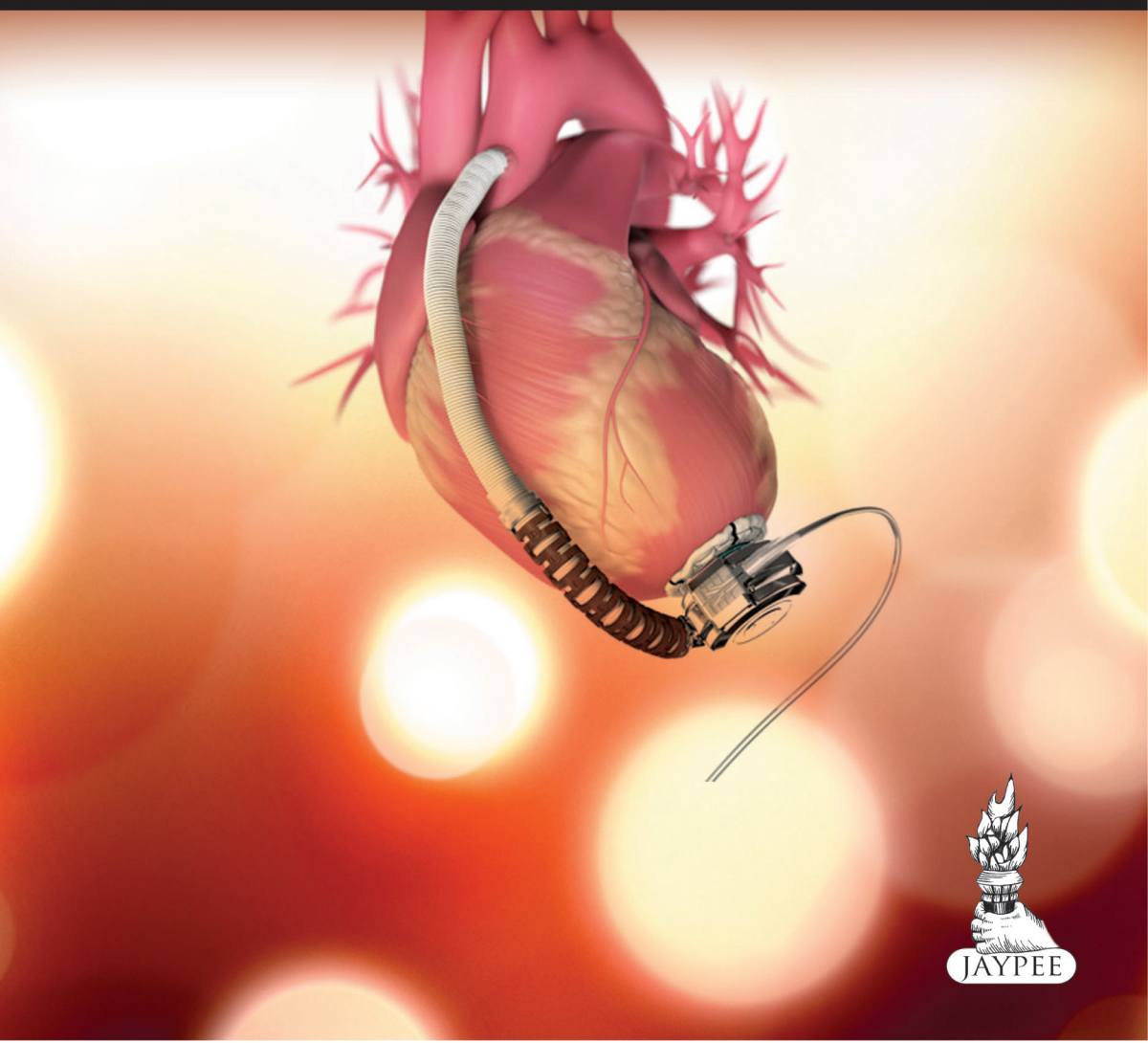
Drug & Device Selection in Heart Failure

