq 0.40	3152	Losartan, 50 mg/d, vs. captopril, 50 mg 3 times daily	18.5	All-cause mortality	No significant difference in mortality rate (average annual rate, 11.7% for losartan vs. 10.4% for captopril; hazard ratio, 1.13; $P = 0.16$); trend toward fewer sudden deaths or cardiac arrests with captopril ($P = 0.08$); fewer patients receiving losartan discontinued treatment
Valsartan in Heart Failure Trial (74)	Stable NYHA class II–IV, LVEF \leq 0.40, left ventricular dilatation	5010	Valsartan, 160 mg twice daily, vs. placebo	23	All-cause mortality; mortality or cardiac arrest or hospitalization for heart failure	Similar overall mortality rate (hazard ratio, 1.02; $P > 0.2$); reduced rate of composite end point, mainly because of fewer hospitalizations (hazard ratio, 0.87 [95% CI, 0.77–0.97]; $P < 0.001$); absolute risk reduction, 3.3%
Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (72)‡	Age \geq 50 y, acute myocardial infarction with signs of heart failure, or LVEF \leq 0.35 or left ventricular dilatation, or anterior Q waves	5477	Losartan, 50 mg/d, vs. captopril, 50 mg 3 times daily	32	All-cause mortality	Mortality rate, 18.2% for losartan group and 16.4% for captopril group; hazard ratio, 1.13 (95% CI, 0.99–1.28; $P = 0.069$); more cardiovascular deaths with losartan ($P = 0.03$)
Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Added (75)	NYHA class II–IV, LVEF \leq 0.40, treated with an ACE inhibitor	2548	Candesartan, 32 mg/d, vs. placebo	41	Cardiovascular death or hospitalization for heart failure	Hazard ratio, 0.85 (95% CI, 0.75–0.96; $P = 0.011$); absolute risk reduction, 4%; trend toward lower all-cause mortality rate ($P = 0.086$)
Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Alternative (69)	NYHA class II–IV, LVEF \leq 0.40, intolerance to ACE inhibitor	2028	Candesartan, 32 mg/d, vs. placebo	33.7	Cardiovascular death or hospitalization for heart failure	Hazard ratio, 0.77 (95% CI, 0.67–0.81; $P < 0.001$); absolute risk reduction, 7%; trend toward lower all-cause mortality rate ($P = 0.11$)
VALsartan In Acute myocardial iNfarcTion (73)‡	Acute myocardial infarction within 0.5–10 days, signs of heart failure, LVEF \leq 0.35 to 0.40, systolic blood pressure $>$ 100 mm Hg	14 703	Valsartan, 160 mg twice daily, vs. captopril, 50 mg 3 times daily, vs. captopril, 50 mg 3 times daily, plus valsartan, 80 mg twice daily	24.7	All-cause mortality	Valsartan vs. captopril: hazard ratio, 1.00 (97.5% CI, 0.90–1.11; $P > 0.2$); combination therapy vs. captopril: hazard ratio, 0.98 (97.5% CI, 0.89–1.09; $P > 0.2$); valsartan not inferior to captopril ($P = 0.004$)

* LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

† Target dose.

‡ Study of patients with left ventricular dysfunction of myocardial infarction.

excretion of potassium, and tissue inflammatory response and stimulates cytokine secretion, fibroblast growth, and collagen turnover (78). These phenomena in turn lead to myocardial fibrosis and adverse ventricular remodeling.

Inhibition of ACE may only transiently suppress aldosterone production (the aldosterone escape phenomenon).

Aldosterone may also be secreted independent of angiotensin II concentrations. These observations suggest that direct blockade of aldosterone may have a salutary effect in patients with heart failure (79).

