Section 2 Treatment modalities

4 Neurohormonal blocking agents in the treatment of patients with left ventricular dysfunction and heart failure

Ruchika Dutta, MD and Barry H. Greenberg, MD

Division of Cardiology, University of California, San Diego, California, USA

Introduction

Heart failure is a clinical syndrome characterized by inability of the heart to provide adequate tissue perfusion or its ability to do so only at elevated filling pressures. Numerous structural and/or functional disorders of the heart, including coronary artery disease, hypertension, valvular abnormalities, infiltrative or congenital diseases, infections, and familial cardiomyopathies can cause heart failure. As these conditions damage and/or increase load on the myocardium they activate a variety of compensatory mechanisms to increase pre-load, promote myocardial hypertrophy (often in association with cardiac chamber dilation), and elevate heart rate. Many of these compensatory changes are the result of neurohormonal activation that occurs both systemically and within the heart itself. While neurohormonal activation may help to sustain cardiac function in the short-term, the long-term impact is recognized to be highly deleterious [1]. This latter insight has provided the pathophysiologic rationale for using neurohormonal blocking agents for the treatment of heart failure.

Involvement of neurohormonal activation in the pathogenesis and progression of heart failure has been studied extensively. The most important pathways are the renin-angiotensin-aldosterone (RAAS) and the sympathetic nervous system (SNS). As noted above, these systems initially help maintain organ perfusion, but over time their activation is maladaptive and leads to further deterioration in left ventricular (LV) function [2]. Some of the adverse effects of neurohormonal activation are fluid retention, vascular dysfunction, and most importantly, cardiac remodeling (Figure 4.1). Over the past two decades results of large-scale clinical trials have provided incontrovertible evidence that inhibiting RAAS and SNS activation significantly reduces morbidity and mortality in a broad spectrum of heart failure patients [1,2,3]. Hence, treatment with drugs that target these systems have emerged as the cornerstones of heart failure therapy. The specific pharmacologic agents, namely, beta-blockers, ACE inhibitors (ACEI), angiotensin receptor blockers (ARBs), and aldosterone blockers, along with practical strategies for their utilization, will be discussed in this chapter. The clinical data supporting use of these agents in chronic heart failure and in patients with recent myocardial infarction (MI) will be presented using a format based on the American College of Cardiology/American Heart Association (ACC/AHA) staging classification [4] (Table 4.1).
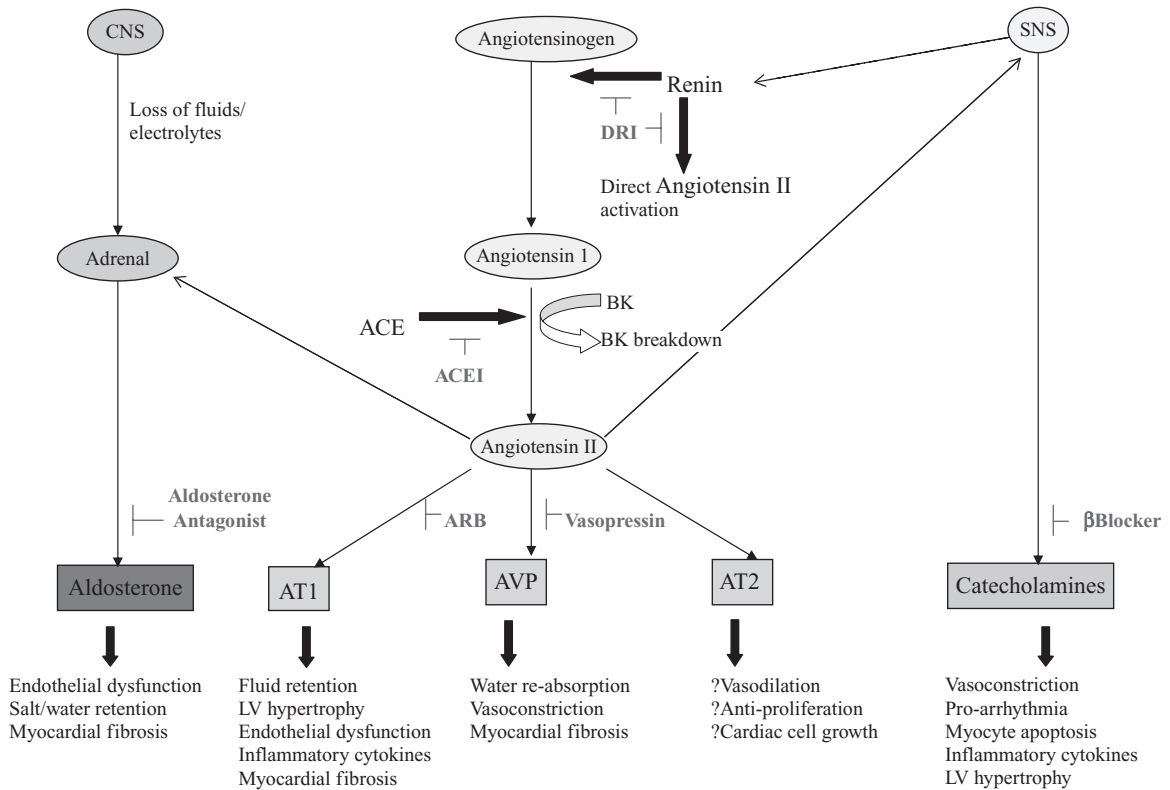
Figure 4.1 Neurohormonal pathways and sites of action of pharmacologic agents

DRI = direct renin inhibitors; Ang II = angiotensin II; ACEI = ACE inhibitors; ARB = angiotensin receptor blockers; AT1 = angiotensin receptor 1; AT2 = angiotensin receptor 2; AVP = arginine vasopressin; BK = bradykinin; LV = left ventricle; SNS = sympathetic nervous system.

Beta-adrenergic blocking agents (beta-blockers)

Beta-blockers inhibit beta-adrenergic receptor activation by catecholamines (Figure 4.1). In the setting of heart failure they inhibit and/or reverse LV remodeling, have anti-arrhythmic effects, improve myocardial diastolic perfusion, reduce myocardial oxygen consumption, and possibly decrease production of pro-inflammatory cytokines [1,3].

The effects of beta-blockade on cardiac remodeling, ventricular performance, morbidity, and mortality have been extensively evaluated in heart failure and post-MI patients. Several large randomized,

placebo-controlled trials (RCTs) have confirmed the role of beta-blockers in slowing the progression of heart failure and improving survival [5–13]. These are summarized in Table 4.2. It is important to note that beta-blockers are a heterogenous group of agents with differences in relative potency of beta-1 and beta-2 blockade, and some possess additional alpha-1 or non-adrenergic related properties (Table 4.3). Hence, beta-blockers should not be considered a homogenous class of drugs and their efficacy may vary considerably. At present only three agents have been shown to improve survival in chronic heart failure, these are: sustained-release metoprolol succinate, bisoprolol, and carvedilol.

Table 4.1 ACC/AHA stages of heart failure

Stage A	Stage B	Stage C	Stage D
Patients at high risk of developing heart failure due to presence of conditions that are strongly associated with the development of heart failure. Such patients have no identified cardiac structural abnormality and have never shown signs or symptoms of heart failure.	Patients who have developed structural heart disease that is strongly associated with the development of heart failure but who have never shown signs or symptoms of heart failure.	Patients who have current or prior symptoms of heart failure associated with underlying structural heart disease.	Patients with advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy and who require specialized interventions.

Reference: 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 (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation. 2005 Sep 20;112(12):e154–235. Reproduced with permission from the American Heart Association.

Table 4.2 Clinical trials with beta-blockers

Study	Population	Total (n)	Beta-blocker	ACC Stage	Results
U.S. Carvedilol	EF $\leq$ 40%	1,094	Carvedilol	C, D	48% RR heart failure progression[*] (1° endpoint) 65% RRR overall mortality 27% reduction CV hospitalization
COPERNICUS	EF < 25%	2,289	Carvedilol	D	35% RRR overall mortality (1° endpoint) 24% reduction in composite death and hospitalization
MERIT-HF	EF $\leq$ 40%	3,991	Metoprolol XL	C, D	34% RRR overall mortality (1° endpoint) 41% reduction in SCD
CIBIS II	EF $\leq$ 35%	2,647	Bisoprolol	C, D	34% RRR in overall mortality (1° endpoint) 32% RRR death/hospitalization 42% RRR sudden cardiac death
REVERT	EF < 40%	149	Metoprolol XL	B	200 mg dose: LVEF ↑ 6% LVESVI ↓ 14 mL/m^2 (1° endpoint) 50 mg dose: LVEF ↑ 4%
CAPRICORN	EF $\leq$ 40% 3–21 days post-MI	1,959	Carvedilol	B, C, D	23% reduction all-cause mortality (1° endpoint) 59% reduction atrial arrhythmias 70% fewer ventricular arrhythmias

[*]Heart failure progression was defined as death due to heart failure, hospitalization for heart failure, or a sustained increase in heart failure medications.
COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival trial; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; REVERT = REversal of VEntricular Remodeling with Toprol-XL; CAPRICORN = Carvedilol Post-Infarct Survival Control in LV Dysfunction; RRR = relative risk reduction; Metoprolol XL = extended-release metoprolol; SCD = sudden cardiac death; CV = cardiovascular; LVEF = left ventricular ejection fraction; LVESVI = Left ventricular end-systolic volume index; MI = Myocardial Infarction.

Table 4.3 Pharmacologic properties of various beta-blockers

Beta-blocker	β1/ β2 activity	α1-receptor antagonist	Vasodilator activity
Bisoprolol	$1 \gg 2$	−	−
Bucindolol	$1 = 2$	−	+
Carvedilol	$1 = 2$	+	+
Metoprolol	$1 \gg 2$	−	−
Nebivolol	$1 \gg 2$	−	+
Propranolol	$1 = 2$	−	−

Reference: Abraham WT, Krum H. Heart Failure: A Practical Approach to Treatment. McGraw-Hill Medical Publishing. June 2007.

Evidence

Stage B heart failure

Patients with Stage B heart failure have structural heart disease without current or prior signs or symptoms of heart failure [4].

Post-MI

The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial established the role of beta-blockers in patients with post-MI LV dysfunction (LVD), either with or without symptoms of heart failure [5]. This study enrolled 1959 patients with evidence of LV dysfunction (LVEF ≤40) between 3–21 days after an acute-MI. Patients in CAPRICORN received standard therapy, including ACEIs, aspirin, anticoagulants, and revascularization (if indicated). The primary endpoints included all-cause mortality, and all-cause mortality or hospital admission for cardiovascular (CV) causes. Patients who were randomized to carvedilol (uptitrated to a target dose of 25 mg twice daily) experienced a significant 23% reduction in all-cause mortality and a 40% reduction in the risk of subsequent fatal and non-fatal MIs. There was no significant difference between the carvedilol and placebo groups for the co-primary endpoint of all-cause mortality or CV hospitalization. In a subset of the CAPRICORN trial population, the incidence of atrial and ventricular arrhythmias was also reduced in the carvedilol group [6]. In the CAPRICORN Echo Substudy, quantitative echocardiography was performed on 127 patients before randomization to placebo or carvedilol group, and repeated after 1, 3, and 6 months of treatment [7]. Addition of carvedilol to ACEI therapy had beneficial effects on LV remodeling with reduction in LV end-systolic volume and an average increase in LVEF by 5% at 6 months, in contrast to lack of improvement in the placebo group.

Asymptomatic LV dysfunction

The REversal of VEntricular Remodeling with Toprol-XL (REVERT) trial provided valuable information regarding benefits of beta-blockade on LV remodeling in asymptomatic patients with LV dysfunction of either ischemic or non-ischemic etiology [8]. Patient with LVEF < 40% on stable ACEI or ARB therapy, who were without signs or symptoms of heart failure were randomized to either placebo or metoprolol succinate titrated to target doses of either 50 mg or 200 mg daily. The primary endpoint was reduction in LV end systolic volume index (LVESVI), a variable that reflects changes in both LV size and systolic function. As shown in Figure 4.2, after 12 months improvements in LVEF and LVESVI were noted in the metoprolol succinate groups. Additionally, there was a dose dependant improvement in LVEF with superior results obtained in patients receiving 200 mg metoprolol succinate compared to the 50 mg dose.

