2 Medical Therapy for Heart Failure

Neal K. Lakdawala, MD
and Akshay Desai, MD

CONTENTS

INTRODUCTION
DIGITALIS GLYCOSIDES
DIURETIC THERAPY FOR HEART FAILURE
VASODILATOR THERAPY
ALDOSTERONE RECEPTOR ANTAGONISTS
BETA-ADRENERGIC RECEPTOR BLOCKERS
ANTICOAGULATION
STATINS
MEDICATIONS TO AVOID
CONSENSUS STATEMENTS
REFERENCES

Abstract

Heart failure due to a decline in cardiac performance initiates compensatory neurohormonal mechanisms in an effort to maintain systemic perfusion. Ongoing neurohormonal activation may have deleterious consequences for cardiac performance, ventricular remodeling, myocardial function, and heart failure progression. The fundamental objective of modern medical therapy for heart failure is to relieve symptoms (largely through relief of volume overload) and to stall (or even reverse) disease progression through combined utilization of neurohormonal antagonists that help to restore normal hemodynamics, maintain normal plasma volume, and prevent ventricular enlargement. This chapter focuses on the key elements of medical therapy for heart failure.

Key Words: Heart failure; Medical therapy; Neurohormones; Renin–angiotensin system; Digitalis; Systolic dysfunction; Remodeling; Hemodynamics.

From: *Contemporary Cardiology: Device Therapy in Heart Failure*
Edited by: W.H. Maisel, DOI 10.1007/978-1-59745-424-7_2
© Humana Press, a part of Springer Science+Business Media, LLC 2010

1. INTRODUCTION

Heart failure begins from a primary myocardial injury (for example, myocardial infarction) that precipitates a decline in cardiac performance and initiates a variety of compensatory neurohormonal mechanisms in an effort to maintain systemic perfusion. Chief among these mechanisms is activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) which promotes salt and water retention as well as peripheral vasoconstriction that helps to increase plasma volume, restore cardiac output, and preserve mean arterial pressure. While beneficial in the short term, ongoing neurohormonal activation generates sustained increases in ventricular preload and afterload that may have deleterious consequences for cardiac performance, fueling a vicious cycle of ventricular remodeling, further decline in myocardial function, additional neurohormonal activation, and heart failure progression. The fundamental objective of modern medical therapy for heart failure is to relieve heart failure symptoms (largely through relief of volume overload) and to stall (or even reverse) this cycle of myocardial remodeling and heart failure progression through combined utilization of neurohormonal antagonists that help to restore normal hemodynamics, maintain normal plasma volume, and prevent ventricular enlargement. Our focus in this chapter will be on the key pharmacologic elements of this approach, highlighting the evidence supporting the utilization of digitalis glycosides, diuretics, RAAS antagonists, other vasodilators, and beta-blockers in the management of patients with chronic heart failure. It should be noted that medical therapy for heart failure described in this chapter applies to patients with heart failure with decreased (<40%) systolic ejection fraction (EF), including patients with ischemic heart disease and idiopathic dilated cardiomyopathy. Currently, there are few large-scale trials that inform the management of the syndrome of heart failure with preserved systolic function (i.e., diastolic heart failure); thus, we limit the scope of this chapter to only those patients with demonstrated systolic dysfunction.

2. DIGITALIS GLYCOSIDES

Digitalis and its derivatives have been used in the therapy of heart failure dating to William Withering's description of the use of foxglove in 1785 *(1)*. Digoxin is the prototypical drug in this class, and the only one currently in widespread use. By reversibly inhibiting Na^+/K^+ ATPase pump in the cell membrane of the cardiac myocyte, digoxin increases intracellular Na^+ and potentiates calcium influx via the membrane-associated Na^+/Ca^+ exchanger. Enhanced cytosolic calcium in turn enhances calcium loading of the sarcoplasmic reticulum, increasing calcium release during systole and enhancing the force of myocyte contraction. As well, digoxin has important effects on the autonomic nervous system, including a vagotonic property that accounts for its slowing of heart rate and slowing of conduction velocity through the atrioventricular node, and a sympatholytic effect resulting from

diminished sensitivity of carotid baroreceptors. As it is a relatively weak inotropic agent in the doses utilized in clinical practice, the primary mechanism of digoxin benefit in heart failure patients is thought to be related to its ability to modulate the activity of the autonomic nervous system and to limit downstream activation of the renin–angiotensin–aldosterone system *(2*, *3)*.

Extensive evidence from randomized clinical trials exists to support the use of digoxin for relief of symptoms in patients with chronic heart failure, though there is no evidence of an impact on cardiovascular mortality. The Randomized Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme Study (RADIANCE) randomly assigned 178 patients to continued digoxin therapy or digoxin withdrawal. The study population was made up of patients with NYHA class II–III heart failure and sinus rhythm, who were clinically stable on a regimen of digoxin, diuretics, and an ACE inhibitor. The result was a sixfold (RR 5.9, 95% CI 2.1–17.2) excess in worsening heart failure symptoms when digoxin was withdrawn from these otherwise stable patients *(4)*. These results were extended by the Digitalis Investigators Group (DIG) trial, which prospectively randomized 6800 patients with mild–moderate heart failure (54% class II and 31% class III) to standard medical therapy with or without digoxin. In this trial, patients randomized to digoxin experienced a 28% reduction in the risk of hospitalization for heart failure and an 8% relative risk reduction in all-cause hospitalization, but no difference in mortality relative to those assigned to placebo (Fig. 1). Although there was a trend toward fewer deaths from progressive pump failure in the digoxin group, this benefit was offset by deaths related to arrhythmia and coronary disease. Subgroup analysis suggested that patients

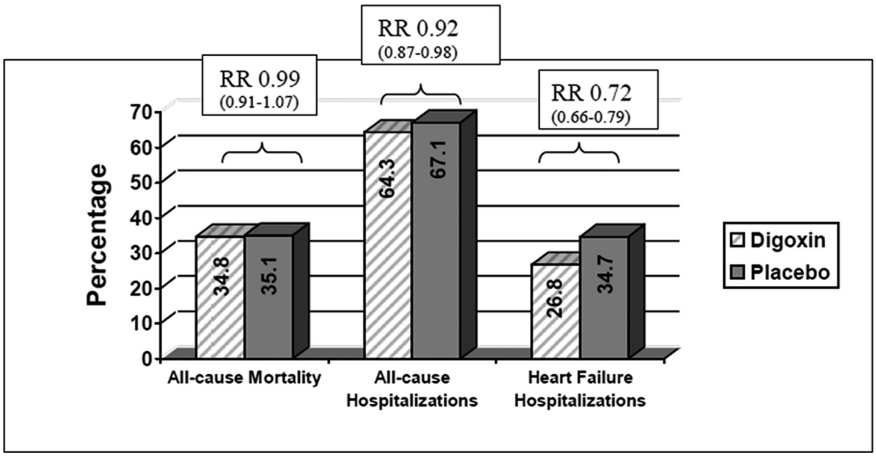


Fig. 1. Major outcomes in the Digitalis Investigators Group (DIG) Trial. Patients randomized to digoxin in the DIG trial experienced reductions in the risk of heart failure and all-cause hospitalizations but not mortality when compared to patients assigned to placebo.

with more advanced heart failure (class III, very low EF) derived a larger benefit from digoxin *(5)*.

The primary limitation to utilization of digoxin in heart failure patients is its narrow therapeutic index and its interaction with many other drugs that are commonly utilized in this population (Table 1). Digoxin toxicity is a potentially lethal complication characterized by atrial and ventricular arrhythmias, vomiting, visual disturbances, confusion, and potassium abnormalities that may be challenging to manage despite the availability of an antidote. The toxic effects of digoxin are more common in the setting of active ischemia, electrolyte disturbance, or hypothyroidism and may not be accurately predicted by the measured serum digoxin concentration. However, post hoc analyses of the DIG trial have suggested an increase in mortality in patients with plasma digoxin levels greater than 0.8 ng/mL *(6)*. Another post hoc analysis of the DIG trial suggested excess mortality in women in the digoxin-treated group (HR 1.23, $p = 0.014$) but was not adjusted for plasma digoxin level *(7)*; subsequent analysis that accounted for digoxin level failed to find this association *(8)*. Since the salutary effect of digoxin on ventricular function and neuroendocrine activation is evident

Table 1
Potential drug interactions with digoxin

Drug	*Mechanism of digoxin interaction*	*Result*
Non-potassium-sparing diuretics	Hypokalemia and/or hypomagnesemia	Increased risk of arrhythmias
Intravenous calcium	Increased myocyte calcium	Increased risk of arrhythmias
Quinidine, verapamil, amiodarone, propafenone, spironolactone	Reduced digoxin clearance	Increased serum digoxin concentration
Macrolides, tetracycline	Decreased intestinal digoxin metabolism and resultant increase in digoxin absorption	Increased serum digoxin concentration
Antacids, bran, cholestyramine, metoclopramide, neomycin	Decreased digoxin absorption	Decreased serum digoxin concentration
Thyroid medications	Increased metabolic state	Decreased serum digoxin concentration
Beta-blockers, non-dihydropyridine calcium channel blockers, flecainide	Decreased sinoatrial or atrioventricular node conduction	Increased risk of bradyarrhythmias and heart block

even at lower serum concentrations (0.5–1.0 ng/mL) *(9)*, efforts should be made to maintain serum digoxin concentrations <1.0 ng/mL and to avoid up-titration of digoxin dose for heart rate control, even in patients with atrial fibrillation.

Practically speaking, the use of digoxin is no longer mandated in heart failure and this was reflected in the guidelines which downgraded digoxin from a class I to a class IIa recommendation. In the language of the ACC/AHA guidelines, digoxin *may be considered* for persistent heart failure symptoms in patients already receiving therapy with diuretics, ACEi, and beta-blockers. In light of the results of RADIANCE and other digoxin withdrawal studies *(10)*, it is not recommended that digoxin be withdrawn from patients unless they are taking an ACEi and a beta-blocker *(11)*.

3. DIURETIC THERAPY FOR HEART FAILURE

Diuretics play an essential role in the medical management of heart failure patients. By interfering with the kidney's ability to reabsorb sodium, diuretics reduce extracellular fluid volume and rapidly relieve symptoms of congestion. There is universal acknowledgement of their utility in improving symptoms and functional capacity; however, increasing evidence suggests that diuretics may have detrimental vascular, hemodynamic, and neurohormonal effects. The net impact of diuretics on mortality in heart failure patients remains unknown, largely due to the ethical and practical considerations precluding conduct of a randomized, controlled clinical trial.