Prakash C Deedwania • Paul J Mather



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Contents

1. **Renewed Understanding of the Pathophysiology of Heart Failure** 1
   Kanu Chatterjee
2. **New Diuretics in Heart Failure** 10
   Jagroop S Basraon, Prakash C Deedwania
3. **Guideline-Based Standard Therapy for Heart Failure: The Role of RAAS Blockers and Beta Blockers** 25
   Prakash C Deedwania, Enrique Carbajal
4. **Emerging Role of Aldosterone Receptor Blockers in Heart Failure** 43
   Manjunath C Harlapur, Prakash C Deedwania
5. **Inotropic Therapy for Heart Failure: Past, Present, and Future** 56
   Paul J Hauptman, Patrick McCann
6. **Hospitalization for Heart Failure: Pathophysiology, Classification, and Management Considerations** 78
   Muthiah Vaduganathan, Mihai Gheorghiade
7. **Traditional Mechanical Support** 97
   Raphael E Bonita, Kariann Abbate
8. **Percutaneous Mechanical Support** 110
   Raphael E Bonita, Kariann Abbate
9. **Cardiac Resynchronization Therapy** 124
   Toshima Okabe, Behzad B Pavri
10. **Sudden Cardiac Death and Implantable Cardioverter-Defibrillator** 156
    Toshima Okabe, Behzad B Pavri
11. **Atrial Arrhythmias in Heart Failure** 184
    Sumeet K Chhabra, Daniel R Frisch

12. Ventricular Tachyarrhythmias in Patients with Congestive Heart Failure **203**
Andrew Yin, Reginald T Ho

13. Heart Transplantation **218**
Gordon R Reeves, Paul J Mather

14. Heart Failure **237**
Anne P Canny

Index **247**

CHAPTER

Guideline Based Standard Therapy for Heart Failure: The Role of RAAS Blockers and Beta Blockers

3

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INTRODUCTION

Heart failure (HF) is associated with increased morbidity and mortality. With the improved survival of patients with myocardial infarction (MI), those with long-standing hypertension as well as increased life expectancy, it is likely that prevalence of HF will escalate further in the coming years. In general, the prognosis of patients with HF can be worse than many cancers, however, with the increasing use of guideline recommended therapies, such as neurohormonal blockade, there has been considerable improvement in the prognosis of patients with HF. During the last several decades, many studies have demonstrated the benefits of treatment with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and beta-blocking (BB) drugs.[1,2] Based on the evidence available from well-designed randomized controlled trials (RCT), various national and international guidelines have now established specific recommendations for the use of renin angiotensin aldosterone system (RAAS) blockers and beta blocking agents in HF.[1,2]

In the following section, we will review the evidence supporting the use of RAAS blockers and BB agents in patients with HF secondary to left ventricular (LV) systolic dysfunction.

GUIDELINE-BASED THERAPY FOR HEART FAILURE

Because HF is a progressive disorder early identification of those at risk of developing signs and symptoms of HF is of critical importance. The most recent ACC/AHA guidelines (Fig. 1) have emphasized identification of individuals in stages A/B of HF with the goal of early intervention to prevent progressive deterioration in cardiac dysfunction and subsequent prevention of symptomatic HF. Stage A patients are those who have risk factors [e.g., those with hypertension (HTN), diabetes mellitus (DM), obesity, coronary artery disease (CAD), etc.] that can subsequently lead to cardiac dysfunction and development of HF. Treatment of these underlying risk factors should attenuate/prevent the subsequent development of cardiac dysfunction.