Stage C heart failure

Stage C heart failure is defined as the presence of structural disease and current or prior symptoms of
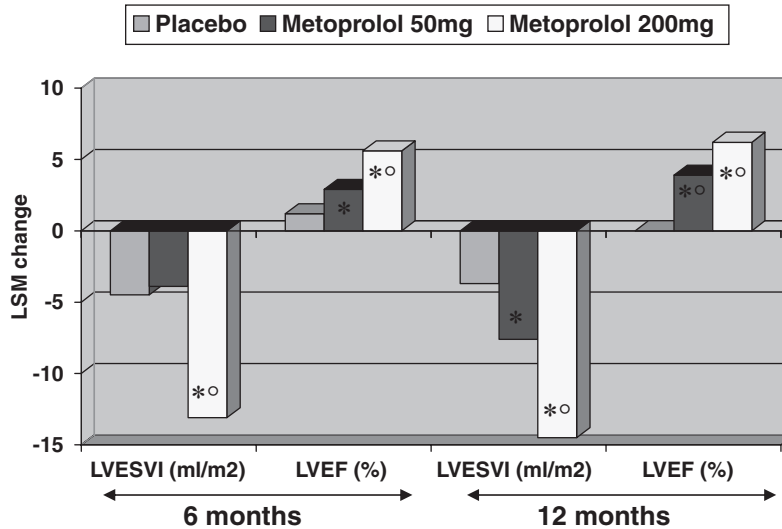
Figure 4.2 Improvement in LV remodeling with metoprolol succinate in the REVERT study

[*]P < 0.05 compared to baseline; [°]p < 0.05 compared to placebo.

LVESVI = left ventricular end-systolic volume index; LVEF = left ventricular ejection fraction; LSM = least square mean.

Reference: Colucci WS, Kolias TJ, Adams KF et al. (2007). Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction: the REversal of VEntricular Remodeling with Toprol-XL (REVERT) trial. Circulation 116(1), 49–56. Reproduced with permission from the American Heart Association.

heart failure [4]. The benefits of beta-blocker therapy in patients with symptomatic heart failure despite standard therapy including an ACEI have been demonstrated in the U.S. Carvedilol Heart Failure Study, Metoprolol Controlled-Release Randomized Intervention Trial in Heart Failure (MERIT-HF), and Cardiac Insufficiency Bisoprolol Study II (CIBIS II) (9–11). In all of these trials the addition of beta-blockers to standard therapy significantly reduced all-cause mortality. Improvements were also noted in secondary endpoints such as the risk of sudden death and cardiovascular hospitalizations (Table 4.2).

Stage D heart failure

Patients with Stage D heart failure have advanced disease and refractory symptoms of heart failure at rest despite standard therapy [4]. The safety and efficacy of beta-blockers was uncertain in patients with severe heart failure due to concerns of hemodynamic compromise as cardiac function in these pa-

tients was hypothesized to be critically dependent on catecholamine support. However, subgroup analysis of MERIT-HF and CIBIS-II, in combination with results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial have shown that the benefits of beta-blockade extend to patients with more severe heart failure (12–13). COPERNICUS was a placebo-controlled study of carvedilol in patients with LVEF < 25% and advanced heart failure symptoms despite conventional therapy with diuretics and an ACEI or ARB. The severity of heart failure in this population was evident by the 1-year mortality rate in the placebo group which was approximately double that seen in placebo treated patients in the MERIT-HF and CIBIS II populations. As shown in Figure 4.3, carvedilol therapy resulted in a highly significant 35% reduction in annual risk of death (primary endpoint of the study). It also caused a 27% decrease in the combined risk of cardiovascular mortality or hospitalization and a 31% reduction in combined risk of death or
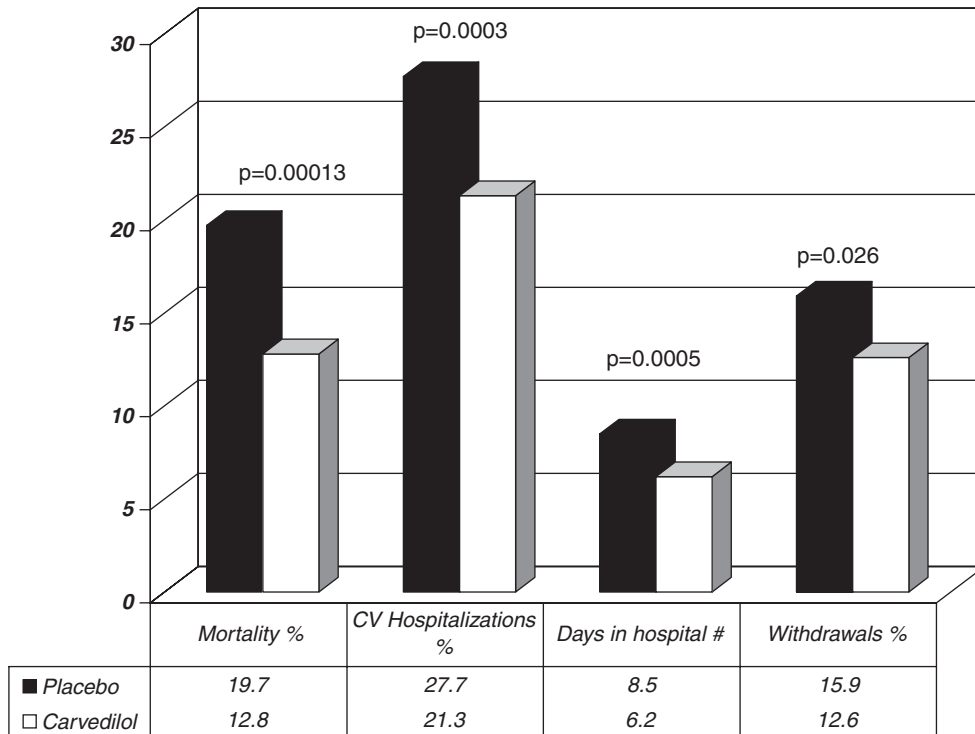
	Mortality %	CV Hospitalizations %	Days in hospital #	Withdrawals %
■ Placebo	19.7	27.7	8.5	15.9
□ Carvedilol	12.8	21.3	6.2	12.6

Figure 4.3   Results from COPERNICUS study

CV = cardiovascular

Reference: Packer M, Fowler MB, Roecker EB et al. (2002). Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 106(17), 2194–9. Reproduced with permission from the American Heart Association.

hospitalizations due to heart failure in the study group. In addition, patients in the carvedilol group spent 40% fewer days in the hospital for heart failure. Of particular importance was evidence that carvedilol was well tolerated in the COPERNICUS trial, with no excess withdrawals in patients treated with active drug as compared with placebo (Figure 4.3).

Beta-blockers in patients with heart failure and preserved EF

Some small studies have shown augmentation in diastolic filling and relaxation [14], decrease in B-type natriuretic peptide (BNP) and symptomatic improvement [15] with beta-blocker therapy in patients with heart failure and preserved EF. But conclusions re-

garding the effect of beta-blockers on clinical parameters including mortality and heart failure hospitalizations have not been established in past trials. At present the role of beta blockade in treating patients with heart failure and preserved EF is uncertain and more information from clinical trials is needed. The Japanese Diastolic Heart Failure Study (J-DHF) is currently underway to assess the effects of carvedilol on cardiovascular endpoints in this important group of patients [16].

ACC/AHA recommendations [4]

- Beta-blockers should be used in all patients with a recent or remote history of MI regardless of EF.

- Use of clinically proven beta-blocking agent (sustained release metoprolol, carvedilol, or bisoprolol) is recommended for all stable patients with reduced LVEF, whether or not they have experienced an MI.

Practical approach to treating patients with beta-blockers

Agent of choice

As noted earlier, beta-blocking agents have different pharmacologic properties and are not equivalent in their efficacy for treatment of heart failure (Table 4.3). Only metoprolol succinate, bisoprolol, and carvedilol have been shown to reduce mortality in RCTs. The Carvedilol or Metoprolol European Trial (COMET) directly compared carvedilol with immediate release metoprolol tartrate in patients with NYHA functional class II-III and LVEF $\leq$ 35% on background therapy, including an ACEI and diuretic [21]. The primary endpoint of all-cause mortality was reached with a significant 17% decrease in mortality noted with carvedilol compared to metoprolol tartrate. Notably, this benefit was due entirely to a reduction in cardiovascular mortality. However, in COMET carvedilol was titrated to its recommended dose of 25 mg twice daily, whereas metoprolol tartrate was titrated only up to 50 mg twice daily, which is less than the recommended dose of 100 mg twice daily. Also, this study compared carvedilol with metoprolol tartrate while the REVERT and MERIT-HF trials used extended release metoprolol succinate. Head to head comparisons between carvedilol and metoprolol succinate designed to assess differences in relevant clinical endpoints have not been performed.

Other beta-blocking agents have been evaluated in RCTs. In the Beta-blocker Evaluation of Survival Trial (BEST), bucindolol, a non-selective beta-blocker with additional vasodilating properties, did not reduce overall survival in patients with advanced heart failure [22]. Additionally, in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial, nebivolol, a selective beta-1 agent with vasodilatory properties, failed to significantly improve survival in elderly heart failure patients [23].

Whether the differences in outcomes with these two drugs are due to populations studied or to the actions of the agents remains a topic of controversy. Nonetheless, the recommendation is to only use of one of the three beta-blockers that have shown mortality benefit in RCTs (carvedilol, bisoprolol, and metoprolol succinate) in heart failure patients.

Initiation and contraindications

In a survey by Butler et al., the likelihood of patients treated in the year post-MI with a beta-blocker was increased several fold if the drug was initiated in-hospital prior to discharge [17] (Figure 4.4). Similarly, the IMPACT-HF study in patients hospitalized for heart failure compared beta-blocker treatment rates based on inpatient or outpatient strategies for initiation [18]. The results demonstrated a significantly greater likelihood of being on a beta-blocker at 60 days if the drug was started during hospitalization. Additional data from the OPTIMIZE-HF registry indicates that initiation of pre-discharge beta-blocker is well tolerated by patients, with well over 80% of beta-blocker eligible patients discharged on drug, and that pre-discharge beta-blocker initiation is associated with lower post-discharge mortality risk [19].
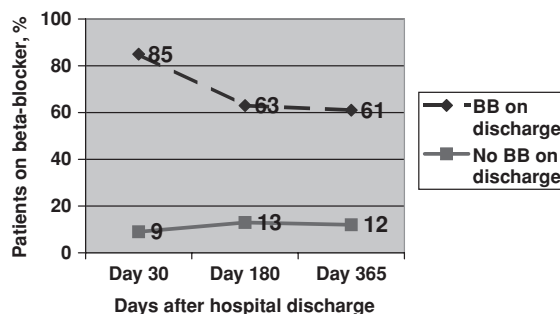

Figure 4.4 Adherence to beta-blocker therapy after an acute MI with initiation pre- versus post-hospital discharge.

BB = beta-blocker.
Reference: Butler J, Arbogast PG, BeLue R, et al. (2002). Outpatient adherence to beta-blocker therapy after acute myocardial infarction. Journal of the American College of Cardiology, 40(9), 1589–95. Reproduced by permission of Elsevier.

Table 4.4   Target dosing for beta-blockers

Beta-blocker	Initial dose	Target dose
Bisoprolol	1.25 mg qd	10 mg qd
Carvedilol	3.125 mg bid in heart failure	25 mg bid (50 mg bid for weight > 85 kg)
	6.25 mg bid in post-MI	80 mg qd of CR preparation
	10 mg qd of CR preparation	
Metoprolol succinate	12.5 mg qd	200 mg qd

Reference: ACC/AHA guidelines for management of patients with chronic heart failure [4]

Based on these findings, we recommend that beta-blocker therapy be initiated in hospitalized patients with chronic heart failure or recent MI as soon as the patient reaches (or is approaching) a euvolemic state. Similarly, if the patient is diagnosed with de-novo heart failure or a prior MI in the outpatient setting, we recommend that beta-blockade be instituted at the earliest opportunity.

Beta-blockers should be withheld if there is symptomatic hypotension or SBP < 80 mmHg, symptomatic bradycardia, greater than first-degree AV block, severe reactive airway disease, or brittle diabetes with recurrent hypoglycemic episodes.

Dosing and titration

Beta-blockers should be started at low doses (Table 4.4). In the hospital setting it is our practice to uptitrate by doubling the dose every few days in patients who remain hypertensive during hospitalization. After discharge or as an outpatient, the dose is increased on a biweekly basis until target dose is reached or patient develops limiting symptoms. Patients with severe heart failure may require slower titration (which may extend over 3–6 months in extreme cases), particularly if they develop fatigue or worsening fluid retention early.