Diuretics are commonly classified by their site of action within the nephron, which is the primary determinant of their effect on the filtered sodium load *(12)* (Fig. 2). Agents active in the proximal tubule, such as carbonic anhydrase inhibitors (e.g., acetazolamide), are relatively ineffective natriuretic agents, since most of the sodium that escapes the proximal tubule is reabsorbed downstream in the loop of Henle. As well, these agents tend to enhance urinary bicarbonate loss, generating a metabolic acidosis that lessens their efficacy. As a consequence, carbonic anhydrase inhibitors are used infrequently in the management of heart failure patients. By contrast, loop-type diuretics, of which furosemide is a prototypical agent, are the cornerstone of heart failure therapy. These agents inhibit the $Na^+2Cl^-K^+$ co-transporter at the thick ascending limb of the loop of Henle and are extremely effective natriuretic agents, capable of increasing the fractional excretion of sodium (FENA) to 25% of the filtered sodium load. Thiazide-type diuretics (e.g., hydrochlorothiazide, metolazone) inhibit the Na^+Cl^- co-transporter in the distal convoluted tubule, and when used alone, they are associated with only a modest natriuretic effect (5–8% of filtered sodium load, 1/5–1/3 potency compared to loop diuretics). However, when used in combination with loop diuretics, they are a potent tool for enhancing natriuresis and diuresis, a property which is frequently exploited for the management of patients with refractory volume overload. Potassium-sparing

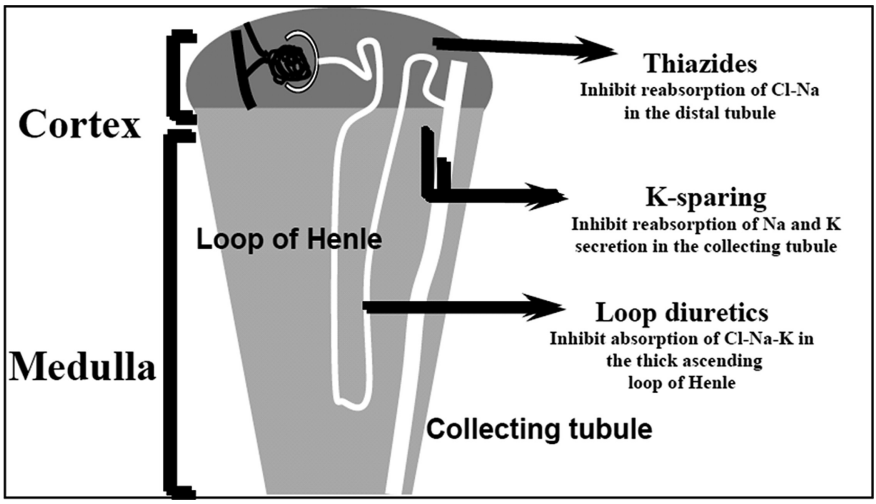


Fig. 2. Diuretics typically used in the treatment of heart failure: mechanism of action.

diuretics (e.g., spironolactone, triamterene, amiloride) inhibit sodium reabsorption either by inhibiting synthesis or by directly blocking the epithelial sodium channel in the principal cells of the collecting duct. These agents are weak natriuretic and diuretic agents, but may be useful as adjunctive agents to stem urinary potassium losses and prevent hypokalemia in patients receiving loop diuretics. The mineralocorticoid receptor antagonist spironolactone is a special case, as it is the only diuretic agent demonstrated to improve mortality in patients with advanced heart failure (see separate discussion below).

To be effective, diuretics must be delivered to their active sites in the renal tubule at the threshold concentration necessary to elicit a natriuretic response *(13)*. Loop diuretics exhibit a characteristic sigmoidal dose–response curve; this implies that for any given patient, the diuretic dose must be titrated to a therapeutic concentration before any significant diuretic effect can be achieved, and that beyond a certain "ceiling" dose, no further natriuresis will occur. In patients with congestive heart failure, the normal dose–response to loop diuretics is disturbed, and the maximal achievable sodium excretion is limited. This may be due in part to diminished renal blood flow (as a consequence of decreased cardiac output), which reduces the filtered sodium load, and as well to enhanced proximal tubule reabsorption of sodium in the face of sustained SNS and RAAS activation. Further, in the face of prolonged exposure to loop diuretics, there is hypertrophy of the distal tubule with resultant increase in sodium reabsorption (diuretic "resistance"). This can lead to a decrease in loop diuretic responsiveness and is occasionally remediable with the addition of a diuretic

active in the distal tubule (e.g., thiazide). Intrinsic renal disease and progressive renal failure often further complicate the management of heart failure patients since even with optimal dosing and combination diuretic therapy, the maximal sodium excretion in response to full-dose diuretic may be limited to as little as 25 mmol of sodium excretion (300–400 cc of urine).

The effects of diuretics are not limited to an increase in sodium excretion. Relief of heart failure symptoms in patients receiving furosemide occurs prior to the onset of diuresis, perhaps due to acute preload reduction related to venodilation *(14)*. Despite clear symptomatic benefits, several studies have shown that RAAS activation is markedly enhanced following loop diuretic administration with an associated increase in systemic vascular resistance and decrease in cardiac output. Long-term RAAS activation may have deleterious effects due to increased systemic vasoconstriction, enhanced sodium and water retention, and aldosterone-mediated myocardial fibrosis. These impacts on neurohormonal activation may account for the relationship between loop diuretic dose and mortality seen in both hospitalized heart failure patients *(15)* and those with chronic heart failure in the outpatient setting *(16)* though these studies are heavily confounded by the tight association between loop diuretic requirement and heart failure severity. Due to the potential adverse effects, however, maintenance diuretic therapy should be reserved for patients with symptomatic heart failure and clinical evidence of volume overload.

Choice of a diuretic, dose, and frequency of administration requires knowledge of the pharmacokinetics of the individual diuretic drugs, including the duration of effect and the bioavailability of the individual agents (Table 2). As it is familiar and inexpensive, furosemide is the most widely utilized loop diuretic agent, but it is considerably less potent and less bioavailable orally than bumetanide and torsemide. No large, randomized, blinded studies comparing different loop diuretics have been conducted to help inform the choice of one agent over another, although there are some discernible differences in effects on potassium excretion and neurohormonal activation that may impact on patient outcomes *(17)*.

For patients who fail to respond to maximal doses of loop diuretics, combination diuretic therapy, particularly with addition of a thiazide diuretic, can enhance effective natriuresis due to "sequential blockade" of sodium reabsorption within the nephron. As well, for hospitalized patients, continuous intravenous infusions of loop diuretics may enhance urine output and sodium excretion, perhaps due to more constant maintenance of adequate serum levels. For patients refractory to conventional measures, mechanical fluid removal with ultrafiltration or hemodialysis may be necessary. A number of additional therapies have been investigated for the diuretic refractory patient including early ultrafiltration *(18)*, natriuretic peptides (e.g., nesiritide) *(19)*, vasopressin receptor antagonists *(20)*, and adenosine receptor antagonists *(21)*; these therapies are the subject of active, ongoing

Table 2
Diuretics typically used in the treatment of heart failure

Class	Daily oral dose (mg)		Duration of action (hours)	Effect on FENA	Effect on serum sodium concentration	Oral bioavailability (%)
	Initial dose (mg)	Maximum dose[a] (mg/day)				
Loop diuretics						
Furosemide	20–40	600	6–8	↑20–25%	Increase	10–100[b]
Bumetanide	0.5–1.0	10	4–6			80–100
Torsemide	10–20	200	12–16			80–100
Thiazide diuretics						
Chlorthalidone	12.5–25	100	6–12	↑5–10%	Decrease	65–75
HCTZ	25–50	200	6–12			ND
Metolazone	2.5–5	20	12–24			ND

FENA – Fractional excretion of filtered sodium; ND – No reliable data.

[a]The average starting dose is an increment of one- to twofold of the minimum effective dose, rarely the maximum dose will be indicated

[b]The average bioavailability is ∼50% but varies widely.

investigation and have not yet become part of the standard heart failure armamentarium. For all patients with refractory heart failure, dietary sodium restriction and limitation of agents which further diminish glomerular filtration (such as non-steroidal anti-inflammatory drugs, NSAIDs) must be emphasized.

The primary risks associated with diuretics are electrolyte disturbances (and associated arrhythmias) and hypovolemia, which can be prevented with careful monitoring. Hypokalemia is the most frequent complication and may enhance the risk of ventricular arrhythmias and sudden cardiac death. In fact, in retrospective analyses of large clinical trials (SOLVD), patients taking non-potassium-sparing diuretics appear to experience a higher risk of arrhythmic death than those taking potassium-sparing diuretics *(22)*. However, widespread use of potassium-sparing diuretics such as spironolactone carries its own risk of life-threatening hyperkalemia *(23)*. Careful monitoring of serum potassium during diuretic therapy is therefore critically important to maintain normal balance. Hyponatremia is another potential complication, more commonly observed with thiazide diuretics which enhance sodium excretion and impair maximal urinary dilution. However, because diuresis is usually iso-osmotic, true diuretic-induced hyponatremia is uncommon; most heart failure patients with hyponatremia have free water excess rather than salt depletion and actually improve with administration of additional loop diuretics and restriction of free water intake. Though hypomagnesemia is also seen commonly in patients receiving chronic loop diuretics, the clinical significance of this is unclear, especially as serum magne-

sium levels do not reliably assess intracellular magnesium stores. Among patients with gout, both loop and thiazide-type diuretics appear to increase the risk of precipitating a flare by two- to threefold *(24, 25)*.

4. VASODILATOR THERAPY

4.1. Angiotensin-Converting Enzyme (ACE) Inhibitors

ACE inhibitors (ACEi) were established as the cornerstone of heart failure therapy after their efficacy was validated in several large clinical trials in the 1980s and 1990s. The primary action of ACE inhibitors is to block the conversion of angiotensin I to angiotensin II, attenuating myriad downstream consequences of RAAS activation (Fig. 3). Through signaling at the angiotensin type 1 receptor, angiotensin II promotes myocyte hypertrophy and apoptosis, enhances arteriolar tone, stimulates fibroblast and smooth muscle cell proliferation, and increases circulating levels of norepinephrine and aldosterone. Enhanced activation of the SNS further potentiates systemic vasoconstriction and increases the load on the failing heart. As has been well described in the post-infarction setting, persistent neurohormonal activation leads to maladaptive ventricular enlargement and remodeling, which in turn reduce myocardial reserve and enhance vulnerability to heart failure development. Within the kidney, activation of angiotensin II and aldosterone stimulates tubular reabsorption of salt and water, enhancing circulating plasma volume, and ultimately precipitating heart failure symp-

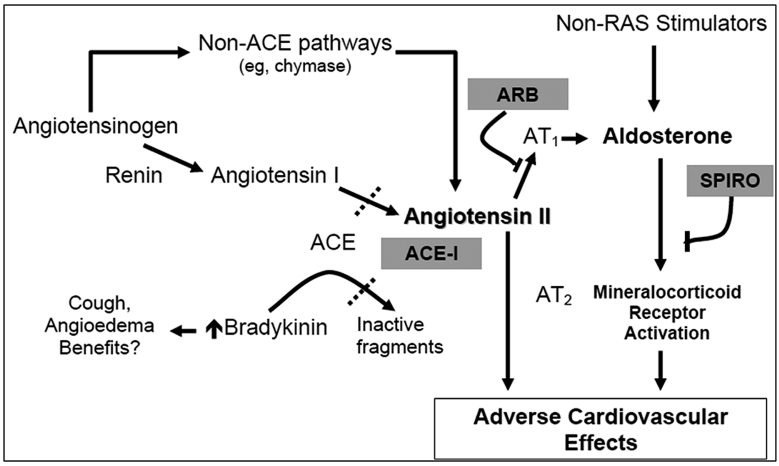


Fig. 3. The renin–angiotensin–aldosterone system (RAAS) and its inhibitors: angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and aldosterone antagonists. ACEi are active by blocking the conversion of angiotensin I to angiotensin II as well as by blocking the degradation of bradykinin. The pathologic effects of angiotensin II can be directly antagonized through the mechanism of selective AT1 blockers (ARBs).

toms including dyspnea and peripheral edema. Interruption of angiotensin II generation therefore retards myocardial hypertrophy and fibrosis, while simultaneously providing hemodynamic benefits to the failing heart by reducing ventricular preload and afterload *(26)*. ACEi also prevent the breakdown of bradykinin, with additional vasodilatory benefits.