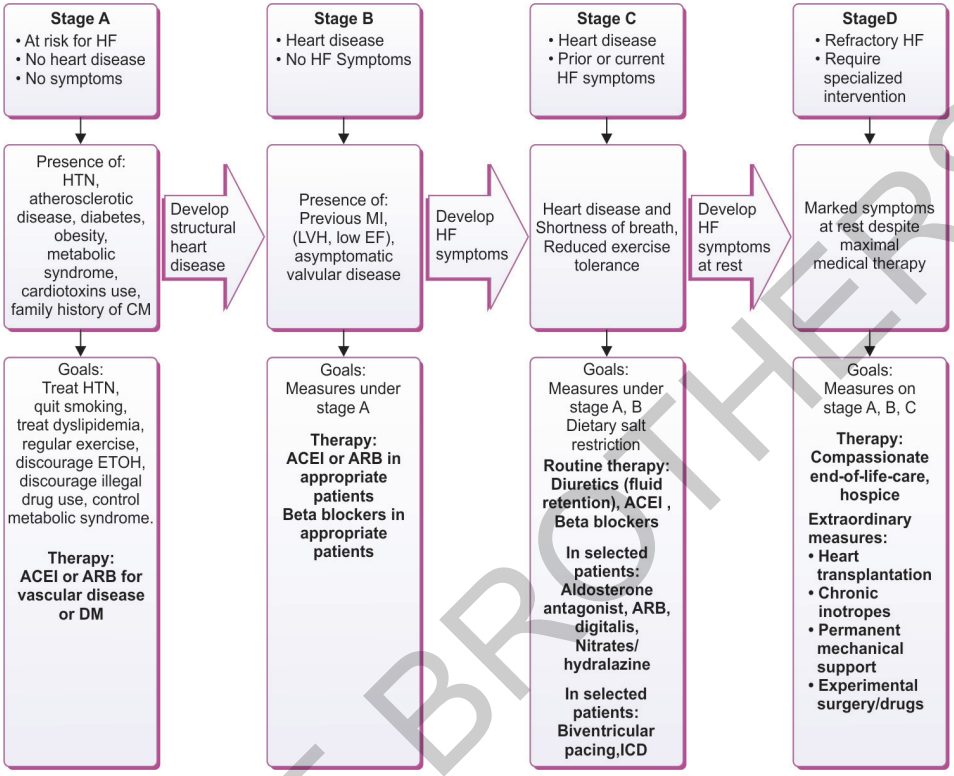

Figure 1: Staging of heart failure and recommended therapy at various stages. HF, heart failure; HTN, hypertension; CM, cardiomyopathy; LVH, left ventricular hypertrophy; EF, ejection fraction; MI, myocardial infarction; ETOH, alcohol; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DM, diabetes mellitus; ICD, implantable cardioverter-defibrillator.

Source: *Adapted from* Hunt SA, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults. Circulation. 2009;119:e391-479.

Stage B patients are those who have LV hypertrophy and/or impaired LV function but who are still asymptomatic. Early intervention with neurohormonal blockers with RAAS blockers and BB as appropriate should prevent the process of cardiac remodeling and further progression of LV dysfunction. The stage C denotes patients who have developed symptoms of HF due to the underlying cardiac dysfunction and require treatment for both symptoms of HF as well as improvement of the related adverse prognosis. Stage D patients are those who have significantly advanced and/or refractory HF who are generally candidates for specialized advanced treatment strategies including mechanical support devices, inotropic drugs, and consideration for cardiac transplantation and/or other surgical procedures.

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The drugs that have proved to be unequivocally beneficial in prolonging survival and improving symptoms in patients with LV systolic dysfunction and HF are primarily those that block the heightened neuroendocrine activity and include RAAS, blocking drugs (ACEIs, ARBs, and ARB agents), and beta blocking agents. Although diuretics are frequently used and necessary in patients with congestive symptoms with fluid accumulation, there is no evidence that the chronic use of diuretic therapy improves survival. Furthermore, it is important to keep in mind that appropriate therapy for myocardial ischemia when present in the setting of HF is also associated with improved clinical outcome.

In this chapter, we will primarily focus on guideline-based therapy focused on neurohormonal blockade of the RAAS and sympatho-adrenergic systems. As shown in figure 2, both RAAS and sympathetic nervous system (SNS) are activated with the onset of myocardial dysfunction in response to decreased cardiac output. Initially, such a response is adaptive and helps to maintain adequate tissue perfusion of vital organs by causing peripheral vasoconstriction. However, continued chronic activation of RAAS and SNS has significant adverse consequences due to continued peripheral vasoconstriction, sodium retention and hemodynamic alterations (Fig. 3). In addition, activation of these systems, in particular the RAAS, has been shown to be associated with progressive myocardial remodeling which leads to worsening LV dysfunction. Because of the critical role of these neuroendocrine alterations in the pathophysiology of LV dysfunction and HF, there has been continued effort during the past several decades to use agents