There is evidence that uptitration of beta-blockers to target dosing helps to optimize the beneficial effects of therapy. Most RCTs have used high-dose therapy, and some dose ranging studies have even shown superior effect at these higher doses. Two such trials are the Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) and REVERT [8,24]. The MOCHA trial randomized 345 patients with

mild-moderate chronic heart failure to receive treatment with placebo, low-dose (6.25 mg), medium-dose (12.5 mg), or high-dose carvedilol (25 mg) for 6 months. In this study the primary endpoint was a change in EF. Carvedilol therapy resulted in a dose-related improvement in LV function (Figure 4.5). There were also dose-related reductions in mortality and hospitalizations but the number of events was relatively small. Similarly, dose-related improvement in EF and reversal of maladaptive remodeling was observed in the REVERT study with better results obtained with metoprolol XL 200 mg daily dosing as compared to the metoprolol XL 50 mg dose.
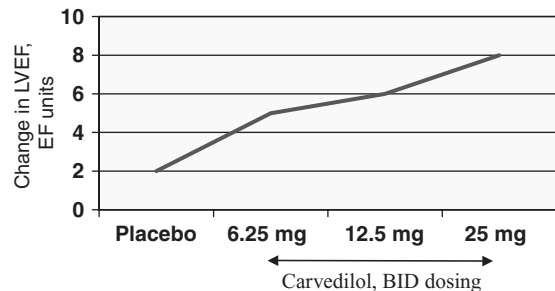

Figure 4.5   Dose-related improvement in LVEF with Carvedilol: MOCHA trial.

P< 0.001 for linear dose response.
LVEF = left ventricular ejection fraction;
EF = ejection fraction.
Reference: Bristow MR, Gilbert EM, Abraham WT et al. (1996). Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation 94(11), 2807–16. Reproduced with permission from the American Heart Association.

Management of adverse effects

1. Symptomatic hypotension may be seen with all beta-blockers particularly early after initiation and following dose titration. Given the natural history of post-MI and heart failure patients, it is highly recommended that practitioners attempt to maintain patients on at least some dose of beta-blocker whenever possible. The stepwise approach that we use for this purpose is outlined in Figure 4.6.

2. Worsening heart failure manifesting as increasing fatigue or fluid retention can occur when beta-blockers are started or uptitrated. Patients who experience worsening fatigue often overcome this symptom over time. In some cases a limited or more gradual uptitration protocol may be required. Patients should be reminded to measure their daily weights during initiation and uptitration of beta-blocker therapy. Some patients will retain excess fluid during the initial three to four months of therapy. A small amount
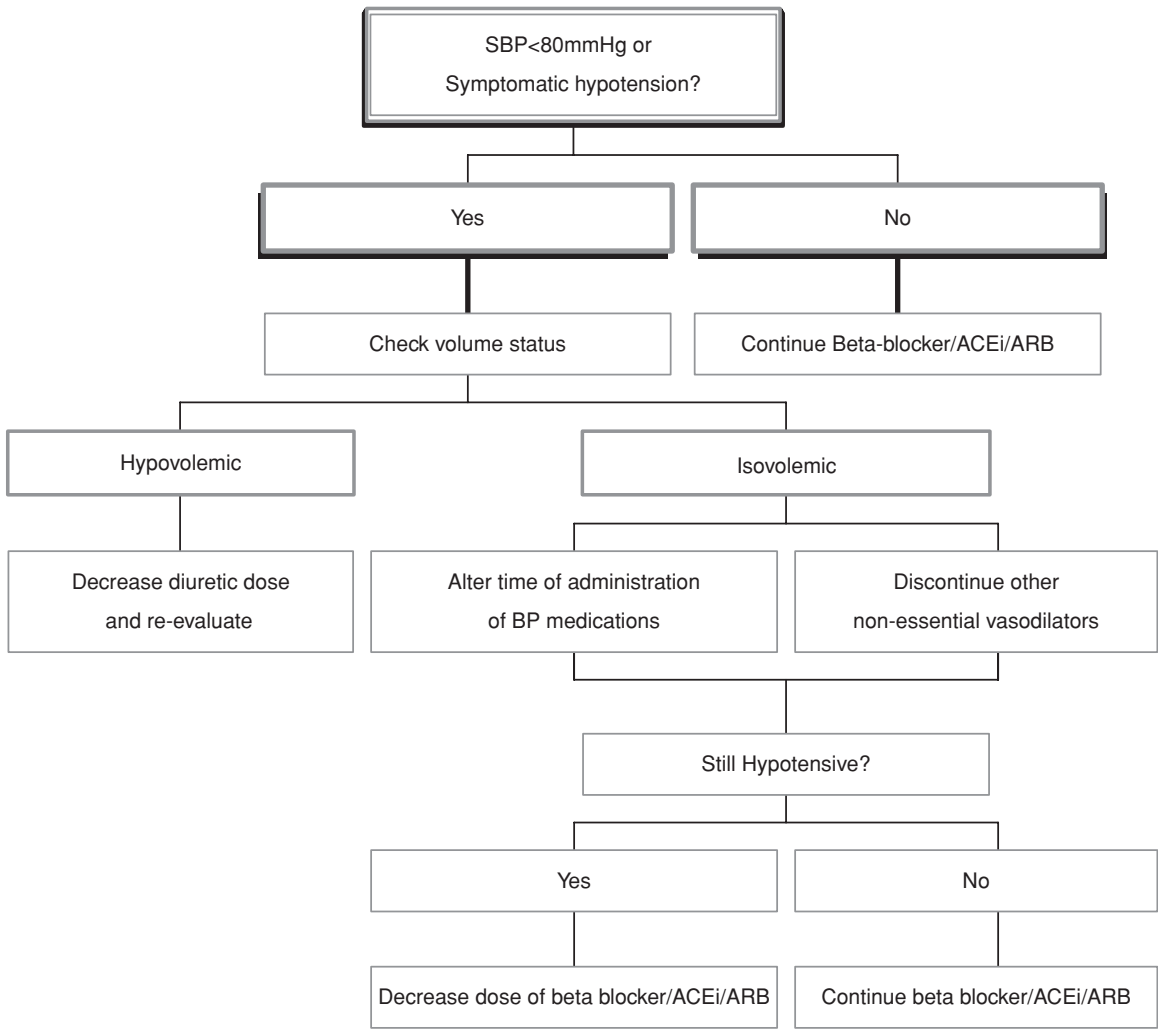

Figure 4.6 Management of Hypotension associated with beta-blocker, ACEI, or ARB use

of weight gain can be treated with diuretics; beta-blocker dose should be only decreased in the setting of severe decompensation or resistant edema. In the rare case of decompensated heart failure secondary to initiation of beta-blockers, the dosage may be halved or even temporarily discontinued. When the patient is at euvolemic status, initiation and uptitration of beta-blocker can be again cautiously resumed.

For patients on chronic beta-blocker therapy (i.e., >3 months) who present with decompensated heart failure, the ACC/AHA guidelines recommend continuing the beta-blocker and intensifying the diuretic therapy unless the patient is hypotensive or requiring inotropic support. In the latter case the beta-blocker may have to be held until patient is hemodynamically stabilized (Figure 4.7).

3. Bradycardia may limit or prevent treatment with a beta-blocker. In patients with slow heart rates
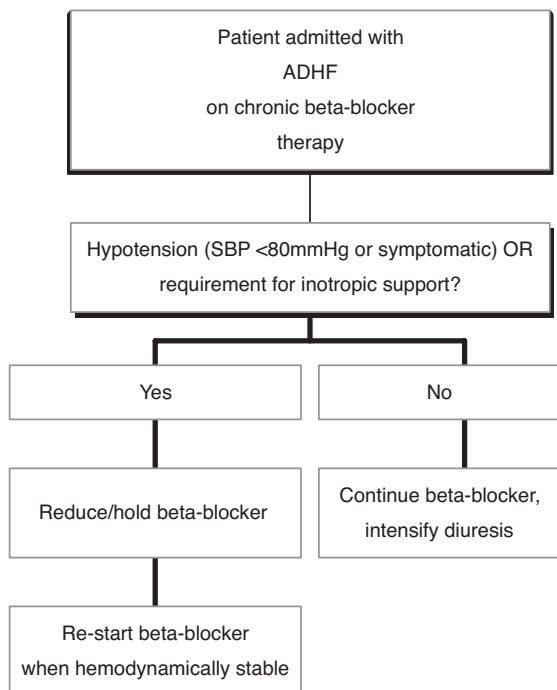

Figure 4.7   Treatment with beta-blockers in acute decompensated heart failure

a careful history should be obtained regarding symptoms of syncope or pre-syncope, and evidence of greater than 1st degree AV block should also be excluded by electrocardiogram (Figure 4.8). When symptomatic bradycardia is present, consider discontinuing other non-essential nodal-blocking agents such as calcium channel blockers (2). Beta-blocker should be discontinued if symptomatic bradycardia persists or if there is evidence of advanced heart block (unless treated with a pacemaker). In the absence of symptoms or an advanced heart block, and HR >55, the beta-blocker may be continued.

4. Bronchospasm: beta-blockers are usually well tolerated in patients with chronic obstructive pulmonary disease (COPD). In a meta-analysis of beta-blocker trials [25], there was no change in FEV1, frequency of bronchodilator use, or worsening of respiratory symptoms with beta-blocker use in patients with COPD. In patients with severe asthma or those with a reactive component to COPD, a selective beta-1 agent is preferred and non-selective beta-blockers like carvedilol should probably be avoided in most cases. Minor bronchospasm with beta-blockers can generally be managed with bronchodilators, although patient with severe exacerbation or requiring steroids for reactive airway disease should not be initiated on beta-blocker therapy.

5. Although many post-MI and heart failure patients have evidence of peripheral vascular disease, most experts recommend continuing beta-blocker therapy unless they experience severe worsening of symptoms.

Special populations

Diabetics

Diabetics with heart failure have a higher risk of mortality and hospitalizations for heart failure compared with the non-diabetic heart failure population [26,27]. In MERIT-HF trial the risk of hospitalization due to heart failure was 76% higher in diabetics compared with non-diabetics [26]. Treatment with metoprolol XL significantly reduced the risk of hospitalization by
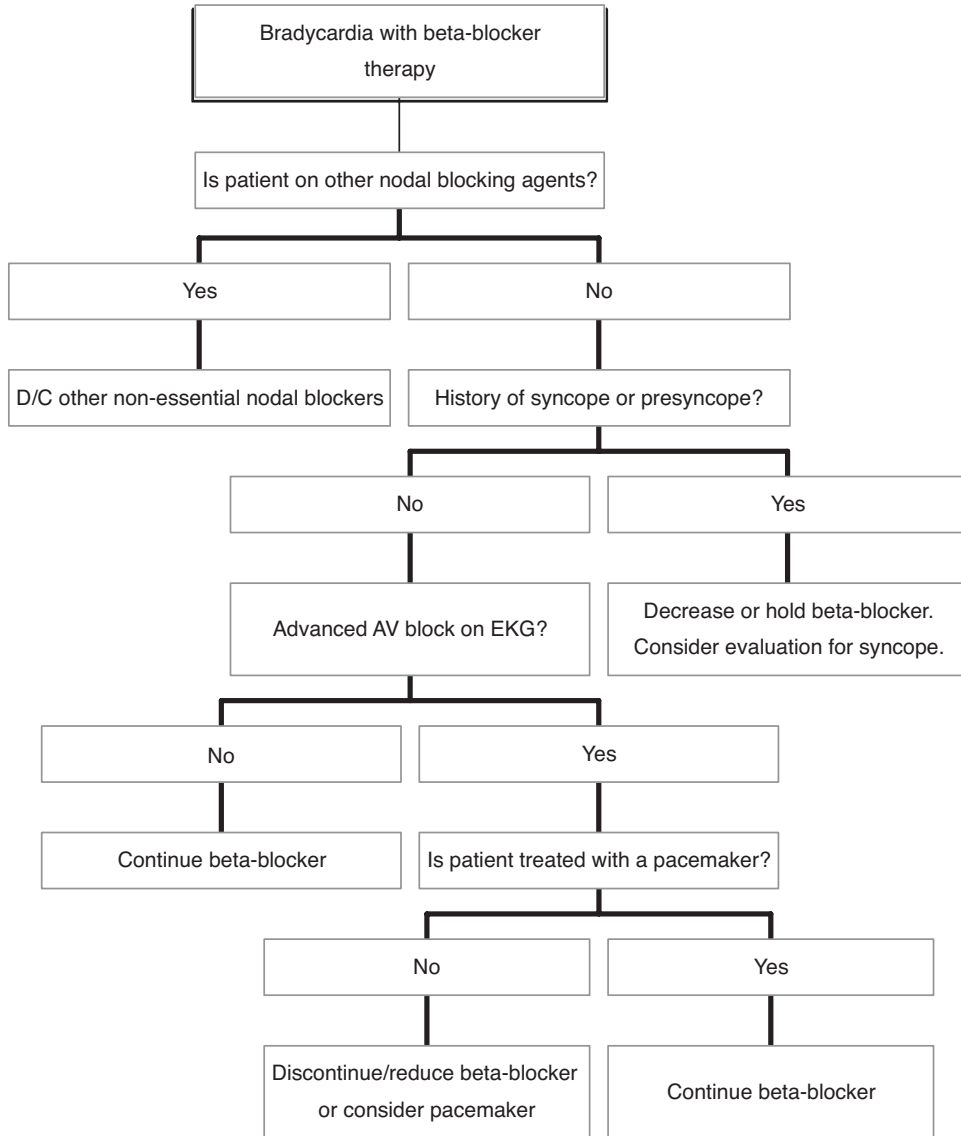
Figure 4.8 Management of bradycardia with beta-blocker treatment

a similar percent in the diabetic subgroup compared to the non-diabetic subgroup (37% vs. 35%). Similar benefits were noted in the pooling of mortality data from the CIBIS II, MERIT-HF, and COPERNICUS trials, which revealed a 25% reduction in mortality in the diabetic group compared with 36% reduction in patients without diabetes.