Table 5 shows the results of the 2 large randomized, placebo-controlled trials of aldosterone receptor blockers

Table 5. Major Randomized, Double-Blind, Controlled Trials of Aldosterone Antagonists in the Treatment of Heart Failure*

Trial	Eligibility Criteria	Patients, <i>n</i>	Drug Regimen†	Duration of Follow-up, <i>mo</i>	Primary Outcome	Main Results and Comments
Randomized Aldactone Evaluation Study (80)	NYHA class III or IV, LVEF \leq 0.35, treatment with angiotensin-converting enzyme inhibitor and loop diuretic	1663	Spironolactone, 25 mg/d‡, vs. placebo	24	All-cause mortality	Trial terminated early; hazard ratio, 0.70 (95% CI, 0.60–0.82; $P < 0.001$); absolute risk reduction, 11%; lower risk for hospitalization due to worsening heart failure
Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (81)§	Acute myocardial infarction within 3–14 days, LVEF \leq 0.40, diabetes or signs of heart failure	6642	Eplerenone, 50 mg/d, vs. placebo	16	All-cause mortality, death from or hospitalization for cardiovascular causes	Hazard ratio for mortality, 0.85 (95% CI, 0.75–0.96; $P = 0.008$); absolute risk reduction, 2.3%; reduction in rate of death from and admissions for cardiovascular causes

* AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

† Target dose.

‡ After 8 weeks, the dose can be increased to 50 mg/d if patients have symptoms and signs of progressive heart failure without hyperkalemia.

§ Study of patients with left ventricular dysfunction after myocardial infarction.

(80, 81). The smaller absolute risk reduction observed in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (81) may reflect the lower risk profile (higher left ventricular ejection fraction and better functional class) and the higher prevalence of β -blocker use in the sample. Serious hyperkalemia (potassium level > 6.0 mmol/L) occurred in 2% to 5.5% of patients, whereas the risk for hypokalemia was significantly reduced from 13.1% to 8.4%. However, recent studies report a higher incidence of serious hyperkalemia among patients receiving spironolactone in the “real world”; careful patient selection and monitoring are therefore warranted (82, 83). Of note, patients with renal dysfunction (serum creatinine concentration > 221 μ mol/L [>2.5 mg/dL]) or hyperkalemia (potassium level > 5.0 mmol/L) were excluded from the clinical trials. Therapy with spironolactone or eplerenone should be initiated at a dosage of 25 mg/d. Electrolytes and creatinine should be measured within 1 week and then monthly or bimonthly until the patient is stable. The dose can be increased to 50 mg/d if tolerated. If hyperkalemia occurs, the dose can be reduced to 25 mg every other day or 12.5 mg/d.

DIGITALIS GLYCOSIDES

Digitalis glycosides have been used to treat heart failure for more than 2 centuries. Their clinical benefits were previously attributed to the positive inotropic action through inhibition of sodium–potassium–adenosine triphosphatase. Recent evidence suggests that digitalis can sensitize cardiac baroreceptors, decrease sympathetic outflow by its vagolytic effect, and suppress renin secretion from the kidneys. Therefore, in heart failure, digitalis probably acts primarily as a neurohormonal modulator rather than a weak positive inotropic agent (84).

Early small, short-term studies showed that therapy with digitalis alleviated symptoms of heart failure and improved exercise tolerance and left ventricular ejection fraction (85–87). In 2 prospective, double-blind studies that randomly assigned patients with systolic heart failure and normal sinus rhythm to withdrawal or continuation of digoxin therapy, withdrawal of digoxin therapy led to worsening heart failure and functional capacity (88, 89).

The Digitalis Investigation Group study (main trial) was a randomized, double-blind, placebo-controlled trial of the effects of digoxin, in addition to diuretics and ACE inhibitors, on rates of mortality and hospitalization in 6800 patients with systolic heart failure (left ventricular ejection fraction ≤ 0.45) (90). The overall mortality rate over 3 years did not differ between the 2 groups. Although digoxin slightly reduced the risk for death from worsening heart failure, an excess of deaths, presumably from arrhythmia, was observed. Fewer digoxin-treated patients were hospitalized for worsening heart failure, and the number of all-cause hospitalizations was reduced by 6%. The beneficial effect of digoxin on the rate of hospital admission is independent of age (91), but post hoc subgroup analysis showed that women treated with digoxin had a higher risk for death (92).