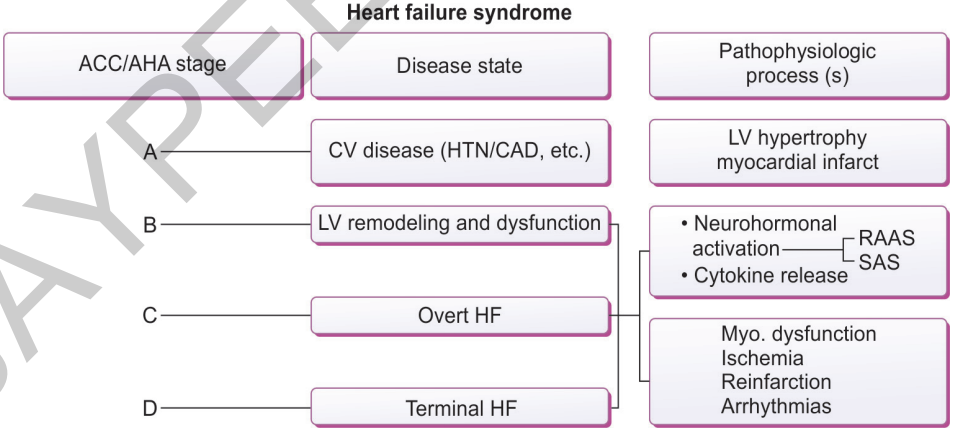

Figure 2: Various ACC/AHA stages of heart failure, the corresponding cardiovascular disease/alterations and the underlying pathophysiology showing activation of RAAS and SAS with onset of LV dysfunction and related consequences. ACA, American College of Cardiology; AHA, American Heart Association; CV, cardiovascular; HTN, hypertension; CAD, coronary artery disease; LV, left ventricle; RAAS, renin angiotensin aldosterone system; SAS, sympathetic adrenergic system; HF, heart failure; Myo., myocardial.

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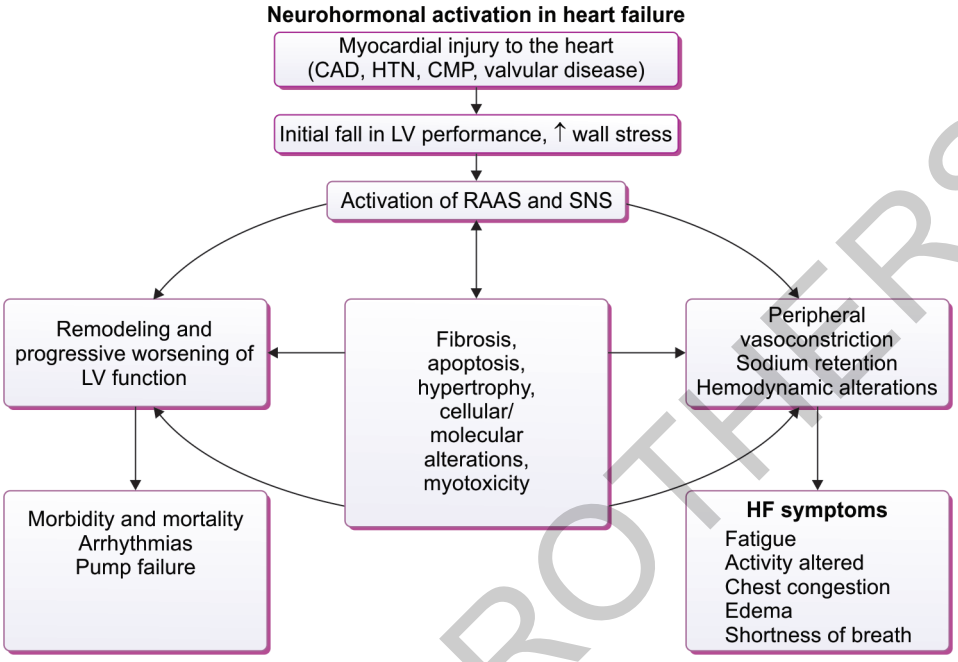

Figure 3: Importance of RAAS and SNS activation in pathophysiologic process of heart failure. RAAS, renin angiotensin aldosterone system; SNS, sympathetic nervous system; CAD, coronary artery disease; HTN, hypertension; CMP, cardiomyopathy; LV, left ventricle; ↑, increased; HF, heart failure.