There is some concern about deleterious effects of beta-blockers on metabolic parameters such as glucose control and lipid metabolism. However, there are differences between beta-blockers regarding their metabolic effects. In the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, 1235 participants with

hypertension and type 2 diabetes mellitus were randomized to receive either carvedilol or metoprolol tartrate, and both agents were titrated to achieve good hypertensive control [28]. After 5 months of therapy the HbA1c increased in the metoprolol tartrate group (0.15%, P< 0.001), while the carvedilol group had no change from baseline HgA1c. Carvedilol also had more favorable effects on microalbuminuria and insulin sensitivity in comparison with metoprolol tartrate. Currently, it appears that there is a beneficial metabolic effect with carvedilol, although there are no specific guidelines supporting carvedilol as the preferred agent in post-MI or heart failure patients with diabetes.

Women

Under-representation of women in post-MI and heart failure clinical trials has limited the conclusions that can be drawn regarding the benefit of beta-blockers in this population. Pooled analyses of results from MERIT-XL, CIBIS II, and COPERNICUS trials have shown similar beneficial effects in men and women [27]. We recommend using beta-blockers in women with heart failure unless otherwise contraindicated.

Race

The BEST study failed to reach its primary endpoint of improved survival in advanced heart failure patients treated with bucindolol. Subgroup analysis, however, suggests that blacks did less well with bucindolol versus placebo while whites did better [29]. These results question the safety and efficacy of beta blockade in blacks with heart failure. However, this adverse outcome with a beta-blocker does not appear to be universal. Recently, the Carvedilol Heart Failure Registry (COHERE) investigated 4280 heart failure patients on carvedilol therapy in a community setting [30]. In a post-hoc analysis, blacks (n = 523) had more severe heart failure symptoms compared with whites (n = 3433) despite similar systolic function. Patients on carvedilol therapy, however, had improvement in symptoms (33% of blacks versus 28% of whites), and heart failure hospitalization rates were reduced similarly in both groups.

In a meta-analysis of major RCTs (excluding the BEST trial) by Shekelle et.al [27], similar results were found in the black subgroup. Blacks were found to have the same relative risk reduction in mortality as whites treated with bisoprolol, metoprolol, or carvedilol. Therefore, clinically proven beta-blockers are recommended as first line treatment for black patients with heart failure.

Elderly

The efficacy and tolerability of beta-blocker treatment in the elderly heart failure population has been analyzed in the SENIORS trial and in a post-hoc analysis of the MERIT-HF trial. As mentioned earlier, there was a lesser degree of risk reduction in all-cause mortality or cardiovascular hospitalizations in the SENIORS trial (nebivolol treatment in heart failure patients aged > 70 years) as compared with other large beta-blocker trials. In contrast, subgroup analysis of patients over 65 years of age treated with metoprolol succinate in the MERIT-HF trial [31] showed a significant 37% risk-reduction in mortality, 43% in sudden death, and 36% in heart failure hospitalizations compared with placebo (Table 4.5). In addition to these trials, the Carvedilol Open Label Assessment (COLA II) study [32] also assessed the safety and tolerability of beta-blockers in the elderly. In the COLA II study, 80% of patients above the age of 70 years were able to tolerate carvedilol at a mean dose of 31.2 mg daily. Similarly in the SENIORS trial, 90% of patients were able to tolerate nebivolol and 67% of total patients successfully reached the target dose of 10 mg once daily. Based on the above results, concerns regarding tolerability should not preclude elderly patients with heart failure from receiving the appropriate beta-blocker therapy that has been shown to improve survival in this group.

Angiotensin-converting enzyme inhibitors (ACEIs)

In 1983, the Captopril Multicenter Research Group published a seminal study demonstrating that targeting the RAAS with an ACEI had beneficial effects in heart failure patients [33]. Since then numerous RCTs have provided incontrovertible evidence that ACEIs favorably affect hemodynamics and cardiac functional capacity. Even more important is that these agents greatly reduce hospitalizations and mortality in heart failure patients (Tables 4.6A and 4.6B).

Table 4.5 Efficacy and tolerability of metoprolol succinate in heart failure patients <65 years old versus >65 years old (MERIT-HF trial)

	<65 year old (n = 2009)	≥65 year old (n = 1982)
RR in all-cause mortality	38% (p = 0.019)	43% (p = 0.032)
RR in mortality due to heart failure	**8%** (p = ns)	**61%** (p = 0.0005)
Heart failure hospitalizations	**22%** (p = 0.0035)	**36%** (p = 0.0006)
Yearly discontinuation rate (all patients)	**12.8%** (p = ns)	**17.8%** (p = ns)
Yearly discontinuation rate (severe heart failure)	**13.1%** (p = 0.018)	**21.9%** (p = ns)

RR = risk reduction; ns = non-significant. p values refer to comparison of metoprolol XL versus placebo in the 2 age groups. Reference: Efficacy, safety and tolerability of beta-adrenergic blockade with metoprolol CR/XL in elderly patients with heart failure. European Heart Journal, 25(15), 1300–9. Reproduced by permission of Oxford University Press.

Table 4.6A Clinical trials with ACEI: chronic heart failure

Study	Population	Total (n)	ACEI	ACC Stage	Results
CONSENSUS I	Clinical evidence of severe heart failure	253	Enalapril	D	40% RRR in mortality at 6 mo (1° endpoint) 50% RRR mortality from worsening heart failure
SOLVD Treatment	EF ≤ 35%	2,569	Enalapril	C	16% RR mortality (1° endpoint) 26% combined reduction mortality/hospitalization from progressive heart failure
SOLVD Prevention	EF ≤ 35%,	4,228	Enalapril	B	Non-significant reduction in all-cause mortality (1° endpoint) 20% reduction in combined incidence of death or heart failure hospitalization
ATLAS	EF ≤ 30%	3,164	Lisinopril Low dose (2.5–5 mg) vs. High dose (32.5–35 mg)	C, likely D	8% non-significant RRR mortality (1° endpoint) 12% RRR mortality + hospitalization in higher dose group. 24% RRR heart failure hospitalization

CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; SOLVD = Studies Of Left Ventricular Dysfunction trial; ATLAS = Assessment of Treatment with Lisinopril and Survival trial; EF = ejection fraction; RRR = relative risk reduction; CV = cardiovascular.

Table 4.6B Clinical trials with ACEI: post-MI

Study	Population	Total (n)	ACEI	Results
AIRE	3–10 days post-MI. Clinical evidence of heart failure	1,986	Ramipril	23% RRR overall mortality (1° endpoint) 19% RRR combined death, AMI, worsening heart failure, stroke
SAVE	EF ≤ 40% 3–16 days post-MI	2,231	Captopril	19% RRR overall mortality (1° endpoint) 25% RR recurrent MI 21% RRR CV mortality
TRACE	EF ≤ 35% 3–7 days post-MI	1,749	Trandolapril	22% RRR all-cause mortality (1° endpoint) 29% reduction in progression of heart failure
GISSI-3	Within 24 hrs of AMI	18,895	Lisinopril	11% decrease in mortality at 6 weeks (1° endpoint)
ISIS-4	Within 24 hrs of AMI	58,050	Captopril	7% reduction in mortality at 5 weeks (1° endpoint)
CONSENSUS II	Within 24 hrs of AMI.	6,090	Enalapril (Intravenous followed by oral enalapril)	No improvement in survival 6 months post-MI (1° endpoint)
SMILE	Within 24 hrs of AMI	1,556	Zofenopril	33% RRR in combined death or progression to severe heart failure at 6 weeks (1° endpoint) 29% RRR mortality at 1 year

SAVE = Survival and Ventricular Enlargement; TRACE = Trandolapril Cardiac Evaluation Study; GISSI-3 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; ISIS-4 = International Study of Infarct Survival; AIRE = Acute Infarction Ramipril Efficacy trial; SMILE = Survival of Myocardial Infarction Long-Term Evaluation; AMI = acute myocardial infarction; EF = ejection fraction; RRR = relative risk reduction; CV = cardiovascular.

Efficacy

Stage B heart failure

Post-MI

A series of well-designed clinical trials have evaluated the effects of long-term and short-term ACEI therapy in post-MI patients. Based on the data from the Survival and Ventricular Enlargement (SAVE), Trandolapril Cardiac Evaluation (TRACE), and Acute Infarction Ramipril Efficacy (AIRE) studies, the long-term benefits of ACEI therapy are clear [34–36]. The SAVE trial randomized 2231 patients with evidence of LVD (LVEF ≤ 40%) within 3–16 days following AMI to captopril (50 mg TID) or placebo. Patients with overt heart failure on admission were excluded from this study. At an average of 42-month follow-up, captopril therapy was associated with significant risk reductions in mortality (19%), heart failure hospitalizations (22%), and re-

current ischemic events (25%) (Table 4.7). In a separate analysis of the SAVE database, captopril reduced the need for revascularization (percutaneous transluminal coronary angioplasty, PTCA, or coronary artery bypass grafting, CABG) compared with placebo (15% versus 19%), but the number of hospitalizations for unstable angina was similar in both groups [37].

The short-term benefits of intravenous ACEI therapy initiated immediately after MI are, however, less apparent as evidenced by the results of the Cooperative North Scandinavian Enalapril Survival Study II (CONSENSUS II) [38]. This study randomized 6090 patients within 24 hrs of AMI, regardless of symptoms of heart failure or evidence of LV dysfunction, to enalapril or placebo. The active treatment group, which received intravenous (IV) enalaprilat immediately upon admission for AMI, followed by oral enalapril, demonstrated a trend towards increased

Table 4.7 Effect of captopril on CV outcomes post-MI: data from SAVE trial

Event	Placebo group (%)	Captopril group (%)	Risk reduction	P value
Severe heart failure	16%	11%	37%	P < 0.001
Heart failure hospitalizations	17%	14%	22%	P = 0.019
Recurrent MI	15%	12%	25%	P = 0.015

Reference: Rutherford JD, Pfeffer MA, Moyé LA et al. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. SAVE Investigators. Circulation 1994, 90(4), 1731–8. Reproduced with permission from the American Heart Association.

mortality. This has been attributed to deleterious effects of early decrease in blood pressure after AMI. In contrast, other large clinical trials [39–41] have shown a small but significant improvement in survival with institution of early ACE inhibitor therapy (within 24 hours) in patients with AMI. In the Survival of Myocardial Infarction Long-term Evaluation (SMILE) study, 1556 patients with an anterior MI and systolic blood pressure above 100 mmHg who did not receive thrombolytic therapy were randomized to zolfenopril versus placebo for 6 weeks. Therapy was started within 24 hours of onset of chest pain and zolfenopril dose was gradually doubled until target dose of 30 mg BID was reached. At 6 weeks follow-up, the primary endpoint of reduction in mortality or severe heart failure was reached, with a significant 34% relative risk reduction in mortality or progression to severe heart failure observed in the treatment group. Additionally, 6 weeks of treatment with zolfenopril resulted in a 29% reduction in mortality at 1-year follow-up. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) and the International Study of Infarct Survival (ISIS-4) trials there was also small but significant improvement in survival at 5 to 6 weeks post-MI in patients treated with an ACEI.