A recent systematic review indicates that therapy with digoxin reduces the incidence of hospitalization and improves the clinical status of symptomatic patients (93). However, given the lack of mortality benefit (90, 93), therapy with digoxin is recommended only in patients who continue to experience symptoms while receiving optimal medical treatment, including ACE inhibitors and β -blockers. Serum digoxin concentrations do not correlate with clinical efficacy (94), and higher levels were associated with increased adjusted mortality rates in a post hoc analysis of

the Digitalis Investigation Group study (95). Routine repeated measurement of serum digoxin levels is therefore not necessary (13), unless nonadherence or toxicity is suspected. The usual maintenance dosage of digoxin is 0.125 mg/d; smaller doses that achieve a low serum concentration (<0.9 ng/mL) should be recommended.

CALCIUM-CHANNEL BLOCKERS

Calcium-channel blockers with negative inotropic properties may worsen heart failure and are generally contraindicated in such patients (96–98). The Vasodilator-Heart Failure Trial III showed that felodipine prevented worsening exercise tolerance and quality of life at 2 years, with no increase in the rate of death or hospitalization (99).

In the Prospective Randomized Amlodipine Survival Evaluation study, the combined end point of all-cause mortality and hospitalization for cardiovascular illness did not significantly differ between the 2 groups (100). However, in the small subgroup of patients with nonischemic cardiomyopathy, amlodipine significantly reduced the risk for death. The Prospective Randomized Amlodipine Survival Evaluation 2, which specifically investigated the effect of amlodipine in patients with nonischemic cardiomyopathy, failed to reproduce the previously observed mortality benefits (101). Combined analysis of both trials shows that amlodipine has a neutral effect on survival in patients with severe heart failure.

Because long-term data showed a neutral effect of felodipine and amlodipine on survival, these drugs may be considered for treating concomitant hypertension or angina. However, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (102) and a recent meta-analysis (103) suggested that hypertensive patients treated with calcium-channel blockers are at increased risk for heart failure. Maximization of the dose of β -blockers and ACE inhibitors, which extend survival in heart failure, is thus preferred over addition of calcium-channel blockers to control hypertension and angina.

VASOPEPTIDASE INHIBITORS

The natriuretic peptides play an important role in regulation of blood pressure and plasma volume. They exert multiple physiologic effects, including natriuresis, diuresis, vasodilation, and inhibition of vascular smooth-muscle proliferation and the renin–angiotensin–aldosterone axis (104). Natriuretic peptides are degraded by neutral endopeptidase, a metalloprotease that is found in renal tubules and endothelial cells (105).

Vasopeptidase inhibitors are a new class of pharmaceutical agents that simultaneously inhibit neutral endopeptidase and ACE (105). Several such agents have been developed, of which omapatrilat has been studied most extensively. Although a pilot study suggested that omapatrilat was superior to an ACE inhibitor (106), the Omapat-

rilat Versus Enalapril Randomized Trial of Utility in Reducing Events trial did not confirm this finding. In the latter trial, 5770 patients with New York Heart Association class II to IV heart failure, left ventricular ejection fraction of 0.30 or less, and recent hospitalization for heart failure were randomly assigned to double-blind treatment with enalapril or omapatrilat (107). Nevertheless, the study demonstrates the importance of evaluating new therapies with an adequate sample size and the challenge of translating mechanistic benefits to the bedside in patients with heart failure.

ENDOTHELIN-RECEPTOR BLOCKERS

Endothelins are a family of peptides synthesized by endothelial and smooth-muscle cells. Endothelin-1, the major isoform in the cardiovascular system, plays an important role in the pathophysiology of heart failure by causing vasoconstriction, myocardial hypertrophy, and retention of sodium and water (108). Although short-term pilot studies of endothelin-receptor antagonists indicated that these agents produce favorable hemodynamic results (109–111), no benefit was seen in the ENdothelin Antagonism with Bosentan for Lowering of Events study (112). Currently, no established indication exists for endothelin-receptor antagonists in the treatment of heart failure.