A wealth of clinical trial evidence now supports the benefits of ACE inhibitors across the spectrum of patients with chronic heart failure, ranging from patients with asymptomatic left ventricular dysfunction to those with disabling class IV symptoms (Table 3). The Studies of Left Ventricular Dysfunction (SOLVD) enrolled a broad population of patients (NYHA I–III) with symptomatic heart failure and LVEF <35% and randomized them to treatment with enalapril or placebo *(27)*. Over 41 months, enalapril therapy was associated with a 16% relative risk reduction in all-cause mortality (HR 0.84, $p = 0.0036$). Patients with asymptomatic LV dysfunction were enrolled in an ancillary study (SOLVD-Prevention) and derived similar benefits from enalapril therapy (HR for death or HF with enalapril 0.80, $p < 0.001$ relative to placebo). The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) extended the benefits of ACE inhibition to the population of patients with advanced heart failure, demonstrating potential for mortality benefit with enalapril among those with class III–IV heart failure despite a mortality rate of 52% at 1 year in the placebo arm *(28)*. In that study, overall mortality was reduced by 31% in the group treated with enalapril (HR 0.69, 95% CI, $p = 0.001$) largely due to a marked decrement in the incidence of progressive pump failure.

In addition to chronic heart failure, long-term studies of patients following myocardial infarction (Survival and Ventricular Enlargement: SAVE *(29)*, Acute Infarction Ramipril Study: AIRE *(30)*, and Trandolapril Cardiac Evaluation: TRACE *(31)*) have demonstrated the benefit of ACE inhibitors in heart failure prevention and mortality reduction. SAVE studied patients with little or no clinical heart failure, who were enrolled on the basis of a reduced LVEF (≤40%). Among the post-MI ACEi trials, this was a less sick group, with an estimated 1-year mortality rate of 11% in the placebo group. In this study, initiation of captopril 3–16 days after myocardial infarction was associated with a 19% reduction in all-cause mortality, at a median of 42 months post-infarction. The AIRE trial studied a highly selected group (52,019 screened and 1986 enrolled) of patients with symptomatic heart failure, but without evidence of reduced perfusion, early (2–6 days) after an MI. In this population (slightly sicker than SAVE, with estimated 1-year mortality in the placebo arm of 20%), there was a 27% reduction in all-cause mortality in the ramipril group that became evident after several weeks. The TRACE study was an important contribution to the growing field of post-MI ACEi studies in that it had loosely defined inclusion criteria that more closely approximated "real-life" practice and enrolled 1749 patients of the 6676 screened (the majority excluded on the basis of EF>35%). There was a 22% reduction in mortality with trandolapril compared to placebo; and mor-

Table 3
Major angiotensin-converting enzyme inhibitor (ACEi) trials in heart failure

Trial name, date, and number of participants (N)	*Drug (and control group in the case of active comparator)*	*NYHA or Killip classification*	*Effect on all-cause mortality HR*[d]	*Affect on hospitalizations*	*1-year mortality in the control group*	*Caveats*
Chronic heart failure trials						
CONSENSUS 1987 $N = 253$	Enalapril Goal 10 mg BID[a] Achieved: 9.2 mg BID	IV 100%	0.69 ($p = 0.002$)[a]	Not reported	52%	
V-HeFT II 1991 $N = 804$	Hydralazine/isordil Goal 300 mg/160 mg Achieved: 270 mg/136 mg Vs Enalapril Goal 20 mg daily Achieved: 18.6 mg	I 6% II 51% III 43% IV <1%	0.72 ($p = 0.016$)[b]	None	No placebo group	
SOLVD 1991 $N = 2569$	Enalapril Goal 20 mg daily Achieved: NA		ARR 4.5%, RRR 16% (at 41 months)		16% est.	
Post-myocardial infarction trials						
SAVE 1992 $N = 2231$	Captopril Goal: 50 mg TID (reached by 79% of patients still taking captopril)	I 60% II III IV [c]	0.81 (0.68–0.97)	All-cause hospitalization not reported, 22% RRR in HF hospitalizations	11% est.	The mortality curves began to separate after 1 year.

(Continued)

Table 3
(Continued)

Trial name, date, and number of participants (N)	*Drug (and control group in the case of active comparator)*	*NYHA or Killip classification*	*Effect on all-cause mortality HR*[d]	*Affect on hospitalizations*	*1-year mortality in the control group*	*Caveats*
AIRE 1993 $N = 1986$	Ramipril Goal 5 mg BID Achieved: 4.1 mg BID	Not published	0.73 (0.60–0.89)		20% est.	Mortality curves separated almost immediately
TRACE 1995 $N = 1749$	Trandolapril Goal 4 mg daily		5.6% ARR 22% RRR NNT∼18 (at 12 months)		26% est.	Broad inclusion criteria
Asymptomatic left ventricular dysfunction						
SOLVD-Prevention 1992 $N = 4228$	Enalapril Goal: 10 mg BID Achieved: 6.35 mg BID	I 67% II 33%	0.92 (0.79–1.08)	No difference in all-cause hospitalization, 36% RRR in HF hospitalization	5% est.	Enalapril was associated with a significant reduction in the development of HF; HR 0.71 (0.64–0.79)

[a]95% confidence interval not published.

[b]hazard ratio after 2 years of follow-up, 95% CI not published.

[c]baseline Killip class beyond class I was not published.

[d]HR – Hazard ratio provided except as noted in table.

NYHA – New York Heart Association., NA = not available

ARR – Absolute Risk Reduction; RRR – Relative Risk Reduction; NNT – Number Needed to Treat

tality curves began to diverge within weeks. Taken together, the ACEi trials in diverse HF populations have found that beyond reducing all-cause mortality (26% risk reduction), ACEi have also decreased hospitalizations for heart failure (27% risk reduction), reduced re-infarction (20% risk reduction), and improved quality of life *(32, 33)*. Moreover, ACEi have been shown to attenuate progressive LV remodeling in patients with heart failure, consistently improving LVEF and reducing left ventricular volumes *(34)*.

Given demonstrated benefits of a range of different ACE inhibitors across the spectrum of heart failure patients, there is ample evidence supporting a class effect, rather than benefit particular to any given agent. The optimal dose of ACE inhibitor remains a subject of some controversy, even though several clinical trials have been designed to address this question *(35–37)*. Since benefit is proven only at the doses achieved in clinical trials, the consensus recommendations support the use of any of the agents listed in Table 4, with titration targeted to the recommended dose *(11)*. The consensus ACC/AHA guidelines give a strong recommendation (class I) for the use of ACEi across the spectrum of left ventricular dysfunction, in patients both with and without symptoms of heart failure *(11)*.

Table 4
Angiotensin-converting enzyme inhibitor (ACEi) doses recommended in the treatment of heart failure

Drug	*Initial dose (mg)*	*Target dose (mg)*
Captopril	3.125–6.25 TID	50 TID
Enalapril	2.5 BID	10–20 BID
Fosinopril	5–10 QD	40 QD
Lisinopril	2.5–5 QD	20–40 QD
Perindopril	2 QD	8–16 QD
Quinapril	5 BID	20 BID
Ramipril	1.25–2.5 QD	10 QD
Trandolapril	1 QD	4 QD

BID (twice daily), QD (once daily), TID (three times daily).

In general, ACEi are well tolerated. Hypotension and dizziness, cough, azotemia, and angioedema are more commonly reported with ACEi; and in trials, the incidence of each side effect tended to be twofold higher than that with placebo *(38)*. In general, the risk of symptomatic hypotension is low but can be predicted by baseline hyponatremia, renal insufficiency, or a high requirement for potassium replacement; all surrogate measures of RAAS activation *(39)*. In patients with these features, a brief period observation after administration of the first dose of ACEi should be considered. Practically speaking, most of these patients will receive their first dose of medicine in the hospital and can expect a 8–10 mmHg drop in mean blood pressure after the first dose of ACEi *(40)*. The CONSENSUS II study demonstrated

that when given immediately post-infarct, an intravenously administered ACEi may actually worsen the clinical course if it causes hypotension, highlighting the importance of proper patient selection before administration of ACEi *(41)*. Cough and angioedema in ACE-inhibitor-treated patients are thought to be related to inhibition of bradykinin breakdown and may in many circumstances be avoided by substitution of an angiotensin receptor blocking drug (see below) with comparable long-term benefits for the patient. Angioedema is rare, occurring in less than 1% of patients.

4.2. Angiotensin Receptor Blockers (ARBs)

Roughly 9% of patients of European ancestry are ACE-inhibitor intolerant due to development of cough or angioedema, and the intolerance related to cough may be threefold higher in patients of Asian ancestry *(42, 43)*. These side effects are thought to be related to simultaneous inhibition of bradykinin breakdown and may be circumvented through blockade of angiotensin II activity downstream at the receptor level using angiotensin receptor blocking drugs (Fig. 3). As well, it has been demonstrated that levels of circulating angiotensin II return to pre-ACE inhibitor treatment values in patients receiving chronic ACE inhibitor therapy. This increase in angiotensin II levels, or "ACE escape," is incompletely understood but thought to be associated with alternate synthesis pathways for angiotensin II. Enzymes such as cathepsin G and elastase are thought to directly convert angiotensinogen to angiotensin II, while chymases and cathepsin G are thought to provide an alternate pathway for conversion of angiotensin I to angiotensin II. This observation supports a rationale for more complete blockade of the RAAS through combined utilization of ACEi/ARB.

Several large-scale clinical trials of ARBs have now been conducted to assess whether or not these theoretical benefits are borne out in clinical practice. Broadly speaking, the trials can be divided into those that tested ARBs as an alternative to ACEi and those that added ARBs to patients already taking ACEi. Each strategy has been explored in both chronic heart failure patients and those with post-MI left ventricular dysfunction (Table 5).

The clearest indication for ARBs is in the patients who are ACE intolerant, a hypothesis examined in the Candesartan Assessment of Reduction in Mortality and Morbidity-Alternative study (CHARM-Alternative) *(44)*. CHARM-Alternative randomized 2028 patients with mild–moderate heart failure, who were previously unable to tolerate an ACEi (primarily because of cough) to treatment with the ARB candesartan or placebo. After a median of 33.7 months of follow-up, there was a significant 23% reduction in the primary outcome of cardiovascular death or heart failure hospitalization (HR 0.77; 95% CI 0.67–0.89, $p < 0.0001$) as well as a statistically significant 17% reduction in the covariate-adjusted rate of all-cause mortality (HR 0.83; 95% CI 0.70–0.99, $p = 0.033$) in patients randomized to ARB.

Taken as a whole, randomized trials of ARB vs ACEi as monotherapy in patients with chronic heart failure suggest no difference in major cardiovas-

Table 5
Major angiotensin receptor blocker (ARB) trials in heart failure

Trial name and publication date	*Drug and control group*	*NYHA or Killip classification of participants*	*Effect on all-cause mortality HR and 95% CI*	*Affect on hospitalizations*	*1-year mortality in the control group*	*Caveats*
Chronic heart failure trials – ARB compared to ACEi or placebo without ACEi						
ELITE II 2000 $N = 3152$	Losartan Goal: 50 mg QD Achieved: NA Captopril Goal: 50 mg TID Achieved: NA	NYHA II 52% III 43% IV 5%	None HR: 1.13 (0.95–1.35)	None HR 1.04 (0.94–1.16)	10.4%	Older population, mean age 71.5 years
CHARM-Alternative 2003 $N = 2028$	Candesartan Goal: 32 mg Achieved: 23 mg (59% at goal)	NYHA II 48% III 48% IV 4%	17% reduction HR: 0.83 (0.70–0.99)*	NS difference	ND	Associated with a 23% reduction in the primary outcome of CV death or hospital admission for HF
Chronic heart failure trials – ARB added to ACEi						
Val-HeFT 2001 $N = 5010$	Valsartan Goal: 160 mg BID Achieved: 127 mg BID (84% achieved goal)	NYHA II 62% III 36% IV 2%	One HR 1.02 (0.88–1.18)	NS difference	9% (est.)	