Asymptomatic LV dysfunction

Asymptomatic patients with evidence of LVD (EF ≤35%) enrolled in the prevention arm of Studies Of Left Ventricular Dysfunction (SOLVD) trial received enalapril (target dose of 20mg daily) versus placebo for an average of 37.4 months [42]. Although there was no significant difference between study groups in the primary endpoint of mortality, a modest 8% reduction in favor of the ACEI was noted. There was,

however, a highly significant decrease in combined incidence of death or hospitalization for heart failure (20% risk reduction) and a notable reduction in the risk of developing new-onset heart failure.

Stage C heart failure

The treatment arm of SOLVD evaluated 2569 patients with mild-moderate heart failure symptoms [43]. When compared with placebo, enalapril resulted in a significant 16% reduction in mortality, the primary endpoint of the trial, and a 26% decrease in the combined secondary endpoint of death or heart failure hospitalization (Figure 4.9 and Table 4.8).

In the AIRE study, patients with clinical evidence of heart failure post-MI were randomized to ramipril (5 mg BID) versus placebo within 3 to 10 days following AMI [36]. At 15-months follow-up, the ramipril group experienced significant reductions in the primary endpoint of mortality (27%), progression to severe heart failure (23%), and the risk of sudden cardiac death (SCD) (30%) compared with the placebo group. There was no difference in the risk of recurrent MI or stroke. This mortality benefit was subsequently shown to extend over a 59-month follow-up in the AIRE Extension (AIREX) study [44] (Figure 4.10).

Stage D heart failure

The benefits of ACEIs in Stage D heart failure patients were demonstrated in the Cooperative North Scandinavian Enalapril Survival study (CONSENSUS I) [45]. In a study population of primarily stage IV NYHA heart failure patients on baseline therapy with diuretics, digitalis, and vasodilators, the addition of enalapril (at a target dose of 40 mg daily) resulted in
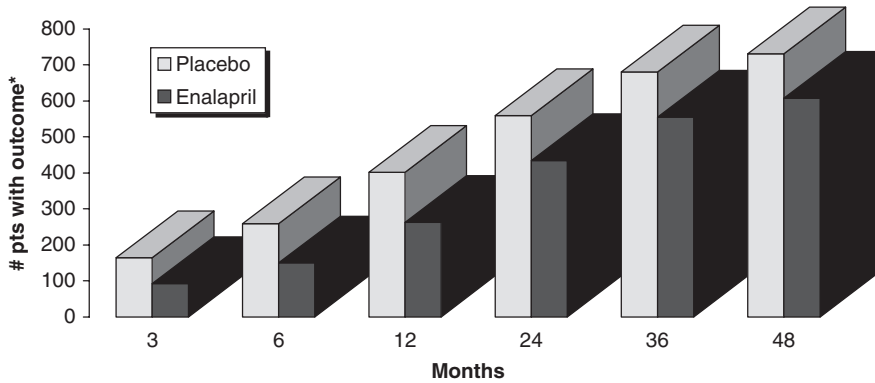
Figure 4.9 Effect of enalapril on death or hospitalization due to heart failure: SOLVED treatment trial.

    [*]Outcome: death or hospitalization due to heart failure.

    Overall p < 0.0001

    Reference: (1991). Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. New England Journal of Medicine, The, 325(5), 293–302

a significant 40% decrease in mortality at 6 months mostly due to reduction in deaths from progressive heart failure. The survival benefits continued at the 4-year follow-up. The severity of heart failure also decreased in the treatment group when compared with placebo (Tables 4.8 and 4.9).

Diastolic heart failure

In contrast to the proven role of ACEIs in the management of heart failure due to systolic dysfunction, their benefits in patients with preserved systolic function are less well known. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial was designed to assess the utility of ACEIs in older population with preserved EF [46]. Unfortunately, low recruitment and low event rates, along with high rate of study drug discontinuation and open-label ACEI use, resulted in a considerable loss of statistical power to show an effect of perindopril on the primary composite outcome of death or heart failure related hospitalization. Uncertainty remains about the effects of ACEIs on long-term morbidity and mortality in this clinical setting. However, improved symptoms and exercise capacity and fewer hospitalizations for heart failure in the first year were observed with perindopril

Table 4.8 Improved survival with ACEI in patients with chronic heart failure

Trial	%Mortality ACEI	%Mortality Controls	RR (95% CI)
CONSENSUS I	39%	54%	0.73
SOLVD (Treatment)	35%	40%	0.84 (0.74–0.95)
SOLVD (Prevention)	15%	16%	0.92 (0.79–1.08)

Reference:

- 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.

- (1991). Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 325(5), 293–302.

- (1992). Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. N Engl J Med 327(10), 685–91.
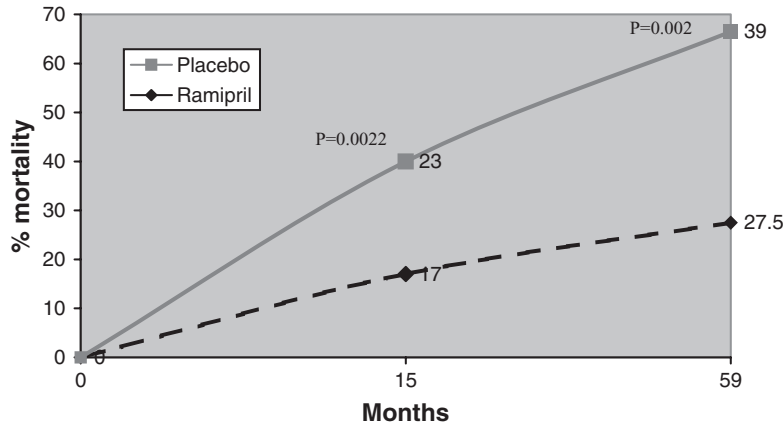
Figure 4.10 Effect on ramipril on mortality after AMI: results of AIRE and AIREX trials.

Reference:
- 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 342(8875), 821–8.

- Hall AS, Murray GD, Ball SG. (1997). Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Acute Infarction Ramipril Efficacy. Lancet 349(9064), 1493–7. Reproduced by permission of Elsevier.

treatment, suggesting that it may be of benefit in this patient population. From a practical perspective many of these patients have a history of MI, hypertension, and/or diabetes with renal dysfunction, and are likely to be treated with an ACEI for these causes [48].

ACC/AHA guidelines
- ACEI therapy is recommended in patients with a recent or remote history of MI regardless of LVEF or heart failure symptoms.

Table 4.9 NYHA classification at the end of CONSENSUS study

NYHA class	Placebo (n = 126)	Enalapril (n = 127)
I	0	3
II	2	13
III	25	38
IV	30	21
Death	68	50

Overall p < 0.001

Reference: 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.

- ACEI therapy is recommended in patients with a reduced EF, regardless of history of MI.

Practical approach to treating patients with ACE inhibitors

Initiation and contraindications

The ACC/AHA guidelines for management of patients after an ST elevation MI (STEMI) give a class I recommendation for initiation of ACEI therapy within 24 hours of AMI. The ACC/AHA guidelines also give a class I recommendation for initiating early ACEI therapy in patients with non-STEMI (NSTEMI) or unstable angina who have concomitant persistent hypertension, symptoms of heart failure, LV dysfunction, or diabetes. The early survival benefit is postulated to be due to neurohormonal effects of ACE inhibition, including a reduction in ventricular remodeling [51]. Similarly, ACEI therapy should be started in patients with LVD unless the following are present: pregnancy, bilateral renal artery stenosis, hyperkalemia (K >5.5 mmol per liter), acute renal failure, ongoing hypotension requiring inotropic

support, or history of ACEI induced angioedema. We personally recommend caution regarding initiation of ACEIs in patients with K $\geq$ 5.0.

Agent of choice

The benefits of ACEIs are likely a class effect. In a systematic review of 32 RCTs involving ACEI therapy for chronic heart failure by Garg et al., various ACEIs demonstrated similar effects on the relevant cardiovascular endpoints [47].

Dosing and titration (Table 4.10)

When initiating therapy in the inpatient setting, a short acting ACEI such as captopril can be started at low dose and rapidly titrated to target dosing (Table 4.10). The agent is then usually switched to a long acting ACEI to improve compliance. In the outpatient setting a long acting ACEI, such as lisinopril, may be initiated at starting dose and titrated over the course of a few weeks to the target dose. In the inpatient setting this process can be accelerated and uptitrations in dose may be done as frequently as every day in some patients. Serum potassium and creatinine should be checked prior to and after initiation or dose adjustment of the drug. In the inpatient setting, the serum creatinine may be checked 1–2 days after dose change; as an outpatient, serum chemistries should be checked within a few days to one week after starting or changing the dose of ACEI.

Table 4.10 Target dosing of ACE inhibitors

Agent	Initial dose	Target dose
Captopril	6.25 mg tid	50 mg tid
Benazepril	10 mg qd	80 mg qd
Enalapril	2.5 mg bid	20 mg bid
Fosinopril	5 to 10 mg qd	40 mg qd
Imidapril	2.5 mg qd	10 mg qd
Lisinopril	2.5 to 5 mg qd	20 to 40 mg qd
Ramipril	2.5 mg qd	10 mg qd
Trandolapril	1 mg qd	4 mg qd
Quinapril	5 mg bid	20 mg bid

Reference: ACC/AHA guidelines for management of patients with chronic heart failure [4]

Clinical trials have shown that ACEIs at higher doses are both safe and beneficial for patients [49,50]. Dose-related effects of lisinopril were evaluated in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial. After 46 months of follow-up, there was a significant 12% reduction in combined mortality or hospitalizations and significantly fewer hospitalizations for heart failure in the high-dose lisinopril (32.5 to 35 mg per day) group when compared with the low-dose (2.5 to 5 mg per day) group. The ATLAS trial also confirmed the excellent safety and tolerability profile of high-dose ACEI. The effect of high dose imidapril on exercise profile was also tested in a double-blind, placebo-controlled trial [50]. Significant improvement in exercise capacity was noted in a period of 3 months in the high-dose (10 mg per day) arm of the study when compared with low dose (2.5 mg or 5 mg per day) and placebo arms (Figure 4.11).

Management of adverse effects

1. Hypotension: unless the patient has symptomatic hypotension (dizziness, pre-syncope,
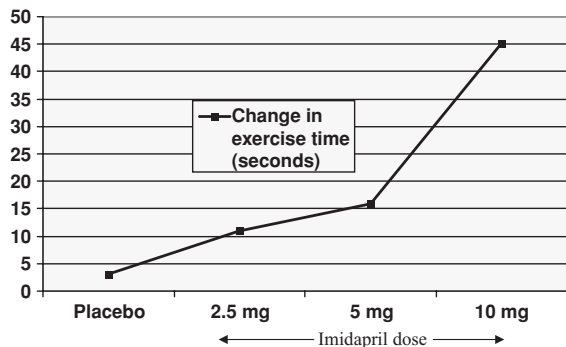
Figure 4.11 Dose related improvement in exercise capacity with imidapril.

P = 0.02 for imidapril 10 mg dose vs. placebo. Non-significant change in the 5 mg and 2.5 mg imidapril group.

Reference: Van Veldhuisen DJ, Genth-Zotz S, Brouwer J et al. (1998). High- versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril. Journal of the American College of Cardiology, 32(7), 1811–8. Reproduced by permission of Elsevier.

syncope) or SBP <80 mm Hg, it is recommended that the dose of ACEI should be continued. A stepwise plan to maintain the patients on ACEI therapy is outlined in Figure 4.6.

2. Renal dysfunction: ACEIs cause vasodilation of the efferent renal arteries, hence causing an initial decrease in the glomerular filtration rate (GFR), which can lead to a transient increase in creatinine. Creatinine levels often return to baseline without the need for dose change. If changes exceed 30% of the baseline level, other causes of renal insufficiency such as pre-renal state, medications, and post-renal obstruction should be ruled out. If renal failure persists, the possibility of bilateral renal artery stenosis should also be investigated. Figure 4.12 illustrates a general schema that may be utilized patients with acute renal failure following ACEI therapy.

3. Hyperkalemia: potassium levels should be closely monitored during initiation and titration of ACEI therapy, especially if the patient is on other medications such as potassium sparing diuretics, potassium supplements, or ARBs. If hyperkalemia is seen, potassium or potassium sparing medications should be reduced first. If hyperkalemia persists, the dose of ACEI should be halved and serum chemistries rechecked in one week.

4. Angioedema: it has been postulated that the accumulation of bradykinin can lead to angioedema. It usually involves the face and upper airway, and is a rare but potentially life-threatening complication of ACEI therapy occurring in up to 0.1–0.2% of patients [52]. ACEI should be stopped in the setting of angioedema. If the angioedema is non-life threatening, i.e., without airway obstruction, the ACEI can be cautiously replaced with an ARB.