VASODILATORS

The Veterans Administration Cooperative Vasodilator-Heart Failure Trial showed that the combination of hydralazine and isosorbide dinitrate improved survival and left ventricular ejection fraction compared with placebo (113). In the Veterans Administration Cooperative Vasodilator-Heart Failure Trial II, enalapril was superior to the combination of hydralazine and isosorbide dinitrate in reducing the overall mortality rate (114). Clinical experience suggests that the addition of hydralazine and long-acting nitrates to optimal evidence-based therapies may be beneficial in patients with persistent low cardiac output and volume overload, respectively. The combination of hydralazine and nitrates is also useful in patients who cannot tolerate ACE inhibitors or angiotensin-receptor blockers because of renal impairment.

INOTROPIC AGENTS

Because chronic heart failure was regarded primarily as a disease of abnormal cardiac contractility in the traditional hemodynamic model, positive inotropic agents appeared to be an appealing treatment. Initial small studies of β -adrenergic agonists, dopamine agonists, and phosphodiesterase inhibitors showed improvements in symptoms and hemodynamics. However, long-term, large-scale randomized trials have uniformly demonstrated increased mortality rates with these agents, with no clearly consistent benefit on quality of life (115–119). Currently, use of inotropic ther-

apy should be limited to patients with refractory acute heart failure; the palliative care setting; or as a bridge to definitive treatment, such as heart transplantation (120).

ANTITHROMBOTIC AGENTS

Patients with heart failure are at increased risk for stroke, probably because of blood stasis in the hypokinetic ventricle; hemostatic abnormalities; and established risk factors, such as hypertension and atrial fibrillation (121, 122). The Warfarin and Antiplatelet Therapy in Heart Failure Trial was terminated early because of slow recruitment after 1587 patients with heart failure were randomly assigned to receive aspirin, warfarin (target international normalized ratio, 2.0 to 3.0), or clopidogrel (123). Rates of the composite end point of death, myocardial infarction, or stroke did not differ among the 3 groups. However, patients receiving warfarin were less likely than those receiving aspirin to require hospitalization for heart failure, suggesting that inhibition of prostaglandin by aspirin may worsen heart failure (123, 124). A meta-analysis also documented a trend toward reduced benefit of treatment with an ACE inhibitor when it is combined with aspirin therapy (125). At present, no strong evidence supports the routine use of antiplatelet or anticoagulant therapies in patients who have heart failure of nonischemic cause and normal sinus rhythm (126). If indicated, aspirin should be administered in the lowest effective dose.

ANTIARRHYTHMIC AGENTS

Patients with heart failure are at high risk for sudden death, presumably from arrhythmias (127). Most antiarrhythmic drugs have negative inotropic effects and are proarrhythmic, especially in the setting of ventricular dysfunction. In general, class IA, IC, and some class III agents (such as sotalol) are contraindicated in patients with heart failure (128).

Amiodarone is an effective class III antiarrhythmic agent that has few deleterious hemodynamic and proarrhythmic effects. The Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina reported fewer deaths and hospitalizations due to worsening heart failure in the amiodarone group (129). In the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure, amiodarone suppressed ventricular arrhythmias and improved left ventricular ejection fraction, but the overall mortality rate (primary end point) and rate of sudden death did not significantly differ between the treatment group and the placebo group over a median follow-up of 45 months (130). In the Sudden Cardiac Death in Heart Failure Trial, in which 2521 patients with heart failure were randomly assigned to receive an implantable defibrillator, amiodarone, or placebo, amiodarone was associated with a nonsignificant 6% increase in the mortality rate compared with placebo (8).

Atrial fibrillation is prevalent in patients with heart

failure and often leads to clinical deterioration. Dofetilide, a novel class III antiarrhythmic agent, is effective in the maintenance of sinus rhythm. In the Danish Investigations of Arrhythmia and Mortality on Dofetilide Study in Congestive Heart Failure, dofetilide did not affect the all-cause mortality rate but significantly reduced the risk for hospitalization for heart failure and recurrence of atrial fibrillation (131). However, because torsade de pointes occurred in 3% of patients who received dofetilide, this agent cannot currently be recommended.