effective in blocking the RAAS and SNS systems in an effort to not only improve the symptoms but also decrease associated morbidity and mortality in patients with HF. Results of numerous studies have demonstrated that neurohormonal blockade of RAAS and sympatho-adrenergic systems controls symptoms of HF, improves clinical status as well as functional capacity, enhances sense of well being, and reduces the associated morbidity and mortality in patients with HF.[3-10] It is because of these well-demonstrated effects of RAAS blocking drugs and beta blockers, treatment with these drugs is now recommended by all guidelines across the world for all patients with HF. In the following sections, we provide the pathophysiologic rationale and practical consideration for clinical use of these therapies in patients with HF.

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM BLOCKING DRUGS

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors are the best studied class of drugs in patients with HF, with multiple beneficial effects. ACEI should be prescribed for all patients with LV dysfunction and HF unless there is a contraindication for their use

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or there is prior history of intolerance due to significant adverse experience with these agents. Because of the well-demonstrated survival benefit even in patients with asymptomatic LV dysfunction treatment with ACEI should not be delayed.

In patients with HF, inhibition of angiotensin-converting enzyme by ACEI produces a moderate increase in cardiac output with a concomitant significant decrease in right and left ventricular filling pressures, pulmonary and systemic vascular resistances, and mean arterial pressure without increasing the heart rate. It is not established whether these effects of ACEI are entirely due to the suppression of angiotensin-II production or increased bioavailability of bradykinin which augments kinin mediated prostaglandin production (Fig. 4). ACEIs have additional beneficial effects including reduction of ventricular arrhythmias, decreased end-systolic and end-diastolic dimensions, and improvements in symptoms, exercise duration, and quality of life.

Angiotensin-converting enzyme inhibitors have been evaluated in a number of RCTs in patients in various stages of HF.[3-9] These trials have consistently shown a significant reduction in mortality rates (Table 1).[3-9] Most trials enrolled patients

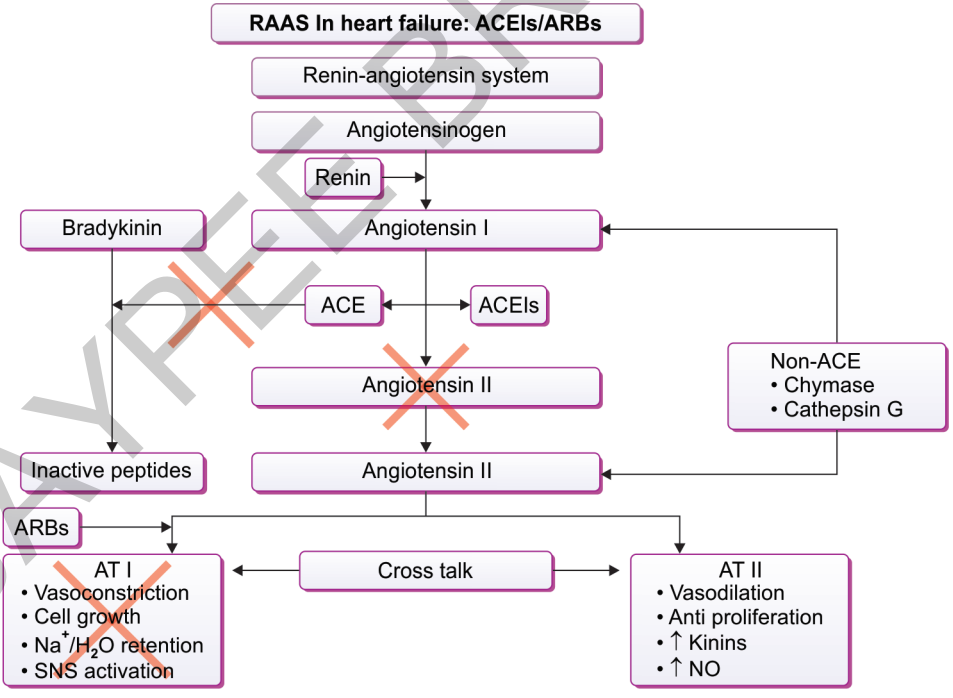

Figure 4: Mechanism of action of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. RAAS, renin angiotensin aldosterone system; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ATI-II, angiotensin II types I-II; Na^+, sodium; H_2O, water; SNS, sympathetic nervous system; ↑, increased; NO, nitric oxide.