5. Cough: the incidence of cough related to ACEI therapy is probably overestimated in the community as it is projected between 5–10% in clinical trials [52]. However, women and Asian patients appear to have a higher incidence of this side effect. Also, cough is not a dose-related side effect of ACEIs. It is important to exclude other causes of cough, such as pulmonary congestion and reactive airway disease. If the cough is persistent and other causes have been excluded, the ACEI may be replaced with an ARB.

Subgroups

Diabetics

Data supporting the benefits of an ACEI in the diabetic population with heart failure comes primarily from a meta-analysis of six ACEI trials [27]. In this analysis the pooled estimate of reduction in mortality was the same for diabetics (95% CI; RR 0.84) and non-diabetics (95% CI; RR 0.85). Additionally, in the Heart Outcomes Prevention Evaluation (HOPE) study, ACC/AHA Stage A/B patients at high risk for CV events (including diabetics) without known heart failure were treated with ramipril (10 mg daily) or placebo [53]. Treatment with ramipril reduced the rate of MI, death from CV outcomes, risk of heart failure, and diabetic complications including nephropathy or retinopathy. The relative risk of heart failure was significantly reduced by 20% in the diabetic population.

Women

Since women are significantly under-represented in RCTs in heart failure, the data from the above meta-analysis [27] was less conclusive regarding the effects of ACEI therapy in women. The pooled analysis shows a significant difference in improvement in survival with ACEI between men (95% CI; RR 0.82) and women (95% CI; RR 0.92). In a post-hoc subgroup analysis, data from three trials in patients with symptomatic heart failure (CONSENSUS, SOLVD Treatment, and TRACE) and three trials in patients with asymptomatic heart failure (SAVE, SOLVD Prevention, and SMILE) were compared. This analysis suggested that women with symptomatic heart failure probably benefit from ACEI therapy, whereas efficacy of ACEI in women with asymptomatic heart failure is unclear. Until more substantial data is available for treatment of women with asymptomatic LVD, experts recommend continuing ACEI treatment in this population.
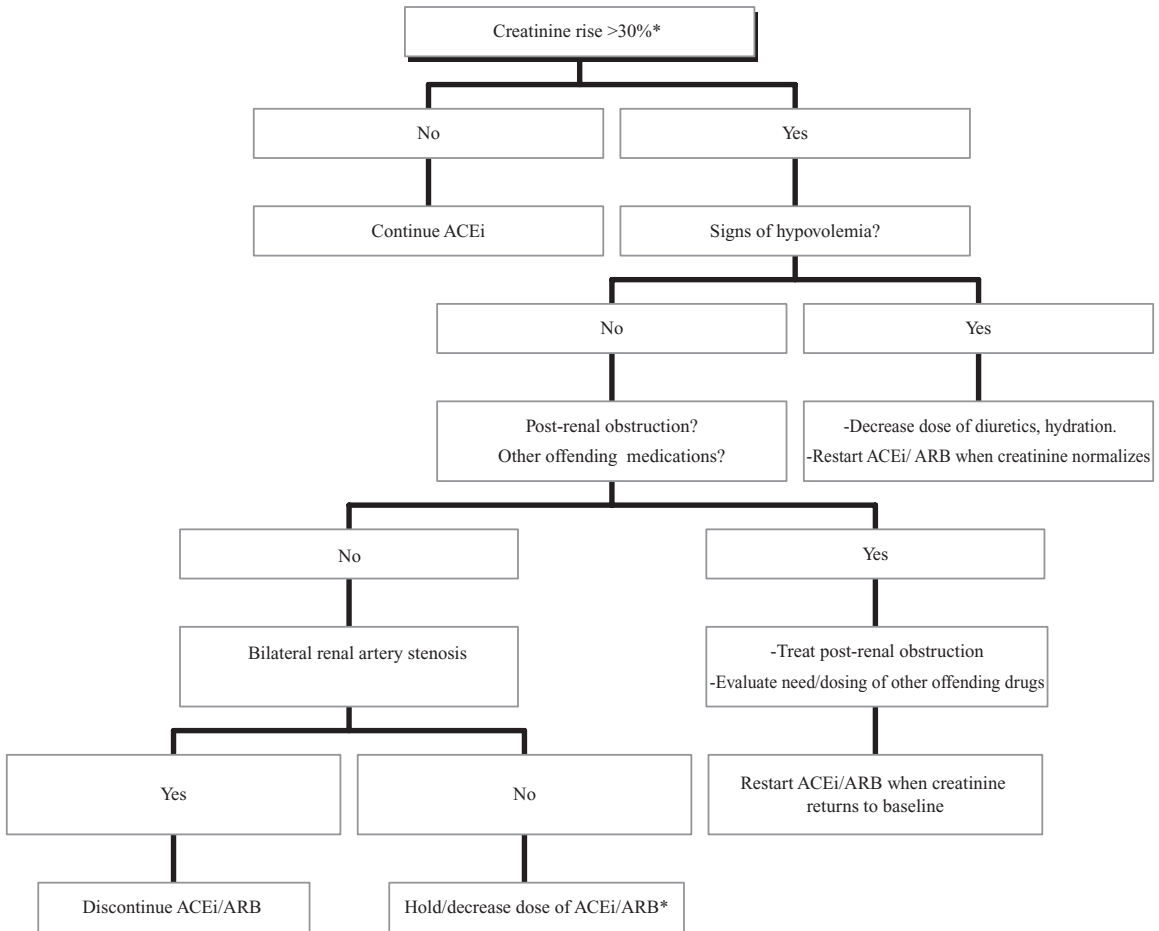
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                          ┌─────────────────────────────┐
                          │     Creatinine rise >30%*    │
                          └─────────────────────────────┘
                   ┌──────────────────┐      ┌──────────────────┐
                   │        No        │      │       Yes        │
                   └──────────────────┘      └──────────────────┘
                   ┌──────────────────┐      ┌──────────────────┐
                   │   Continue ACEi  │      │ Signs of hypovolemia? │
                   └──────────────────┘      └──────────────────┘
                          ┌──────────────────┐      ┌──────────────────┐
                          │        No        │      │       Yes        │
                          └──────────────────┘      └──────────────────┘
```

┌──────────────────────────────────┐   ┌──┐
│ Post-renal obstruction?   │   │ -Decrease dose of diuretics, hydration. │
│ Other offending medications?   │   │ -Restart ACEi/ ARB when creatinine normalizes │
└──────────────────────────────────┘   └──┘

┌──────────────────┐   ┌──────────────────┐
│   No   │   │   Yes   │
└──────────────────┘   └──────────────────┘

┌──────────────────────────────┐   ┌──┐
│ Bilateral renal artery stenosis │ │ -Treat post-renal obstruction   │
└──────────────────────────────┘   │ -Evaluate need/dosing of other offending drugs │
                                     └──┘

┌──────────────────┐   ┌──────────────────┐   ┌────────────────────────────────┐
│   Yes   │   │   No   │   │ Restart ACEi/ARB when creatinine │
└──────────────────┘   └──────────────────┘   │   returns to baseline   │
                                               └────────────────────────────────┘

┌──────────────────────────┐   ┌────────────────────────────────┐
│ Discontinue ACEi/ARB   │   │ Hold/decrease dose of ACEi/ARB* │
└──────────────────────────┘   └────────────────────────────────┘

Figure 4.12 Management of worsening renal failure with initiation of ACEI or ARB therapy.
*Threshold for decreasing or holding dose of ACEI/ARB may be greater for changes in creatinine in patients with normal baseline levels (e.g., increase from 0.6 to 0.8 mg/dL)

Race

Since most early ACEI trials were conducted in European and Scandinavian countries where substantial numbers of black patients were not included, most data regarding efficacy of ACEI versus placebo in black patients is obtained from post-hoc analyses of the SOLVD-prevention and SOLVD-treatment trials. One pooled analysis noted a comparable reduction in the relative risk of the development of symptomatic HF in blacks (RR 0.67, p = 0.01) and whites (RR 0.61, p < 0.001) with ACEI treatment [54]. However, in the post-hoc analysis by Exner et al., enalapril therapy re-

sulted in a significant reduction in hospitalization due to heart failure in white patients, but not among the black patients with LVD [55]. There is also some uncertainty in the comparative effect of ACEI versus combination of hydralazine and isosorbide dinitrate (ISDN) in the Vasodilator-Heart Failure Trial II (V-HeFT II) trial [56]. Enalapril resulted in a less significant reduction of blood pressure and mortality when compared to combination hydralazine and ISDN in the black population.

Until further large-scale trials comparing ACEI with placebo in this population are available, we

recommend the use of ACEI in black patients for the same indications as other subgroups.

Elderly

In a retrospective cohort study using the SAGE (Systematic Assessment of Geriatric drug use via Epidemiology) database, Gambassi et al. compared the effects of ACEI and digoxin in patients aged 85 years or older [57]. The overall mortality was 10% lower in ACEI recipients, and the rate of physical decline was greatly decreased amongst the ACEI group. We hence recommend using ACEIs in elderly heart failure patients unless otherwise contraindicated.

Angiotensin receptor blockers (ARBs)

ARBs use an alternative mechanism of blocking RAAS activation through the direct inhibition of the type I Angiotensin II (AT1) receptors. This gives a theoretical advantage by inhibiting actions of Angiotensin II regardless of whether the peptide is produced through the traditional ACE mediated pathway or through alternative tissue-based pathways. Whereas ACEIs enhance bradykinin level by inhibiting its ACE-mediated breakdown, ARBs do not cause an increase in bradykinin level (Figure 4.1). Although bradykinin has beneficial effects, the clinical significance of bradykinin medicated vasodilation and its anti-growth properties are uncertain. What is known is that by avoiding increases in bradykinin, ARBs are able to largely avoid the problem of ACEI induced cough.

There is convincing evidence that ARBs have similar clinical effects to ACEI for treatment of patients with post-MI LV dysfunction and/or heart failure (Table 4.11). They may be considered as an appropriate alternative for heart failure patients, particularly in patients who are intolerant of ACEI either due to the side effect of cough, or non life-threatening angioedema.

Efficacy

Post-MI:

Two large clinical trials have evaluated the role of ARBs as an alternative RAAS blocking agent in post-MI patients: the Optimal trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) and Valsartan in Acute Myocardial Infarction (VALIANT) [58,59]. OPTIMAAL compared the efficacy of captopril to losartan in patients with LVD or symptoms of heart failure after MI. In OPTIMAAL the dose of captopril was titrated to 50 mg TID, and losartan 50 mg daily. The primary endpoint of all-cause mortality was measured at a mean follow-up of 31 months. The captopril group had a non-significant trend towards lower all-cause mortality (16% versus 18% in the losartan group) and SCD, while the losartan group had significantly lower rate of discontinuation of the drug. However, there have been concerns that the very slow titration schedule and low-dose of losartan used in this study may have diminished the clinical efficacy of the drug [60].

VALIANT randomized patients with post-MI LVD on standard therapy 0.5 to 10 days after an AMI to valsartan, valsartan plus captopril, or captopril. At a median follow-up of 2 years, there were no significant differences between the 3 groups in all-cause mortality, CV death, recurrent MI, or heart failure hospitalization. Notably, the combination arm was associated with higher rate of adverse events and discontinuation of the drugs (Table 4.12). This important study demonstrated non-inferiority of an ARB to ACEI therapy, it also documented decreased tolerability and lack of additional morbidity or mortality benefit when combination ACEI and ARB therapy was used in patients with post-MI LVD.

Chronic heart failure

The CHARM-Alternative study investigated the effects of candesartan in ACEI-intolerant patients with NYHA II-IV symptoms and LVD [61]. Significant improvement in the combined endpoint of CV mortality and heart failure hospitalization was observed in the treatment group. Candesartan was also well tolerated, with a similar rate of drug discontinuation as seen in the placebo group (Figure 4.13).