$* = 0.003$

(Continued)

Table 5
(Continued)

Trial name and publication date	*Drug and control group*	*NYHA or Killip classification of participants*	*Effect on all-cause mortality HR and 95% CI*	*Affect on hospitalizations*	*1-year mortality in the control group*	*Caveats*
CHARM-Added 2003 $N = 2548$	Candesartan Goal: 32 mg daily Achieved: 27 mg (73% achieved goal)	NYHA II 24% III 73% IV 3%	None HR 0.89 (0.77–1.02)	No difference in patients hospitalized, but 12% reduction in total admissions ($p = 0.023$)		Increased hyperkalemia, hypotension, and azotemia in the combination group 15% reduction in the 1° outcome of CV death or admission for HF
Post-myocardial infarction trials – ARB compared to ACE						
OPTIMAAL 2002 $N = 5477$	Losartan Goal: 50 mg daily Achieved: NA Captopril Goal: 50 mg TID Achieved: NA	Killip I 32% II 57% III 10% IV 1.6%	None HR 1.13 (0.99–1.28)		9% (est.)	Non-inferiority criteria were **not** met.
Post-myocardial infarction trials – ARB added to ACEi						
VALIANT	Captopril 25 mg TID (control)	Killip I 28% II 48% III 17% IV 6%	No difference compared to control.	62.8%	13.3%	Non-inferiority criteria **were** met.
	Valsartan 80 mg BID		HR 1.00 (0.90–1.11)	62.5% NS difference		
	Valsartan 40 mg BID and Captopril TID		HR 0.98 (0.89–1.09)	61.3% NS difference		

cular outcomes. Death, cardiovascular death, and hospitalizations for heart failure are no different between patients treated with an ACEi or ARB alone. The largest of these, the Evaluation of Losartan In The Elderly Study (ELITE II) trial, compared an ARB with an ACE inhibitor in patients at least 60 years of age with NYHA class II–IV heart failure, who had not been previously treated with either an ACE inhibitor or an ARB *(45)*. After a mean follow-up of 1.5 years, there were no significant differences in all-cause mortality (11.7% vs 10.4% average annual mortality rate) or in sudden death or resuscitated arrest (9.0% vs 7.3%) between the two treatment groups. Although ARB treatment was not clinically superior to ACE-inhibitor therapy, it was significantly better tolerated, with a withdrawal rate of 9.4%, as compared with 14.5% for ACE-inhibitor therapy ($p < 0.001$). Losartan was also tested in the post-infarction population in the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist losartan (OPTIMAAL) *(46)*. Here 5477 patients not already taking an ACEi were randomized to either losartan or captopril 3 days after a myocardial infarction with associated heart failure or left ventricular dysfunction. There was a non-significant trend toward *increased* all-cause mortality in the losartan group (HR 1.13, 95% CI 0.99–1.28, $p = 0.07$), and for this primary outcome, losartan did not satisfy criteria for non-inferiority to captopril. Similar to the results of ELITE II, losartan was better tolerated, with significantly fewer discontinuations for cough, dysgeusia, and angioedema.

In the post-MI population, the Valsartan in Acute Myocardial Infarction (VALIANT) trial compared three different regimens, captopril, valsartan, or both, in 14,703 patients who had post-infarction heart failure and/or left ventricular dysfunction *(47)*. There was no significant difference in primary or secondary outcomes between any of the treatment groups. After a median follow-up of little over 2 years, the mortality rate was not statistically different between the groups: 19.5% in the captopril group, 19.9% in the valsartan group, and 19.3% in the valsartan and captopril groups (compared to captopril, HR 1.00; CI 0.90–1.11 and HR 0.98; CI 0.89–1.09). The study authors concluded that valsartan was noninferior to captopril in the post-myocardial infarction setting, and that the combination of ACE/ARB offered no significant mortality advantage over monotherapy in this population. Subgroup analysis found no variation in the effect of these three regimens in any subgroup, including those receiving background beta-blocker therapy.

Building on the notion that more effective ARBs might potentiate ACEi-induced blockage of angiotensin II, several trials have been conducted to examine the benefits of ARB and ACEi in combination in patients with chronic heart failure. The earliest of these, the Valsartan Heart Failure Trial (Val-HeFT), randomized 5010 patients with NYHA class II–IV heart failure to valsartan or placebo, in addition to the existing heart failure regimen (93% were already receiving an ACEi). After a mean follow-up of 23 months, no difference was observed in all-cause mortality. However, patients treated with valsartan showed a significant 13.2% reduction in the combined mortal-

ity and morbidity endpoint. This was primarily due to a significant ($p<0.001$) 24% reduction in hospitalizations for worsening heart failure. A subgroup analysis of Val-HeFT showed that among the 35% of trial participants that were taking an ACEi and a beta-blocker, there was statistically significant excess mortality in the valsartan group ($p = 0.009$), raising concern that excessive neurohormonal inhibition with ACEi/ARB/beta-blocker might be harmful in patients with heart failure; however, this finding was not borne out in subsequent studies. CHARM-Added randomized 2548 patients already taking an ACEi (~100%) to placebo or candesartan *(48)*. The treatment group received a 15% reduction in the primary outcome of death or heart failure hospitalization. Compared to Val-HeFT, a higher percentage (55%) of this population was also taking a beta-blocker and these patients received the same benefit from candesartan administration as did patients not previously taking beta-blockers ($p = 0.14$ for treatment interaction), highlighting the safety of adding an ARB to optimal medical therapy with ACEi/beta-blocker.

A meta-analysis of 17 trials comparing ARB with either placebo or an ACE inhibitor in patients with heart failure found that although ARBs were not superior to ACE inhibitors in reducing mortality or hospitalizations for heart failure, the combination of an ARB and an ACE inhibitor was superior to ACE-inhibitor monotherapy in reducing hospitalizations for heart failure but not mortality *(49)*. In addition, in patients not receiving an ACE inhibitor (but receiving other heart failure drugs), there was a nonsignificant trend favoring ARBs over placebo for both reductions in all-cause mortality (OR 0.68, 95% CI 0.38–1.22) and hospitalizations for heart failure (OR 0.67, 95% CI 0.29–1.51). In this context, the ACC/AHA heart failure guidelines state that while ACEi remain first-line therapy for patients with heart failure (both chronic and post-MI), ARBs are a suitable substitute in ACE-intolerant patients, and may be considered as add-on therapy in patients who are already optimally treated with an ACEi and a beta-blocker. However, the guidelines state that an ARB should not be used in patients receiving ACEi and aldosterone antagonist because of a perceived high risk of hyperkalemia and a lack of clinical trial data to support this strategy *(11)*.

With regard to side effects, one benefit of ARBs that has been consistently demonstrated in ACEi/ARB comparison studies has been the lower rate of drug discontinuation in the ARB group related to less cough, dysgeusia, and angioedema. Although the reported incidence and severity of angioedema are much lower with ARBs, these medicines should be used with great caution in patients with a history of life-threatening ACEi-induced angioedema. The composite of these studies that added an ARB to patients taking an ACEi showed that azotemia, hyperkalemia, and hypotension were significantly and substantially more common in patients randomized to dual ACEi and ARB therapy. Common ARBs and their suggested doses are displayed in Table 6.

Table 6
Angiotensin receptor blocker (ARB) doses recommended in the treatment of heart failure

Drug	*Initial dose (mg)*	*Target dose (mg)*
Candesartan	4–8 QD	32 mg QD
Losartan	25–50 QD	50–100 QD
Valsartan	20–40 BID	160 BID

BID (twice daily), QD (once daily).

4.3. Other Vasodilators

Other than ACE inhibitors and ARBs, the only additional "vasodilator" regimen shown to be effective in chronic heart failure is the combination of hydralazine and isosorbide dinitrate (Hyd-Iso). Though other vasodilators have been tested, most (e.g., felodipine *(50)*, amlodipine *(51)*, and prazosin *(52)*) have been ineffective in improving cardiovascular outcomes, despite doses causing measurable reductions in blood pressure consistent with systemic hemodynamic effects. This raises the possibility that there are unique properties to Hyd-Iso that are beneficial and independent of the physiologic vasodilator properties of these medications. It is hypothesized that this combination works by reducing oxidant stress (hydralazine) and improving nitric oxide availability (isosorbide dinitrate); changes in both are felt to be part of the pathophysiology of heart failure *(53*, *54)*.

In 1986, the seminal Vasodilator therapy in Heart Failure study (V-HeFT I) showed that when compared with placebo (or prazosin) the combination of hydralazine and isosorbide dinitrate caused a reduction in all-cause mortality in patients with advanced heart failure *(52)*. After 2 years of follow-up, there was a 34% reduction in mortality in the Hyd-Iso group (HR 0.66, 95% CI 0.46–0.96, $p < 0.028$) but over the entire period of follow-up, the survival difference was of marginal statistical significance. This was the first large trial to show that any particular pharmacotherapy could reduce mortality in chronic heart failure, but the role of Hyd-Iso was quickly supplanted by ACE inhibitors following the publication of V-HeFT II. This second V-HeFT study directly compared enalapril to Hyd-Iso (without a placebo group) and had identical enrollment criteria as V-HeFT I. It found that enalapril was associated with a significant 33.6% reduction in mortality by 1 year ($P = 0.016$), but this difference waned with time and by the end of the trial the mortality reduction was no longer statistically significant ($p = 0.08$). The improved survival with enalapril was driven by a significant reduction in sudden cardiac death that was not seen with Hyd-Iso. Subgroup analysis showed that the 179 patients with advanced heart failure (NYHA III and IV) fared no better on enalapril than on Hyd-Iso (RR 0.99, 0.72–1.35). Between

the treatment arms there was no significant difference in hospitalizations and somewhat paradoxically, Hyd-Iso was associated with a larger improvement in ejection fraction and exercise capacity *(55)*. Based on ease of administration, less side effects, and improved efficacy, ACEi became the preferred agent for management of heart failure patients, with the combination of isordil/hydralazine being reserved for patients who were intolerant of ACE inhibitors and ARBs *(56)*.

A provocative post hoc analysis of pooled data from V-HeFT I and II suggested that the benefits of Hyd-Iso varied by patient race. In this analysis, nearly all of the benefit seen in the overall trial was attributable to a reduction in mortality seen in patients who self-identified themselves as black *(57)*. The observation that race may have influenced the efficacy of the Hyd-Iso combination fueled the design of the African-American Heart Failure Trial *(54)* (A-HeFT). This trial randomized 1050 black patients with symptomatic HF (NYHA class II–III) who were already receiving established therapies for heart failure (86% with ACEi or ARB, 74% βB, 39% spironolactone) to additional therapy with Hyd-Iso (goal dose: hydralazine 225 mg/isosorbide dinitrate 120 mg divided three times daily). They found that the fixed-dose combination of Hyd-Iso was associated with a 43% improvement in survival at an average follow-up of 10 months (HR 0.57, $p = 0.01$) as well as significant improvements in quality of life and need for heart failure associated hospitalization (Fig. 4). As a result of A-HeFT, the FDA approved the fixed-dose combination of Hyd-Iso for the therapy of advanced heart failure in self-identified black patients, though this decision has met with some controversy *(58 – 60)*.