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Table 1 **Summary of results from various studies showing effects of angiotensin converting enzyme inhibitors on mortality**

	Mortality		
Trial	*ACEI (%)*	*Controls*	*(%) RR (95% CI)*
Heart failure			
CONSENSUS I	39	54	0.56 (0.34–0.91)
SOLVD (Treatment)	35	40	0.82 (0.70–0.97)
SOLVD (Prevention)	15	16	0.92 (0.79–1.08)
Postmyocardial infarction			
SAVE (Captopril)	20	25	0.81 (0.68–0.97)
AIRE (Ramipril)	17	23	0.73 (0.60–0.89)
TRACE (Trandolapril)	35	42	0.78 (0.67–0.91)
SMILE (Zofenopril)	5	6.5	0.75 (0.40–1.11)

ACEI, angiotensin converting enzyme inhibitor; RR, relative risk; CI, confidence interval; CONSENSUS, Co-operative North Scandinavian Enalapril Survival Study; SOLVD, studies of left ventricular dysfunction; MI, myocardial infarction; SAVE, survival and ventricular enlargement; AIRE, acute infarction ramipril efficacy; TRACE, TRAndolapril Cardiac Evaluation; SMILE, survival of myocardial infarction long-term evaluation.

with reduced left ventricular ejection fraction (LVEF <35–40%) who were already being treated with diuretics with or without digitalis and in many trials patients were also getting vasodilating drugs. The aggregate results of these studies demonstrate a reduction in mortality of 20–25% in those treated with ACEI as compared to control groups. With consistent results seen in these RCTs, there is universal recommendation by all guideline committees to use ACEI in all patients with LV dysfunction and/or HF due to systolic dysfunction.

Practical Considerations Regarding Use of Angiotensin-Converting Enzyme Inhibitors

Treatment with ACEI should generally be initiated at low doses (Table 2) and followed by gradual increase in dosage. Renal function and serum potassium need to be assessed within 1–2 weeks of initiation of ACEIs and periodically thereafter, specifically in patients with preexisting hypotension, hyponatremia, diabetes, and chronic kidney disease [CKD; estimated glomerular filtration rate (eGFR) <60].

Differences among various ACE, are primarily related to pharmacokinetic and hemodynamic properties. Captopril has the shortest duration of action whereas enalapril, lisinopril, and other newer ACEIs have delayed onset of action and prolonged duration of hemodynamic effects. Because of its shorter duration of action, many clinicians prefer to start treatment with captopril specially in hospitalized patients who are ACEI naive and/or fluid depleted (due to excessive diuresis) to

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Table 2 List of evidence-based drugs and their dosage for heart failure

Drug	*Initial daily dosage*	*Maximum dosage*
Angiotensin-converting enzyme inhibitors		
Captopril	6.25 mg 3 times	50 mg 3 times
Enalapril	2.5 mg twice	10–20 mg twice
Fosinopril	5–10 mg once	40 mg once
Lisinopril	2.5–5 mg once	20–40 mg once
Perindopril	2 mg once	8–16 mg once
Quinapril	5 mg twice	20 mg twice
Ramipril	1.25–2.5 mg once	10 mg once
Trandolapril	1 mg once	4 mg once
Angiotensin receptor blockers		
Candesartan	4–8 mg once	32 mg once
Losartan	25–50 mg once	50–100 mg once
Valsartan	20–40 mg twice	160 mg twice
Aldosterone antagonists		
Spironolactone	12.5–25 mg once	25 mg once or twice
Eplerenone	25 mg once	50 mg once
Beta blockers		
Bisoprolol	1.25 mg once	10 mg once
Carvedilol	3.125 mg twice	25 mg twice; 50 mg twice if >85 kg
Metoprolol succinate extended release (CR/XL)	12.5–25 mg once	200 mg once
Hydralazine/isosorbide dinitrate in combination		
With ACEI/ARB	Hydralazine 75 mg every 8 hours plus isosorbide dinitrate 40 mg every 8 hours	
Without ACEI/ARB	Hydralazine 50 mg every 6 hours plus isosorbide dinitrate 40 mg every 6 hours	

ACEI, angiotensin-converting enzyme inhibitor; mg, milligrams; kg, kilograms; ARB, angiotensin receptor blocker.