Despite some similarities it is important to recognize that ACEI inhibitors and ARBs inhibit the RAAS system through different mechanisms. Moreover, Ang II levels have shown to return to pretreatment levels in patients receiving chronic ACEI therapy [1]. As a result, combination therapy versus ACEI alone has been studied in two separate heart failure studies, the Valsartan Heart Failure Trial

Table 4.11 Clinical trials with ARBs

Study	Population	Total (n)	ARB	ACC Stage	Results
OPTIMAAL	Acute-MI and clinical evidence of heart failure or EF < 35%	5,477	Losartan (Losartan vs. captopril)	B, C, D	NS superiority in captopril group for all-cause mortality (1° endpoint) Losartan better tolerated than captopril.
VALIANT	EF ≤ 35% and/or clinical evidence of heart failure. 0.5–10 days post-MI	9,818	Valsartan (Valsartan vs. valsartan + captopril vs. captopril)	B, C, D	NS for mortality (1° endpoint); SCD; hospitalization.
CHARM-Alternative	EF ≤ 40% Intolerant of ACEI	2,028	Candesartan (Candesartan vs. placebo)	C, D	23% RRR CV death or HF hospitalization (1° endpoint).
ELITE II	EF ≤ 40% Age ≥ 60 yr old	3,152	Losartan (Losartan vs. captopril)	C, D	NS difference in mortality (1° endpoint) or SCD.
Val-HeFT	EF ≤ 40%	5,010	Valsartan (Valsartan + ACEI vs. ACEI)	C, D	13% RRR in combined morbidity* and mortality, no change in all-cause mortality. (1° endpoints) 27% decrease in HF hospitalizations.
CHARM-Added	EF ≤ 40%	2,548	Candesartan (Candesartan + ACEI vs. ACEI)	C, D	15% RRR CV death or HF hospitalization in the combination group (1° endpoint).
CHARM-Preserved	EF > 40%	3,023	Candesartan	C, D	NS improvement in CV death or HF hospitalization (1° endpoint).

*Including hospitalizations for HF, resuscitated cardiac arrest, need for intravenous vasodilator, or inotropic therapy.
OPTIMAAL = Optimal trial in Myocardial Infarction with Angiotensin II Antagonist Losartan; VALIANT = Valsartan in Acute Myocardial Infarction; CHARM: Candesartan in Heart Failure; ELITE = Evaluation of Losartan in the Elderly; Val-HeFT = Valsartan Heart Failure Trial; NS = non-significant; SCD = sudden cardiac death.

(Val-HeFT) and the CHARM-Added study [62,63]. In Val-Heft, the all-cause mortality (first primary endpoint) was similar in both groups but there was a significant reduction in the other primary endpoint of combined mortality and CV morbidity (due largely to a reduction in heart failure hospitalizations), and an improvement in NYHA class in the valsartan-added group. In the CHARM-Added trial, the addition of candesartan also significantly reduced CV mortality and heart failure hospitalizations (primary endpoint). There has been, however, conflicting evidence regarding the risks and benefits of combination ACEI and ARB therapy in heart failure. Post-hoc analysis of the Val-Heft trial raised concerns regarding the

Table 4.12 Adverse events leading to discontinuation of study drug in the VALIANT trial

Cause	Valsartan group (n = 4885) # (%)	Captopril group (n = 4879) # (%)	Valsartan and Captopril group (n = 4862) # (%)
Hypotension	70 (1.4)[*]	41 (0.8)	90 (1.9)[*]
Renal causes	53 (1.1)	40 (0.8)	61 (1.3)[*]
Hyperkalemia	7 (0.1)	4 (0.1)	12 (0.2)
Cough	30 (0.6)[*]	122 (2.5)	101 (2.1)
Angioedema	9 (0.2)	13 (0.3)	12 (0.2)
Any adverse event	282 (5.8)[*]	375 (7.7)	438 (9.0)[*]

[*]Significant difference from the captopril group, p < 0.05

Reference: Pfeffer, MA, McMurray, JJV, Velazquez, EJ et al. Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both. N Engl J Med 2003 349: 1893–1906. Reprinted with permission from the Massachusetts Medical Society.
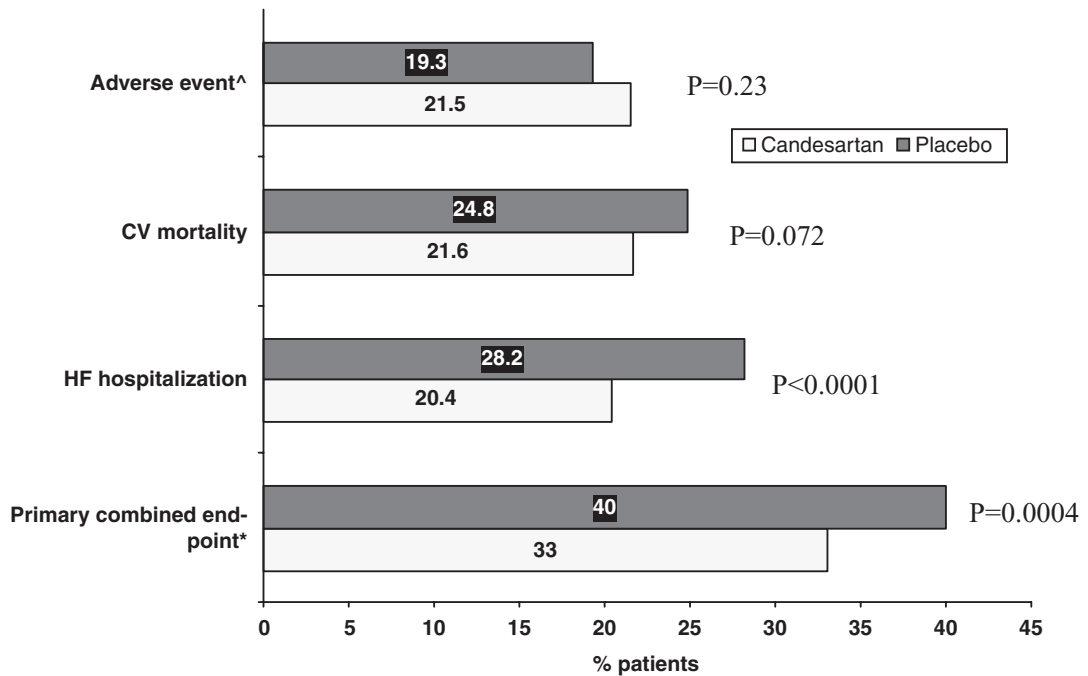

Figure 4.13 Effect of candesartan in heart failure patients intrlerant of ACEI: CHARM-Alternative trial.

HF = heart failure; [*]combined endpoint = cardiovascular death or HF hospitalization; ˆadverse event = hypotension/rise in creatinine/hyperkalemia/cough/angioedema; CV = cardiovascular.

Reference: Granger CB, McMurray JJ, Yusuf S et al. (2003). 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 362(9386), 772–6. Reproduced by permission of Elsevier.
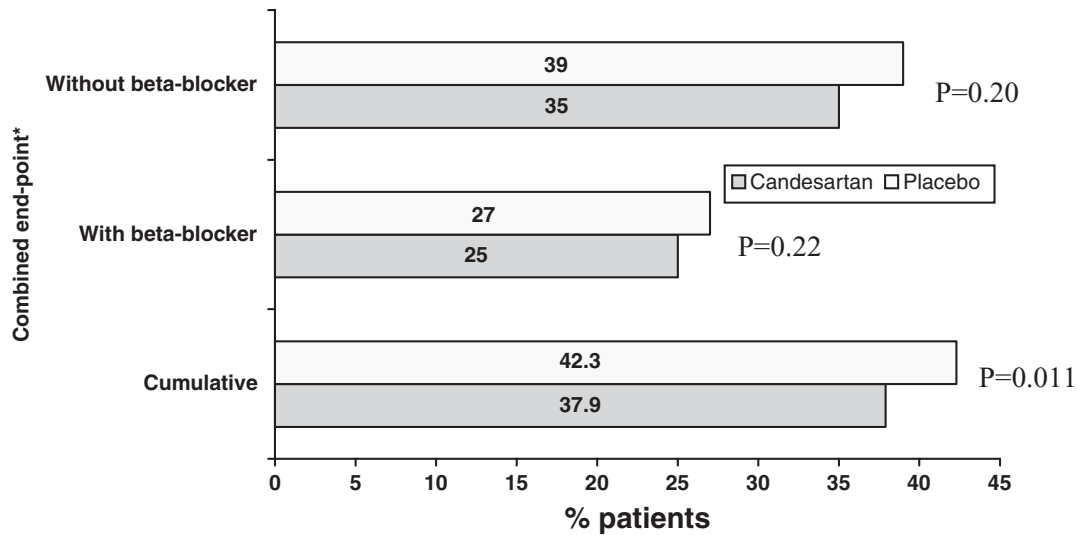
Figure 4.14   Incidence of CV death or HF hospitalization with combination ARB and ACEI therapy in patients with CHF: CHARM-Added trial.

[*]Combined endpoint = cardiovascular death or heart failure hospitalization.
Reference: McMurray JJ, Ostergren J, Swedberg K et al. (2003). 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 362(9386), 767–71. Reproduced by permission of Elsevier.

safety profile of valsartan therapy in patients receiving both ACEI and beta-blockers [62]. However, in the CHARM study, similar or improved benefit with ARB therapy were noted regardless of whether or not patients were receiving ACEI and beta-blockers, alleviating concerns about the adverse consequences of using the 3 neurohormonal modulators together (Figure 4.14). In accordance with the ACC guidelines, we recommend considering combination therapy in patients with heart failure who continue to be symptomatic on optimal standard therapy.

Diastolic heart failure
The CHARM-Preserved trial investigated the role of RAAS blockade with candesartan (target dose 32 mg daily) in patients with symptoms of heart failure and EF $\geq$ 40% [64]. The rate of CV deaths or heart failure admissions (primary endpoint) tended to be lower in the candesartan group but the 11% risk reduction did not reach significance. There were, however, fewer heart failure hospitalizations in the candesartan group. Further data is needed for use of ARBs in

heart failure patients with preserved EF. The irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial is currently underway to further define the role of ARB therapy in this population [65].

Elderly
The Evaluation of Losartan in the Elderly (ELITE) study compared an ARB (losartan) with an ACEI (captopril) in heart failure patients [66]. It was a small study with a primary endpoint of renal dysfunction; unexpectedly a significant decrease in mortality (secondary endpoint) was noted in the losartan group when compared with captopril. However, reduction in mortality was not the primary endpoint of the trial and the absolute number of deaths in the study was relatively small. A larger trial, ELITE-II was hence undertaken to prove survival benefit with valsartan (50 mg daily) compared with captopril (50 mg TID) in patients aged 60 years or older with symptomatic HF and LVEF $\leq$ 40% [67]. Unlike ELITE, this study failed to establish the superiority of ARB therapy for all-cause mortality and SCD. However, losartan

was better tolerated than captopril in this population with significantly fewer rates of discontinuation in the losartan group. Currently the recommendation for use of ARBs in the elderly is similar to the general population; ARBs can be used as an alternative for elderly patients intolerant of ACEI.

ACC Guidelines

- An ARB should be administered to post-MI patients who are intolerant of ACEIs and have a low LVEF.

- ARBs approved for the treatment of HF are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACEI intolerant.

- The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are on conventional therapy.

Practical approach to treating patients with ARBs

Initiation, dosing, and contraindications

In patients with LVD who are intolerant of ACEI, ARBs can be used unless the following contraindications are present: pregnancy, hyperkalemia (K >5.5), acute renal failure, ongoing hypotension requiring inotropic support, and history of ACEI induced life-threatening angioedema. Also, practitioners should exercise increased vigilance when initiating ARBs in patients with K $\geq$ 5.

When starting ARB therapy, similar guidelines should be followed as initiation of ACEIs. ARBs should be started at low dose (Table 4.13), and rapid titration to target dose can usually be achieved with minimal side effects. Serum creatinine and potassium should be checked before initiating, and/or increasing the dose of ARB. Serum creatinine and potassium should be carefully monitored for patients on potassium supplements or other potassium sparing drugs such as ACEI or aldosterone antagonist, or those with baseline renal insufficiency.

If therapy is complicated by symptomatic hypotension/ SBP < 80 mmHg or a rise in serum creatinine, stepwise plans outlined in Figure 4.6 and Figure 4.12 respectively, may be utilized.

Aldosterone antagonists

Neurohormonal activation is widespread in patients with CHF. It has been recognized that the resultant elevation of circulating hormones includes aldosterone (secondary hyperaldosteronism). Initial therapy with upstream RAAS blockers like ACEI or ARBs leads to transient decrease in aldosterone levels, but since aldosterone is regulated by other non-ACE pathways its levels often return to baseline, a phenomenon known as aldosterone escape [68].