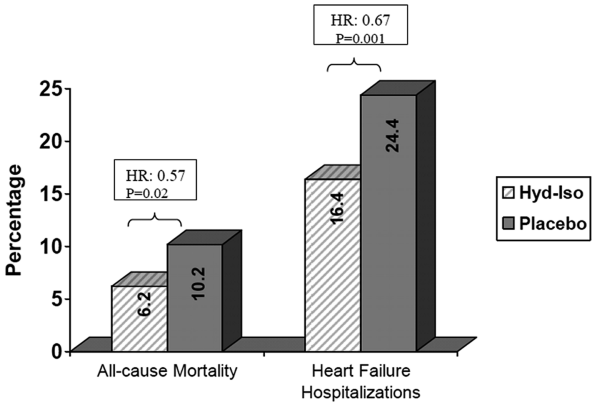


Fig. 4. Major outcomes in the A-HeFT trial. The combination of hydralazine and isosorbide dinitrate (Hyd-Iso) was associated with a significant reduction in mortality, improvement in QOL, and reduction in heart failure hospitalizations compared to placebo in the A-HeFT trial. Heart failure hospitalizations were defined as the rate of first hospitalization for heart failure.

Therapy with the combination of hydralazine and isosorbide dinitrate is associated with two principal side effects: headache and dizziness. These symptoms were extremely common in clinical trials of Hyd-Iso but rarely caused study medication withdrawal. Hyd-Iso caused a small but significant decrease in blood pressure in clinical trials, but the survival benefit was present regardless of blood pressure and thus it is recommended that asymptomatic low blood pressure should not contraindicate the use of Hyd-Iso *(61)*.

The consensus of the heart failure guideline writing committee is that Hyd-Iso is an option for patients who do not tolerate ACEi therapy but should not be given in the place of an ACEi in patients who would otherwise be expected to tolerate ACEi *(11)*. Hyd-Iso can also be considered in patients who remain symptomatic in spite of maximal therapy with beta-blockers and ACEi (class IIa recommendation). The guidelines do not identify race as a factor in selecting Hyd-Iso as a therapy but do acknowledge the results of the A-HeFT trial.

More recently, strategies targeting secondary pulmonary hypertension in heart failure with phosphodiesterase inhibitors such as sildenafil have received increasing attention. Secondary pulmonary hypertension is common in chronic severe left ventricular dysfunction, and may offer an important therapeutic target in this patient population facing high morbidity and mortality. In small trials, PDE-5 inhibition improved exercise capacity, 6-minute walk tests, and quality of life measurements *(62 – 64)*. Larger studies are needed to better define the long-term safety of effectiveness of this approach.

5. ALDOSTERONE RECEPTOR ANTAGONISTS

The importance of aldosterone in the pathogenesis of the volume retention of various disease states has been recognized for decades (Fig. 3). Since its isolation in the urine of heart failure patients, aldosterone has been recognized to contribute to the pathogenesis of heart failure. It either directly or indirectly contributes to heart failure progression (or ventricular arrhythmias) via volume retention, hypertension, hypokalemia, hypomagnesemia, secondary hyperparathyroidism, and myocardial fibrosis *(65*, *66)*. ACEi and ARBs can cause upstream inhibition of aldosterone secretion but this inhibition is not complete (“aldosterone escape”), and, moreover, increased aldosterone levels are maintained due to decreased hepatic aldosterone clearance in the setting of heart failure *(67)*. Sustained aldosterone receptor activation in heart failure patients treated with optimal medical therapy provided the rationale for direct aldosterone inhibition as an additional therapeutic target in heart failure. On the basis of two well-designed trials published within the past decade (Fig. 5), aldosterone antagonists now have an established role in the treatment of certain patients with heart failure.

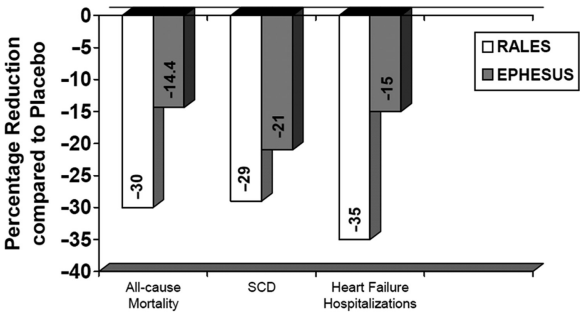


Fig. 5. Relative risk reduction in key outcomes in the major trials of aldosterone antagonism. Compared to placebo, both spironolactone (in RALES) and eplerenone (in EPHESUS) were associated with reductions in major cardiovascular outcomes. All results met statistical significance. SCD: sudden cardiac death.

The Randomized Aldactone Evaluation Study (RALES) randomized 1663 patients who had moderate to severe heart failure and a left ventricular ejection fraction not greater than 35% to either spironolactone (25 mg daily) or placebo against a background of ACEi and diuretics (few patients were taking beta-blockers) *(68)*. RALES was stopped early because of a strongly significant survival advantage in the spironolactone group. There was a striking 11% absolute risk reduction and a 31% relative risk reduction in all-cause mortality by 2 years (HR 0.70, 95% CI 0.60–0.82) that was attributable to both a reduction in sudden death (36% reduction) and progressive pump failure (29% reduction). There was also a 30% reduction in cardiac hospitalizations and a significant improvement in functional status *(68)*. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a larger ($n = 6632$) one of patients immediately after a myocardial infarction who had reduced EF (average LVEF 33%) and signs of heart failure *(69)*. Here patients were randomized to the aldosterone antagonist eplerenone (25–50 mg daily) or placebo against a similar therapeutic background as RALES with the notable exception of much larger beta-blocker usage (75%). Eplerenone caused a 15% reduction in mortality at 1 year (HR 0.85, 95% CI 0.75–0.96) and there were similar reductions in sudden death and heart failure hospitalizations *(69)*.

In clinical trials the aldosterone antagonists were well tolerated, without significant hemodynamic effects; hyperkalemia and gynecomastia (10% with spironolactone and none with eplerenone) were the most frequent major adverse reactions. Although the entry criteria to both major aldosterone antagonist studies enrolled patients with a serum creatinine less than 2.5 mg/dL, there were few patients enrolled with a creatinine greater than 1.5 mg/dL *(11)*. This low prevalence of renal insufficiency, along with the careful monitoring and resources that the clinical trial was able to afford, could explain the wide discrepancy between the amount of symptomatic

hyperkalemia seen in the trials and what has been observed in subsequent community-based studies. Serious hyperkalemia was seen in only 2% of spironolactone-treated subjects in RALES (compared to 1% of patients receiving placebo; *p* not significant for comparison), but in a population-based study of Canadian patients with heart failure there was a dramatic 4.6-fold increase in hospitalizations for hyperkalemia and 6.7-fold increase in hyperkalemic deaths after the publication of the RALES study *(70)*. As a consequence, the most recent heart failure guidelines highlight the imperative for careful patient selection and monitoring when using aldosterone antagonists, particularly in older patients who often have diminished baseline creatinine clearance, in other patients with baseline renal insufficiency, in those using other RAAS inhibitors, or in the presence of comorbidities which impair potassium excretion (e.g., diabetes).

Aldosterone antagonists should be considered for patients with NYHA class III and IV symptoms or post-MI LV dysfunction who do not have significant renal impairment (Cr < 2–2.5 and CrCl > 30–50) or a history of hyperkalemia. The serum potassium should be monitored frequently after starting aldosterone (after 3 days, after 1 week, then monthly for 3 months) and the starting dose should be low (12.5 mg–25 mg daily). This is reflected in the recent heart failure guidelines which gave a class I recommendation for the use of aldosterone antagonists; specifically they stated their use is "reasonable" provided that the risk of hyperkalemia is not high *(11)*. Based on a perceived high risk of hyperkalemia, it is advised that aldosterone inhibitors should not be given to patients already receiving an ACEi *and* an ARB.

6. BETA-ADRENERGIC RECEPTOR BLOCKERS

Beta-adrenergic receptor antagonists (beta-blockers, βB) inhibit the downstream consequences of sustained catecholamine activation in patients with heart failure. The degree of sympathetic nervous system activation has been shown to be an extremely powerful predictor of outcome in patients with heart failure, even better than other clinical (e.g., wedge pressure, pulse) and biochemical factors (e.g., serum sodium) *(71)*; beta-blockers, however, were initially considered to be contraindicated in patients with heart failure due to their negative inotropic activity. Nevertheless, a broad range of clinical studies beginning in the mid-1970s showed these agents to be useful in patients with dilated cardiomyopathy *(72, 73)* (Table 7). The exact mechanism of beta-blocker-induced benefit is not known, but putative effects include antagonism of cardiotoxic levels of circulating catecholamines *(74)* and improvement in systolic function associated with favorable patterns of contractile protein gene expression *(75)*.

Beta-blockers are capable of causing reverse remodeling, causing a *decrease* in left ventricular dimensions, *improvement* in systolic function (as measured by ejection fraction or fractional shortening), and a *return* to

Table 7
Major beta-blocker trials in heart failure[a]

Trial name and date	*Drug and control group*	*NYHA or Killip classification of participants*	*Effect on all-cause mortality HR and 95% CI:*	*Change in all-cause hospitalizations*	*1-year mortality in the control group*	*Caveats*
Chronic heart failure trials						
Carvedilol 1996 $N = 1197$	Carvedilol Goal: 25–50 mg BID Achieved: 23 mg BID (80% achieved goal)	II 53% III 44% IV 3%	HR: 0.35 (0.20–0.61)	All-cause hospitalization not published CV Hospitalization: HR: 0.73 (0.55–0.97)	11%[c]	no change in BP with carvedilol
MERIT-HF 1999 $N = 3991$	Metoprolol succinate Goal: 200 mg QD Achieved: 159 mg (64% reached goal)	II 41% III 55% IV 4%	HR: 0.66 (0.52–0.81)	HR: 0.88 $P = 0.004$[b]	11.0%	
CIBIS-II 1999 $N = 2647$	Bisoprolol Goal: 10 mg QD Achieved: 5.7 mg (43% reached goal)	III 83% IV 17%	HR: 0.66 (0.54–0.81)	HR: 0.80 (0.71–0.91)	13.2%	

Copernicus 2001 $N = 2289$	Carvedilol Goal: 25 mg BID Achieved: 18 mg BID (65% reached goal)	IV 100%	HR: 0.65 (0.52–0.81)	HR: 0.85 $P = 0.003$	19.7%	Carvedilol remained highly effective in the sickest subgroups
Post-myocardial infarction trial						
CAPRICORN 2001 $N = 1959$	Carvedilol 20 mg BID (74% reached target 25 mg BID)	Killip class I 66% II 31% III 3%	HR:0.77 (0.60–0.98)	NS 14% RRR in HF admissions	11%[c]	

[a]The scope of the table is limited to large studies of beta-blockers *approved* for heart failure therapy and in all of these trials, ACEi was the required background therapy if tolerated.

[b]95% confidence interval not published.

[c]Mortality rates estimated from published Kaplan–Meier curves. RRR = Relative Risk Reduction

an elliptical shape *(76)*. Clinical trial results have shown that compared to placebo, beta-blockers may improve left ventricular ejection fraction by as much as 10% (e.g., EF 25–35%) *(77)*. These effects are seen at very low doses but incremental reverse remodeling is seen in a dose-dependent fashion *(78)*.