Given the lack of clear benefit on mortality, antiarrhythmic agents are not routinely recommended to treat heart failure. Of note, the rate of use of β -blockers, which were proven to decrease the overall mortality rate and the risk for sudden death, was low in the early studies. Any possible incremental benefits of antiarrhythmic agents over β -blockers must be weighed against the potential serious side effects. Moreover, the Atrial Fibrillation Follow-up Investigation of Rhythm Management did not demonstrate a benefit of rhythm control in patients with heart failure or depressed left ventricular ejection fraction (132). If indicated for treatment of symptomatic atrial arrhythmias, amiodarone should be used because of its demonstrated safety in patients with heart failure. Device implantation rather than pharmacologic treatment is the mainstay of preventive therapy for sudden cardiac death among patients with heart failure (7, 8, 133).

NOVEL PHARMACOLOGIC AGENTS

Preliminary data suggested that anti-tumor necrosis factor was beneficial in patients with heart failure (134), but subsequent studies did not confirm this finding (135, 136). Matrix metalloproteinases play a crucial role in ventricular remodeling (137), and in animal models of heart failure, matrix metalloproteinase inhibitors preserved left ventricular geometry and function (139–140). Arginine vasopressin antagonists, which induce diuresis and vasodilation, are currently being investigated (141, 142).

CONCLUSION

In recent decades, the dismal prognosis of patients with heart failure has been transformed to one of greater optimism (143–145). At present, strong evidence supports the use of ACE inhibitors and β -blockers as first-line therapies to prevent and treat heart failure. Aldosterone blockers offer additional symptomatic and mortality benefits in patients with advanced heart failure. Angiotensin-receptor blockers are prescribed to reduce death from cardiovascular causes in patients who cannot tolerate ACE inhibitors and as potential add-on therapy to reduce morbidity in patients taking ACE inhibitors and β -blockers. Diuretics and digoxin are used to relieve symptoms. Hydralazine and nitrates are often reserved for patients with clinically significant renal dysfunction. Current evidence does not support the routine use of calcium-channel blockers, vasopeptidase

inhibitors, endothelin-receptor antagonists, inotropic agents, or antithrombotic or antiarrhythmic therapies. Further advances in the understanding of pathophysiology of heart failure, particularly at the genetic and molecular levels, will probably help to identify novel therapeutic targets (146–148). Meanwhile, the challenge lies in the ability of the medical profession and health care system to bridge the gap between evidence-based medicine and clinical practice (30, 31) in providing the most effective therapies and, above all, preventive strategies for heart failure. As the data on pharmacologic and other treatment methods for this condition evolve, their optimal and effective utilization together are hoped to ameliorate this serious cardiovascular epidemic.

Note added in proof: In the recently reported double-blind African-American Heart Failure Trial, 1050 black patients with NYHA class III or IV heart failure and systolic dysfunction were randomly assigned to receive combination therapy with isosorbide dinitrate plus hydralazine or placebo (149). At enrollment, approximately 70%, 74%, and 39% of patients were receiving an ACE inhibitor, a β -blocker, and spironolactone, respectively. The study was terminated early after a median follow-up of 10 months because the mortality rate was significantly reduced in the active treatment group (hazard ratio, 0.57; $P = 0.01$). This therapeutic regimen, which helps to restore the nitroso-redox derangement in heart failure, may be particularly beneficial in black patients because of the lower bioavailability of nitric oxide in this ethnic group.

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Grant Support: In part by grants from the Heart and Stroke Foundation of Ontario and the Canadian Institutes of Health Research, Canadian Heart Failure Research Network, and Tailored Advanced Collaborative Training in Cardiovascular Science Partnership Programs of the Heart and Stroke Foundation and the Canadian Institutes of Health Research. Dr. Liu holds the Heart & Stroke/Polo Chair Professor of Medicine and Physiology at the University Health Network, University of Toronto. Dr. Andrew Yan is supported by Canadian Institutes of Health Research and Canadian Heart Research Centre Fellowship Awards.

Potential Financial Conflicts of Interest: None disclosed.

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