Elevated aldosterone levels lead to adverse cellular, metabolic, and hemodynamic effects. In particular, aldosterone is capable of stimulating fibroblast proliferation and augmenting collagen deposition. The resultant increase in fibrosis adversely affects both systolic and diastolic cardiac function, resulting in cardiac remodeling and conduction abnormalities. This, in combination with electrolyte imbalances, specifically, hypokalemia and hypomagnesemia, also predisposes to cardiac arrhythmias. Finally, aldosterone can cause sodium retention and expansion of the extracellular volume, which may lead to hemodynamic instability and decline in cardiac output. The possibility that direct aldosterone inhibition might be beneficial has been investigated in patients with heart failure (Table 4.14).

Efficacy

Post-MI

Addition of eplerenone to conventional therapy in post-MI patients was investigated in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) study [69]. Patients with symptomatic heart failure and LVD (EF $\leq$ 40%),

Table 4.13 Target dosing for ARBs

ARB	Initial dose	Target dose
Losartan	25 to 50 mg qd	50 to 100 mg qd
Valsartan	40 mg bid	160 mg bid
Candesartan	4 to 8 mg qd	32 mg qd

Reference: ACC/AHA guidelines for management of patients with chronic heart failure [4]

Table 4.14 Clinical trials with aldosterone antagonists

Study	Population	Total (n)	Aldosterone antagonist	ACC Stage	Results
EPHESUS	EF ≤ 40% or diabetes 3–14 days post-MI	6,632	Eplerenone	B, C, D	15% reduction in mortality (1° endpoint)
					13% reduction in CV mortality or CV hospitalization (1° endpoint) 21% reduction in SCD
RALES	EF ≤ 35%	1,663	Spironolactone	D	30% RRR mortality (1° endpoint) 35% RRR HF hospitalization

EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; RALES = Randomized Adactone Evaluation Study; HF = heart failure; SCD = sudden cardiac death; RRR = relative risk reduction.

or diabetics with or without symptoms of heart failure, were randomized to eplerenone (titrated to 50 mg daily) versus placebo 3–14 days after an AMI. Study medication was added to standard therapy, which included diuretics (60%), ACEI (85%), beta-blockers (75%), and aspirin (88%). The two primary endpoints were 1) death from any cause and 2) death or hospitalization due to CV cause, including heart failure, AMI, stroke, or ventricular arrhythmia. During a mean follow-up of 16 months, eplerenone significantly reduced the risk of all-cause mortality (15%) and the risk of combined CV mortality/hospitalization (13%) (Figure 4.15). To determine the effects of eplerenone in the early post-MI period, results from EPHESUS at 30 days post-randomization were examined [70]. Significant reductions in all-cause mortality (RR 31%), CV mortality, and SCD were noted with the study drug within 30 days of initiation after the MI.

Chronic heart failure
In the Randomized Aldactone Evaluation Study (RALES), patients with severe symptomatic heart failure and LVEF ≤ 35% on background therapy with ACEI (95%), diuretic (100%), and in most cases, digoxin (75%) were randomized to spironolactone or placebo [71]. However, only 10% of the study population was receiving beta-blocker therapy. The study was discontinued prematurely as the interim analysis showed a significant 30% relative reduction in the primary endpoint of all cause mortality as well as a 35% reduction in heart failure hospitalizations in the spironolactone group (Figure 4.16). The risk of

hyperkalemia was low, at 2%, in the spironolactone treated group.

In contrast, the Reversal of Cardiac Remodeling with Eplerenone (REMODEL) trial investigated the effects of eplerenone on left ventricular volume and LVEF in patients with mild to moderate heart failure [72]. Most patients (>90%) were receiving optimal conventional therapy for heart failure including ACEI or ARBs and beta-blockers. This study failed to show an added benefit of eplerenone therapy on LV remodeling in patients with Stage C heart failure. The study was not powered, however, to detect effects on morbidity and mortality.

ACC/AHA guidelines:

- Long-term aldosterone blockade should be utilized for post-MI patients without significant renal dysfunction (creatinine should be less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women) or hyperkalemia (potassium should be less than or equal to 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF ≤ 40%, and have either symptomatic heart failure or diabetes.

- Addition of an aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration.
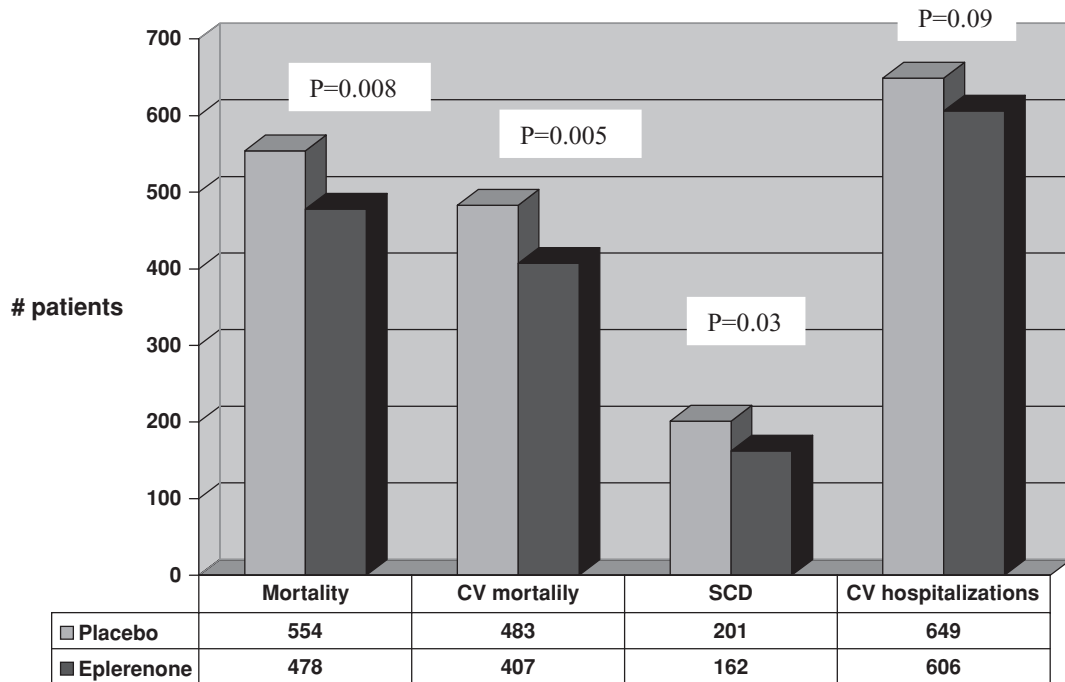
	Mortality	CV mortality	SCD	CV hospitalizations
☐ Placebo	554	483	201	649
■ Eplerenone	478	407	162	606

Figure 4.15   Improvement in mortality and CV outcomes in post-MI patients with eplerenone therapy: EPHESUS study.

SCD: sudden cardiac death, CV: cardiovascular.

Reference: Pitt B, Remme W, Zannad F et al., Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction, N Engl J Med 348 (2003), 1309–1321. Reprinted with permission from the Massachusetts Medical Society.

Practical approach to treatment of patients with aldosterone antagonists

Initiation

In a recent clinical trial by Hayashi et al. [73], early administration of an aldosterone blocker following revascularization after an MI was shown to prevent left ventricular remodeling. In this study, 134 patients with first AMI were treated with an angiotensin-converting enzyme (ACE) inhibitor and spironolactone (25 mg daily) or placebo beginning one day after revascularization. Compared with placebo, addition of aldosterone blockade to standard therapy improved LVEF and inhibited the increase in left ventricular end-diastolic volume index at 1 month. Thus, it would seem appropriate to start eplerenone therapy as an inpatient early following initial post-MI stabilization of the patient.

Aldosterone antagonist therapy in patients with advanced heart failure is usually started after patients have been treated with other agents such as ACEI, beta-blockers, and diuretics.

Contraindications

Aldosterone antagonists should be avoided in patients with baseline elevated potassium (K $\geq$ 5.0) or renal failure (GFR < 30 mL/min).

Agent of choice

Although eplerenone and spironolactone both block the binding of aldosterone to the mineralocorticoid

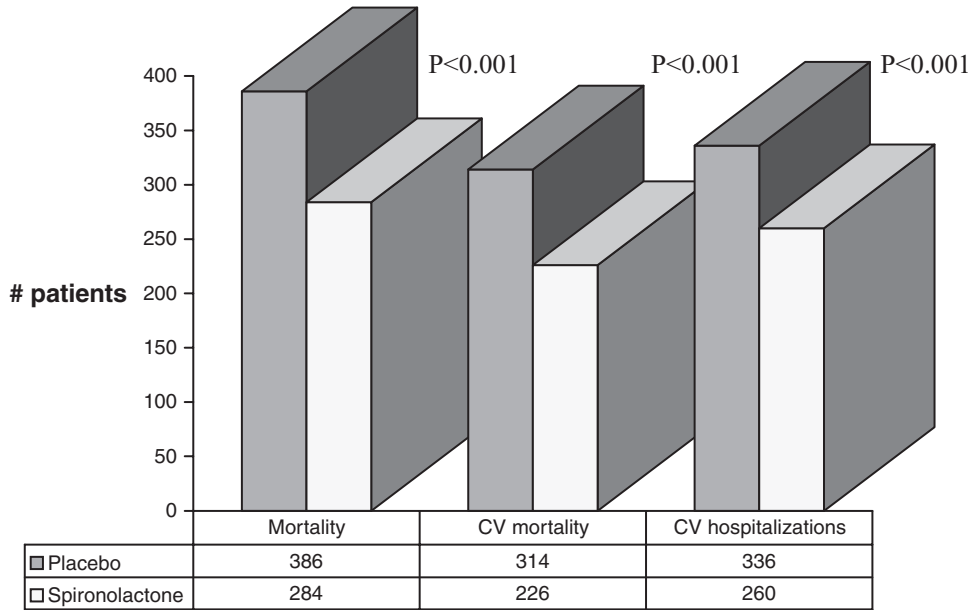| # patients	Mortality	CV mortality	CV hospitalizations
☐ Placebo	386	314	336
☐ Spironolactone	284	226	260

Figure 4.16 Reduction in mortality and CV events with spironolactone therapy in severe HF: RALES trial.

Reference: Pitt B, Zannad F, Remme WJ et al. (1999). The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. The New England Journal of medicine, 341(10), 709–17. Reprinted with permission from the Massachusetts Medical Society.

receptor, they have different affinity for the steroid hormone receptors. Spironolactone has high affinity for steroid hormone receptors (progesterone and estrogen receptors), thus it is commonly associated with gynecomastia, a side effect that is not noted with eplerenone. Also, spironolactone has several active metabolites with long half-lives, which greatly increases its effective half-life compared with that of eplerenone, which has no active metabolites and a relatively short half-life of 4–6 hours [74].

Dosing and titration

Therapy should be started at low dose and titrated over 4 weeks to target dose if the serum creatinine and potassium are within normal limits (Table 4.15). Careful monitoring of serum K+ and renal function should be performed while initiating therapy. The risk of hyperkalemia, which was reported to be low in the carefully orchestrated clinical trials (2% in RALES, 3.4% in EPHESUS), appears substantially higher in clinical practice [75]. In RALES and EPHESUS

Table 4.15 Target dose of aldosterone antagonist

	Starting dose		Target dose	
Drug	GFR >60 mL/min	GFR 30 to 60 mL/min	GFR >60 mL/min	GFR 30 to 60 mL/min
Aldactone	25 mg qd	12.5 mg qd **or** 25 mg every other day	50 mg qd	25 mg qd **or** 50 mg every other day
Eplerenone	25 mg qd	25 mg qd	50 mg qd	50 mg qd

Reference:Pitt B, Rajagopalan S. (2006). Aldosterone receptor antagonists for heart failure: current status, future indications. Cleveland Clinic journal of medicine, 73(3), 257–60, 264. With permission from the Cleveland Clinic Foundation.

trials the serum potassium levels were monitored at 1 week, 1 month, and every 3–6 months thereafter. We recommend checking serum K+ and creatinine at the above-mentioned intervals in patients with normal renal function (GFR ≥ 60 mL/minute). However, in patients with GFR between 30 to 60 mL/minute, those receiving additional potassium elevating drugs (ACEI, ARBs, K+ supplements), in diabetics, and the elderly, the levels should be checked more frequently. Due to the potential risk for hyperkalemia, the ACC/AHA committee recommends that the routine triple combination of ACEIs, ARBs, and an aldosterone antagonist be avoided [4].

Management of adverse effects

1. Hyperkalemia: ensure patient is not on potassium supplements. The dose of aldosterone antagonist should be cut in half for mild hyperkalemia (K >5.0 but <5.5), serum potassium should be rechecked in 1 week. Aldosterone antagonists should be discontinued for K >5.5.

2. Gynecomastia: in the RALES trial, 10% of male patients treated with spironolactone developed gynecomastia, compared with 1% of patients on placebo. Eplerenone has much lower affinity for the sex-hormone receptors hence minimizing its risk of gynecomastia. Patients intolerant to spironolactone due to gynecomastia may be switched to eplerenone.

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