Though initially felt to be contraindicated in heart failure due to their negative inotropic effects, beta-blockers are now recognized as a critical component of standard heart failure therapy. In 1996 the US Carvedilol Heart Failure Study Group published the results of several prospective trials comparing carvedilol to placebo *(79)*. When the separate studies were combined, the patients randomized to carvedilol were 65% less likely to die than those randomized to placebo. Published 3 years later, the second Cardiac Insufficiency Bisoprolol Study (CIBIS II) randomized 2647 patients with class III–IV heart failure to placebo or bisoprolol *(86)*. Because of the emergence of a highly statistically significant decrease in mortality, this study was stopped early. After a mean of 1.3 years of follow-up, patients randomized to bisoprolol had a highly significant 34% reduction in all-cause mortality. Subgroup analysis showed a homogenous treatment effect and there was an associated 32% decrease in hospitalizations for worsening heart failure. Also published in 1999, but studying a slightly less sick group than CIBIS II, the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) randomized 3991 patients with primarily class II and III heart failure to either long-acting metoprolol or placebo *(80)*. MERIT-HF was also stopped early, after a mean follow-up time of 1 year, because of a highly significant 34% reduction in all-cause mortality in the metoprolol group.

Patients with severe heart failure were relatively underrepresented in the aforementioned trials and there remained a concern that patients with the advanced heart failure would not tolerate the addition of a beta-blocker to their regimen. To address the utility of beta-blockers in this population, the Carvedilol Prospective Randomized Cumulative Survival Study Group (COPERNICUS) randomized 2289 patients with NYHA class IV symptoms and left ventricular ejection fraction less than 25% to therapy with carvedilol or placebo *(81)*. The trial was terminated early after interim analyses found that patients randomized to carvedilol experienced a statistically significant 35% reduction in all-cause mortality. Moreover, in a prespecified subgroup analysis of the patients deemed to be at most risk (LVEF $\leq$ 15%, recurrent hospitalizations, any prior use of inotropic agents), there was a 39% reduction in all-cause mortality, indicating benefit to beta-blocker therapy even in the sickest heart failure patients. In aggregate, beta-blockers are associated with roughly a 30% relative risk reduction in 1-year mortality across the spectrum of patients with chronic heart failure due to LV dysfunction. Beta-blockers reduce cardiovascular hospitalizations, improve functional capacity *(82*, *83)*, and reduce mortality by decreasing progressive pump failure and lowering the incidence of sudden death *(84–86)*. Since some beta-blockers have not been clearly associated with successful mortality reductions in

heart failure patients *(87, 88)*, preference should be given to those agents with proven efficacy in prospective clinical trials (bisoprolol, carvedilol, and metoprolol succinate) *(89)*. Recommended dosing regimens for recommended beta-blockers for the treatment of heart failure are displayed in Table 8. The unique metabolic and vasodilatory effects of carvedilol (perhaps a consequence of its mixed alpha- and beta-adrenergic blocking properties) have fueled some enthusiasm about its potential advantages in heart failure patients. At least one trial (COMET) suggested clinical benefits to carvedilol exceeding those of metoprolol tartrate, but these results have been challenged due to concerns about the relative dosing of the two agents *(90)*. Since no head-to-head trials comparing carvedilol, metoprolol succinate, and bisoprolol have been conducted, there is at present little evidenced-based rationale for favoring one agent over another *(11)*.

Table 8
Beta-blocker doses recommended in the treatment of heart failure

Drug	*Initial dose (mg)*	*Target dose (mg)*
Bisoprolol	1.25 QD	10 QD
Carvedilol	3.125–6.25 BID	25[a] BID
Metoprolol succinate	12.5–25 QD	200 QD

BID (twice daily), QD (once daily).

[a]In patients weighing > 85 kg, the recommended target dose of carvedilol is 50 mg BID.

Since both ACE inhibitors and beta-blockers are associated with important clinical benefits in heart failure patients, and since most beta-blocker trials have demonstrated therapeutic efficacy on the background of ACE-inhibitor therapy, there has been some discussion of which agent should be initiated first. Recently, the CIBIS III investigators showed that beta-blocker initiation could precede ACEi initiation in patients with mild to moderate heart failure without evidence of hypervolemia. In that study of 1010 elderly patients who had previously not received a neuroendocrine antagonist, a "bisoprolol first" strategy was non-inferior to starting with enalapril *(91)*. Nevertheless, others have cautioned the more widespread application of these data, especially in more severely ill patients who would otherwise derive an immediate clinical benefit from vasodilators (e.g., ACEi) *(92)*.

Initiation of beta-blockade should occur in patients with no or minimal signs of volume overload, who demonstrate adequate tissue perfusion. In contrast to patients without heart failure who may have a different indication for beta-blockade (e.g., angina, hypertension), patients with heart failure require careful dose up-titration starting at low doses. In accordance with the experience in clinical trials, patients should be reassessed frequently and the dose is typically doubled every 2 weeks until the target dose is reached. If patients develop mild or moderate symptoms of congestion

with beta-blockade, it is recommended that adjustments in other medications (diuretics, ACEi) precede a decrease or cessation of beta-blockers *(93)*. The most common adverse effect of beta-blockers has been symptomatic bradycardia, but this rarely results in need for hospitalization, and a meta-analysis from multiple trials has shown that if 153 patients were treated with beta-blockers for 1 year, only one patient would need to be withdrawn because of symptomatic bradycardia *(94)*. The effect on blood pressure has ranged from a modest decrease (–1.1/1.6 mmHg in COPERNICUS *(95)*) to no affect (in the U.S. Carvedilol study *(79)*) to a surprising *increase* in blood pressure relative to the placebo group in MERIT-HF and CIBIS-II *(85, 86)*. This is felt to reflect an improvement in stroke volume and is paralleled in the sustained and significant improvement in left ventricular ejection fraction. Even in patients with the most advanced disease (class IV, requiring recent hospitalization or treatment with intravenous inotropes or vasodilators), treatment with carvedilol was tolerated by most subjects and was associated with a significant mortality benefit that began after only 2–3 weeks of treatment. Although dose down-titration was more common with carvedilol (as opposed to placebo) in the most advanced disease subgroup, these patients were no more likely to require hospitalization and were less likely to be withdrawn from the study *(95)*. Target doses were often reached in clinical trials (65–80% of the time) but this has proven more difficult in practice outside of clinical trials, where patients tend to be older and have more comorbidities *(96)*. Although there are situations where the use of beta-blockers is either proscribed or potentially dangerous (e.g., high grade AV block, profound resting bradycardia), it may be needlessly withheld from patients with chronic obstructive pulmonary disease or stable mild asthma in spite of demonstrated safety in these populations *(97)*. Similarly, recent analysis from the OPTIMIZE-HF registry *(98)* suggests that beta-blocker therapy withdrawal in patients hospitalized with decompensated heart failure may actually be harmful, although this hypothesis has not yet been tested prospectively. Provided that there are not contraindications as described above, the consensus guidelines strongly support the use of beta-blockers across the spectrum of left ventricular dysfunction (class I recommendation) *(11)*.

7. ANTICOAGULATION

A multitude of patients have benefited from the reduced cardiovascular events associated with the appropriate use of anticoagulant and anti-platelet medications. Many patients with heart failure have pre-existing coronary artery disease, an indication for life-long aspirin therapy, or atrial fibrillation, which in most is an indication for anticoagulation with warfarin. Venous thromboembolism (VTE) is common in chronically ill patients, and heart failure is considered a risk factor for VTE *(99)*. Though the duration and intensity of anticoagulation for patients with a history of VTE

continue to be modified, there remains no question that therapeutic anticoagulation is a fundamental part of therapy for VTE. Nevertheless, in the large number of patients with heart failure and without another indication for anti-thrombotic medications, the role of anticoagulants and anti-platelet agents remains unsettled. Some reports have highlighted the increased relative risk of stroke in heart failure patients (particularly among those with severely reduced ejection fraction), but much of this risk may have been confounded by concomitant atrial fibrillation *(100)*. Data from prospective, randomized trials of prophylactic anticoagulation for prevention of thrombotic events in heart failure patients, however, are lacking. Three trials were designed to guide our strategies to prevent thromboembolism in heart failure patients: Warfarin and Antiplatelet Therapy in Chronic CHF (WATCH), Warfarin and Antiplatelet Therapy in Chronic CHF (WASH), and the ongoing Warfarin–Aspirin Reduced Cardiac Ejection Fraction (WARCEF). The WATCH study was stopped early due to poor recruitment *(101)* and the WASH study was a small pilot study intended to test the *feasibility* of anticoagulation *(102)*. The WARCEF trial is sponsored by the National Institute of Neurologic Disorders and Stroke (NINDS) and looks to enroll 2860 patients with LVEF $\leq$ 35%, on ACEi and without another accepted indication for anticoagulation (e.g., atrial fibrillation, mechanical heart valve). This trial began enrolling in 2002 and the primary outcome will be time to first ischemic stroke, intracerebral hemorrhage, or death from any cause *(103)*. Pending more definitive data, however, the recent AHA/ACC guidelines acknowledge the uncertainty regarding the necessity of prophylactic anticoagulation for prevention of embolic events in patients with heart failure and LV dysfunction, and advise initiation only when an accepted indication exists *(11)*.

8. STATINS

Inhibition of HMG coenzyme – a reductase with statins – has been shown to benefit patients across a wide spectrum of vascular diseases. The pleiotropic effects of these medications are frequently cited to explain apparent improvements in clinical outcomes independent of lipid-lowering effects. Data derived from post hoc analyses initially suggested a possible benefit of statins in patients with systolic heart failure *(104, 105)*. The largest prospective, randomized assessment of this hypothesis was the CORONA Trial *(106)*, which randomized 5011 patients with NYHA class II–IV heart failure to rosuvastatin 10 mg vs placebo. There were no significant differences in the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at a median follow-up of 33 months. Thus, there is no clear evidence supporting the use of statins in patients with heart failure who are not considered to be candidates for this therapy based on established indications.

9. MEDICATIONS TO AVOID

The importance of a careful review of all medications cannot be overlooked. Ensuring that potentially harmful medicines have been avoided complements the prescription of medicines known to be efficacious in the treatment of heart failure (Table 9). The AHA/ACC heart failure guidelines specifically recommend the general avoidance of most antiarrhythmic medications, all non-dihydropyridine calcium channel blockers, and all nonsteroidal anti-inflammatory medications (NSAIDs) *(11)*. In addition, there are other classes of widely used medications that should also be avoided; among these are the thiazolidinediones *(107)* (e.g., pioglitazone) and the type 3 phosphodiesterase inhibitors (cilostazol) *(108)*. Class I antiarrhythmic medications have inherently negative inotropic effects that are more pronounced in the presence of left ventricular systolic dysfunction, and these agents have been shown to be proarrhythmic and associated with an increased risk of mortality in patients with structural heart disease. Two class III agents, amiodarone and dofetilide, have been demonstrated to be safe in this patient population, but other agents in this class, sotalol and ibutilide, have been shown to have high proarrhythmic effects in patients with left ventricular systolic dysfunction. A newer class III agent, dronedarone, was recently shown to increase mortality in patients with severe heart failure and left ventricular dysfunction *(109)*.

L-type calcium channel blockers (e.g., verapamil and diltiazem) exhibit a negative inotropic and chronotropic effect. The limited published experience with these drugs has shown them to be harmful to patients with symptomatic or asymptomatic LV dysfunction. A post hoc analysis of the Diltiazem Multicenter Postinfarction Study (MDPIT) showed that compared to placebo, diltiazem was associated with a highly significant 75% increase in symptomatic heart failure ($p = 0.0017$) when given to patients with an LVEF < 40% *(110)*. Due to a shared pharmacologic effect, and smaller studies suggesting harm, verapamil is also to be avoided in this patient population. Though nifedipine acts at a different calcium channel than diltiazem and verapamil, a small study of short-acting nifedipine showed that when added to stable patients treated with diuretics and digoxin, an ~25% absolute excess risk of decompensated heart failure was observed compared to patients receiving isosorbide dinitrate *(111)*. Two other dihydropyridine calcium channel blockers have been studied in heart failure in large, well-designed clinical trials. Both amlodipine *(51)* and felodipine *(112)* have been shown to be safe in this population but neither was associated with an improvement in mortality or other important endpoints. On this basis, these two agents can be considered for control of blood pressure in patients with heart failure who continue to be hypertensive.

The beneficial and harmful effects of NSAIDs are related to their inhibition of prostaglandin synthesis. The hemodynamic consequence of which is an increase in systemic vascular resistance and decrease in renal perfusion,

Table 9
Commonly used medicines that are potentially harmful to patients with heart failure

Drug	*Example*	*Mechanism of harm*	*Caveats*
Class I antiarrhythmics	Procainamide Flecainide Quinidine	Pro-arrhythmia Negative Inotropy	
Class III antiarrhythmics	Sotalol Ibutilide	Pro-arrhythmia Negative Inotropy (sotalol, amiodarone)	Amiodarone and dofetilide have an acceptable risk profile in patients with heart failure
Calcium channel blockers	Diltiazem Verapamil Nifedipine	Bradyarrhythmia Negative inotropy	Amlodipine and felodipine have an acceptable risk profile in patients with heart failure
NSAIDs[a]	Ibuprofen Diclofenac Celecoxib	Increased SVR Decreased renal perfusion Increased atherothrombotic events	
Thiazolidinediones	Rosiglitazone Pioglitazone	Fluid retention	Can be used cautiously in patients with NYHA class I and II heart failure and should be avoided in more advanced heart failure.
Cilostazol	Pletal	Increased heart rate and ventricular ectopy	

Antiarrhythmic classification based on the Vaughn–Williams schemata.

SVR – systemic vascular resistance.

[a]Does not include ASA, which is not proscribed in this population.

both of which have obvious negative implications for patients with heart failure. Moreover, NSAIDs increase the risk of atherothrombotic events *(113)*, which is a key risk factor for heart failure. One population-based study showed that NSAID use was associated with a twofold increased risk for hospitalization for heart failure and a tenfold increased risk if patients had underlying heart disease *(114)*.

10. CONSENSUS STATEMENTS

The recently published AHA/ACC guidelines (Table 10) provide a framework for the treatment of patients with hitherto asymptomatic LV systolic dysfunction (Stage B HF) and patients with LV dysfunction and current or

Table 10
AHA/ACC guidelines for the pharmacotherapy of chronic heart failure

Class of recommendation	*Stage B heart failure*	*Stage C heart failure*		
		NYHA I	*NYHA II*	*NYHA III–IV*
Class I	ACEi Beta-blockers	ACEi Beta-blockers ARB[a]	ACEi Beta-blockers ARB[a]	ACEi Beta-blockers ARB[a] Aldosterone antagonists[b]
Class IIa	ARB[a]	ARB	ARB	ARB Digoxin Hyd-Iso[c]
Class IIb		Hyd-Iso[d]	Hyd-Iso[d]	Hyd-Iso[d]
Class III	Digoxin CCB	NSAIDs Most antiarrhythmics CCB The combined use of ACEi, ARB, and aldosterone antagonists.		

Stage B: Asymptomatic left ventricular (LV) dysfunction.

Stage C: LV dysfunction with any history of heart failure symptoms.

Class I recommendation: Conditions for which there is evidence and/or general agreement that a given treatment is beneficial, useful, and effective.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy less well established by evidence/opinion.

Class III: Conditions for which there is general agreement that a treatment is not useful/effective and in some cases may be harmful.

[a]An ARB can be substituted for patients with intolerance to ACEi.

[b]The use of aldosterone antagonists is limited to patients without severe renal insufficiency and requires the ability to carefully follow serum potassium levels.

[c]In addition to ACEi and beta-blockers.

[d]In patients not able to tolerate an ACEi or an ARB. Hyd-Iso = hydralazine and isosorbide dinitrate

prior symptomatic heart failure (Stage C HF). Beta-blockers and ACEi are indicated across this spectrum of illness and unless they are not tolerated, all patients with LV dysfunction should be treated with these two agents. If patients do not tolerate an ACEi due to cough, an ARB should be used in their place. An ARB can be combined with ACEi and beta-blocker but should not be added to patients already receiving an aldosterone antagonist. For patients with persistent symptoms (NYHA class III and IV), an aldosterone antagonist is indicated and therapy with digoxin is generally recommended. Hyd-Iso is an option for patients who do not tolerate therapy with either an ACEi or ARB and can be an add-on to ACEi in patients with persistent symptoms. In spite of a wealth of clinical trial data and the reminder provided by consensus guidelines, these medications remained underprescribed in community studies and registry data. Moreover, patients with more advanced disease are incrementally less likely to receive evidence-proven, life-saving therapies such as beta-blockers and ACEi *(115)*.

REFERENCES

1. Eichhorn EJ, Gheorghiade M. Digoxin – new perspective on an old drug. N Engl J Med 2002;347:1394–1395.
2. Bristow MR, Linas S, Port JD. Drugs in the treatment of heart failure. In: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed., vol. 1. Philadelphia: Elsevier Saunders, 2005:569–602.
3. Smith TW. Digoxin in heart failure. N Engl J Med 1993;329:51–53.
4. Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, Smith LK, Van Voorhees L, Gourley LA, Jolly MK. Withdrawl of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. N Engl J Med 1993;329:1–7.
5. Garg R, Gorlin R, Smith T, Yusuf S. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–533.
6. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 2003;289:871–878.
7. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med 2002;347:1403–1411.
8. Adams KF, Patterson H, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, Gheorghiade M. Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigation Group trial. J Am Coll Cardiol 2005;46:497–504.
9. Slatton ML, Irani WN, Hall SA, Marcoux LG, Page RL, Grayburn PA, Eichhorn EJ. 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;29:1206–1213.
10. Adams KF, Gheorghiade M, Uretsky BF, Young JB, Ahmed S, Tomasko L, Packer M. Patients with mild heart failure worsen during withdrawal from digoxin therapy. J Am Coll Cardiol 1997;30:42–48.
11. Hunt S, Abraham W, Chin M, et al., ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation 2005;112:154–235.
12. Greger R. New insights into the molecular mechanisms of the action of diuretics. Nephrol Dial Transplant 1999;14:536–540.

13. Brater DC. Diuretic therapy. N Engl J Med 1998;339:387–395.
14. Pickkers P, Dormans TP, Russel FG, Hughes AD, Thien T, Schaper N, Smits P. Direct vascular effects of furosemide in humans. Circulation 1997;96:1847–52.
15. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol 2006;97:1759–1764.
16. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, Frid DJ, Nye RG, Pressler ML, Wertheimer JH, Packer M; PRAISE Investigators. Prospective randomized amlodipine survival evaluation. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J 2002;144:31–38.
17. Cosin J, Diez J; TORIC investigators. Torsemide in chronic heart failure: results of the TORIC study. Eur J Heart Fail 2002;4:507–13.
18. Costanzo M, Guglin M, Saltzberg M, Jessup M, Bart B, Teerlink J, Jaski B, Fang J, Feller E, Haas G, Anderson A, Schollmeyer M, Sobotka P; UNLOAD Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007 Feb 13;49:675–83.
19. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, Wagnoner LE, Givertz MM, Liang CS, Neibaur M, Haught WH, LeJemtel TH; Nesiritide Study Group. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. N Engl J Med 2000 Jul 27;343(4): 246–53.
20. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. JAMA 2007 Mar 28;297(12):1319–31.
21. Givertz MM, Massie BM, Fields TK, Pearson LL, Dittrich HC; CKI-201 and CKI-202 Investigators. The effects of KW-3902, an adenosine A1-receptor antagonist, on diuresis and renal function in patients with acute decompensated heart failure and renal impairment or diuretic resistance. J Am Coll Cardiol 2007 Oct 16;50: 1551–1560.
22. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E; Studies of Left Ventricular Dysfunction. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol 2003 Aug 20;42:705–8.
23. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med 2004;351:543–551.
24. Janssens HJ, van de Lisdonk EH, Janssen M, van den Hoogen HJ, Verbeek AL. Gout, not induced by diuretics? A case-control study from primary care. Ann Rheum Dis 2006;65:1080–3.
25. Hunter DJ, York M, Chaisson CE, Woods R, Niu J, Zhang Y. Recent diuretic use and the risk of recurrent gout attacks: The online case-crossover gout study. J Rheumatol 2006;33:1341–5.
26. Braunwald E. ACE Inhibitors – A cornerstone of the treatment of heart failure. N Engl J Med 1991;325:351–353.
27. 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.
28. Swedberg K for 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;23:1429–1435.
29. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Cuddy TE, Davis BR, Geletman Em, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM. Effect of captopril on

mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. results of the survival and ventricular enlargement trial (SAVE). N Engl J Med 1992;327:669–677.
30. Ball SG for the AIRE investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993;342:821–828.
31. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333:1670–6.
32. Rogers WJ, Johnstone DE, Yusuf S, Weiner DH, Gallagher P, Bittner VA, Ahn S, Schron E, Shumaker SA, Sheffield LT. Quality of life among 5,025 patients with left ventricular dysfunction randomized between placebo and enalapril: The Studies of Left Ventricular Dysfunction. The SOLVD Investigators. J Am Coll Cardiol 1994;23:393–400.
33. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moye L, Braunwald E. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: A systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000;355:1575–81.
34. Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, Dolan N, Edens TR, Ahn S, Kinan D, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. Circulation 1992;86:431–438
35. Nanas JN, Alexopoulos G, Anastasiou-Nana MI, Kardis K, Tirologos A, Zobolos S, Pirgakis V, Anthopoulos L, Sideris D, Stamatelopoulos SF, Moulopoulos SD. Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: A multicenter study. high dose enalapril study group. J Am Coll Cardiol 2000;36:2090–2095.
36. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF. 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.
37. Poole-Wilson PA for the NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. Eur Heart J 1998;19:481–9.
38. Kostis JB, Shelton B, Gosselin G, Goulet C, Hood WB Jr, Kohn RM, Kubo SH, Schron E, Weiss MB, Willis PW 3rd, Young JB, Probstfield J. Adverse effects of enalapril in the studies of left ventricular dysfunction (SOLVD). SOLVD Investigators. Am Heart J 1996;131:350–355.
39. Packer M, Medina N, Yushak M. Relation between serum sodium concentration and the hemodynamic and clinical responses to converting enzyme inhibition with captopril in severe heart failure. J Am Coll Cardiol 1984;3:1035–43.
40. Hood WB Jr, Youngblood M, Ghali JK, Reid M, Rogers WJ, Howe D, Teo KK, LeJemtel TH. Initial blood pressure response to enalapril in hospitalized patients (Studies of Left Ventricular Dysfunction [SOLVD]). Am J Cardiol 1991 Dec 1;68(15):1465–1468.
41. Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med 1992;327:678–84.
42. Bart BA, Ertl G, Held P, Kuch J, Maggioni AP, McMurray J, Michelson EL, Rouleau JL, Warner Stevenson L, Swedberg K, Young JB, Yusuf S, Sellers MA, Granger CB,

Califf RM, Pfeffer MA. Contemporary management of patients with left ventricular systolic dysfunction. Results from the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) Registry. Eur Heart J 1999;20:1182–1190.
43. McDowell S, Coleman JJ, Ferner RE. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. BMJ 2006;332:1177–1181.
44. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K; CHARM Investigators and Committees. 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;362:772–776.
45. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355:1582–1587
46. Dickstein K, Kjekshus J for the OPTIMAAL Study group. Effects of losartan and captopril on mortality in high-risk patients after acute myocardial infarction: the OPTIMAAL randomized trial. Lancet 2002;360:752–760.
47. Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau J-L, Køber L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM, the Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349: 1893–1906.
48. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. 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 Sep 6;362(9386):767–71.
49. Jong P, Demers C, McKelvie RS, Liu PP. Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. J Am Coll Cardiol 2002;39:463–470.
50. Cohn JN, Ziesche S, Smith R, Anand I, Dunkman WB, Loeb H, Cintron G, Boden W, Baruch L, Rochin P, Loss L. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril. V-HeFT III. Circulation 1997;96:856–863.
51. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer JH, Cropp AB, DeMets DL. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. N Engl J Med 1996;335: 1107–1114.
52. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr K, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B. Effect of vasodilator therapy on mortality in chronic congestive heart failure. N Engl J Med 1986;314:1547–1552.
53. Zimmet JM, Hare JM. Nitroso-Redox interactions in the cardiovascular system. Circulation 2006;114:1531–1544.
54. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel MM, Cohn JN. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure (A-HeFT). N Engl J Med 2004;351:2049–2057.
55. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, Bhat G, Goldman S, Fletcher R, Doherty J, Hughes CV, Carson P, Cintron G, Shabetai R, Haakenson C. A comparison of enalapril with hydralazine-isosorbide in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–310.

56. Braunwald E. ACE Inhibitors – A cornerstone of the treatment of heart failure. N Engl J Med 1991;325:351–353.
57. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. J Card Fail 1999;5:178–187.
58. Moran AE, Cooper RS. Isosorbide and hydralazine in blacks with heart failure. N Engl J Med 2005;352:1041.
59. Bibbins-Domingo K, Fernandez A. BiDil for heart failure in black patients: implications of the U.S. food and drug administration approval. Ann Intern Med 2007;146:52–56.
60. Temple R, Stockbridge NL. BiDil for heart failure patients: The U.S. food and drug administration perspective. Ann Intern Med 2007;146:57–62.
61. Anand IS, Tam SW, Rector TS, Taylor AL, Sabolinski ML, Archambault WT, Adams KF, Olukotun AY, Worcel M, Cohn JN. Influence of blood pressure on the effectiveness of a fixed-dose combination of isosorbide dinitrate and hydralazine in the African-American Heart Failure Trial. J Am Coll Cardiol 2007;49:32–39.
62. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, Tawakol A, Gerzten RE, Systrom DM, Bloch KD, Semigran MJ. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation 2007:116:1555–1562.
63. Behlin A, Rohde LE, Colombo FC, Goldraich LA, Stein R, Clausell N. Effects of a 5′phosphodiesterase four-week long inhibition with sildenafil in patients with chronic heart failure: a double-blind, placebo-controlled clinical trial. J Card Fail 2008 Apri;14(3):189–97.
64. Guazzi M, Smaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. J Am Coll Cardiol 2007 Nov 27;50(22):2136–44.
65. Weber K. Aldosterone in congestive heart failure. N Engl J Med 2001;345:1689–1697.
66. Chhokar VS, Sun Y, Bhattacharya SK, Ashokas R, Myers LK, Xing Z, Smith RA, Gerling IC, Weber KT. Hyperparathyroidism and the calcium paradox of aldosteronism. Circulation 2005;111:871–878.
67. Struthers AD. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. J Card Fail 1996;2:47–57.
68. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709–717.
69. Pitt, B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;342:1309–1321.
70. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med 2004;351:543–551.
71. Cohn JN, TB Levine, MT Olivari, V Garberg, D Lura, GS Francis, AB Simon, and T Rector. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819.
72. Black JW, Crowther AF, Shanks RG, Smith LH, Dornhorst AC. A new adrenergic beta-receptor antagonist. Lancet 1964;283:1080–1081.
73. Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J 1975;37:1022–36.
74. Bristow, MR. β-Adrenergic receptor blockade in chronic heart failure. Circulation 2000;101:558–569.

75. Lowes BD, Gilbert EM, Abraham WT, Minobe WA, Larrabee P, Ferguson D, Wolfel EE, Lindenfield J, Tsvetkova T, Robertson AD, Quaife RA, Bristow MR. Myocardial gene expression in dilated cardiomyopathy treated with beta-blocking agents. N Engl J Med 2002;346:1357–1365.
76. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling – concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol 2000;35:569–582
77. Colucci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB, Krueger SK, Hershberger R, Uretsky BF, Bowers JA, Sackner-Bernstein JD, Young ST, Holsclaw TL, Lukas MA. Carvedilol inhibits progression in patients with mild symptoms of heart failure. Circulation 1996;94:2800–2806.
78. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996;94:2807–2816.
79. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349–1355.
80. Hjalmarson A, Goldstein S, Deedwania P et al. Effects of controlled-release metoprolol on total mortality, hospitalizations and well-being in patients with heart failure (MERIT-HF). JAMA 2000;283:1295–1302.
81. Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau J, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–1658
82. Hjalmarson A, Goldstein S, Deedwania P et al. Effects of controlled-release metoprolol on total mortality, hospitalizations and well-being in patients with heart failure (MERIT-HF). JAMA 2000;283:1295–1302.
83. Packer M, Colucci W, Shusterman NH et al. Double-blind, placebo-controlled study of carvedilol in patients with moderate to severe heart failure. Circulation 1996;94:2793–2799.
84. Kowey PR. A review of carvedilol arrhythmia data in clinical trials. J Cardiovasc Phamacol Theraput 2005;10:S59-S68.
85. Fagerberg B et al. Effect of metoprolol CD/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–2007.
86. Dargie HJ, Lechat P et al. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. Lancet 1999;353:9–13.
87. Eichhorn E, Domanski M; et al for the BEST Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344:1659–1667
88. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, Gilbert EM, Johnson MR, Goss FG, Hjalmarson A. Benefifial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 1993;342:1441–1446
89. Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Bristow MR, Cohn JN, Lukas MA, Young ST, Packer M. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. N Engl J Med 2001;344:1358–65.
90. Poole-Wilson PA, Swedberg K, Cleland JGF, Li Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chromic heart failure in the carvedilol or metoprolol European trial (COMET): randomized controlled trial. Lancet 2003;362:7–13
91. Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, Ponikowski P, Skene A, van de Ven L, Verkenne P, Lechat P. 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;112:2426–2435.
92. Fang J. Angiotensin-converting enzyme inhibitors or β-blockers in heart failure: Does it matter who goes first? Circulation 2005;112:2380–2382.
93. Eichhorn EJ, Bristow MR. Practical guidelines for initiation of beta-adrenergic blockade in patients with chronic heart failure. Am J Cardiol 1997;79:794–798.
94. Ko DT, Hebert PR, Coffey CS, Curtis JP, Foody JM, Sedrakyan A, Krumholz HM. Adverse effects of β-blocker therapy for patients with heart failure. A quantitative overview of randomized trials. Arch Intern Med 2004;164:1389–1394.
95. Krum H, Roecker EB, Mohacsi P, Rouleau JL, Tendra M, Coats AJS, Fowler MB, Packer M. Effects of initiating carvedilol in patients with severe chronic heart failure. results from the COPERNICUS Study. JAMA 2003;289:712–718.
96. Stevenson LW. Beta-blockers for stable heart failure. N Engl J Med 2002;346: 1346–1347.
97. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective β-Blockers in patients with reactive airway disease: A meta-analysis. Ann Intern Med 2002;137:715–725.
98. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB; OPTIMIZE-HF Investigators and Coordinators. 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 Jul 15;52(3):190–9.
99. Beemath A, Stein PD, Skaf E, Al Sibae MR, Alesh I. Risk of venous thromboembolism in patients hospitalized with heart failure. Am J Cardiol 2006:98:793–795.
100. Freudenberger RS, Halperin JL. Should we use anticoagulation for patients with chronic heart failure? Nat Clin Pract Cardiovasc Med 2006;3:580–581.
101. Massie BM, Krol WF, Ammon SE, Armstrong PW, Cleland JG, Collins JF, Ezekowitz M, Jafri SM, O'Connor CM, Packer M, Schulman KA, Teo K, Warren S. The Warfarin and Antiplatelet Therapy in Heart Failure trial (WATCH): rationale, design, and baseline patient characteristics. J Card Fail 2004;10:113–4.
102. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. 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.
103. Pullicino P, Thompson JLP, Barton B, Levin B, Graham S, Freudenberger RS. Warfarin Versus Aspirin in Patients with Reduced Cardiac Ejection Fraction (WARCEF): rationale, objectives, and design. J Card Fail 2006;12:39–46.
104. Khush KK, Waters DD, Bittner V, Deedwania PC, Kastelein JJ, Lewis SJ, Wenger NK. Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. Circulation 2007 Feb 6;115(5):576–83.
105. Domanski M, Coady S, Felg J, Tian X, Sachdev V. Effect of statin therapy on survival in patients with nonischemic dilated cardiomyopathy (from the Beta Blocker Evaluation of Survival Trial [BEST]). Am J Cardiol 2007 May 15:99(10):1448–50.
106. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Janosi A, Kamensky G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel J, Wikstrand J. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007 Nov 29;357(22):2248–61.
107. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LHM, Kahn R. Thiazolidinedione use, fluid retention, and congestive heart failure. A consensus statement from the American Heart Association and American Diabetes Association. Circulation 2003;108:2941–2948.

108. Amabile CM, Spencer AP. Keeping your patient with heart failure safe. Arch Intern Med 2004;164:709–720.
109. Kober L, Torp-Pederson C, McMurray JJ, Gotzsche O, Levy S, Crigins H, Amlie J, Carlsen J; Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008 June 19:358(25):2678–87.
110. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in post-infarction patients with early reduction in ejection fraction. Circulation 1991;83:52–60.
111. Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola S. A prospective, randomized, double-blind, cross-over study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation 1990;82:1954–1961.
112. Cohn, JN, Ziesche, S, Smith, R, Anand, I, Dunkman, WB, Loeb, H, Cintron, G, Boden, W, Baruch, L, Rochin, P, Loss, L. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Circulation 1997;96: 856–863.
113. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs. An update for clinicians: A scientific statement from the American Heart Association. Circulation 2007;115:1634–1642.
114. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients. Arch Intern Med 2000;160:777–784.
115. Lee DS, Tu JV, Juurlink DN, Alter DA, Ko DT, Austin PC, Chong A, Stukel TA, Levy D, Laupacis A. Risk-treatment mismatch in the pharmacotherapy of heart failure. JAMA 2005;294:1240–1247.

http://www.springer.com/978-1-58829-994-9

Device Therapy in Heart Failure
Maisel, W.H. (Ed.)
2009, X, 400 p. 140 illus., 46 illus. in color., Hardcover
ISBN: 978-1-58829-994-9
A product of Humana Press