Source: *Adapted from* Hunt SA et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009;119:e391-479.

avoid the initial risk of hypotension particularly in those patients who have low blood pressure (SBP <80 mmHg). For most patients, stable treatment with longer acting agents starting at low doses should be initiated under careful monitoring. It is important to keep in mind that appropriate stable doses of diuretics need to

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be maintained in conjunction with the use of ACEI as fluid retention can blunt the therapeutic effects and fluid depletion can potentiate the adverse effects of ACEIs.

Angiotensin-converting enzyme inhibitors use is contraindicated if the patient has previously experienced life threatening adverse reactions (angioedema, anuric renal failure). ACEI should also be used with caution in patients who have low systemic blood pressure (SBP <80 mmHg), markedly increased serum creatinine (>3.0 mg/dL), bilateral renal artery stenosis, or elevated levels of serum potassium (>5.5 mEq/L).

Frequently, question is raised regarding the optimal dose of ACEI in patients with HF. RCTs conducted to evaluate the survival benefit of treatment with ACEI, the dose of ACEI was not determined by the patients' therapeutic response but was rather increased until the target dose or maximally tolerated dose was achieved. Despite this, ACEIs are frequently prescribed in clinical practice at much lower doses that are similar to those recommended for initiation of therapy rather than maintenance of therapy (Table 2). Clinician should generally attempt to use the doses that have been shown to reduce the risk of mortality and other cardiovascular events in RCTs. If the target doses of ACEI cannot be used or are poorly tolerated, intermediate doses should be used. It is also important to note that even though in some cases, symptoms may improve within a few days of starting treatment with ACEI, in general, the clinical response to ACEI is delayed and requires several weeks, months, or longer. Even if symptoms do not improve, long-term treatment with ACEI should be maintained to reduce risk of death or hospitalization.

Many patients with HF who have been previously receiving potassium supplementation in conjunction with diuretic therapy will not need such supplement once they are on adequate doses of ACEI. Therefore, it is important to monitor electrolytes and consider discontinuation of such supplementation at appropriate time. Because it is well known that use of nonsteroidal anti-inflammatory drugs (NSAIDs) can interfere with the favorable effects and enhance adverse effects of ACEI in patients with HF, their use should be avoided and/or minimized whenever possible. Concomitant use of aspirin has also been shown to be associated with decreased effects of ACEIs on cardiovascular morbidity and mortality. However, when all available data are considered the beneficial effects of ACEIs were still present, regardless of concomitant aspirin use, and most physicians now believe that when there is an appropriate indication for aspirin use, there is no harm in continuing it in conjunction with ACEI therapy.

Safety and Adverse Effects of Angiotensin-Converting Enzyme Inhibitors

Most of the adverse reactions of ACEIs are related to their principal pharmacological actions: those related to angiotensin suppression and kinin potentiation and general reactions (rash, taste disturbances). Important side effects are reviewed below.

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Hypotension

The most common adverse effects of ACEI in patients with HF are hypotension and dizziness. Blood pressure generally declines without symptoms in almost every patient treated with an ACEI. Therefore, a decrease in blood pressure should be a concern only if it is associated with symptoms of cerebral hypoperfusion, postural symptoms, or worsening renal dysfunction. Significant hypotension when present is usually seen in the first few days of initiation of ACEI therapy or increase in the dosage. Patients who are ACEI naive and those who are dependent on the renin-angiotensin-aldosterone system for blood pressure maintenance are particularly at risk for hypotension. Similarly, patients with hyponatremia or hypovolemia, especially those receiving high-dose diuretic therapy are also at risk of hypotension. Hypotension usually resolves with continued therapy and can be avoided by reducing the diuretic dosage or stopping it for few days (often referred as diuretic holiday). Patients considered to be at risk for hypotension should be monitored closely for the first 2 weeks of treatment and with every dose escalation. In some patients (e.g., those with low blood pressure from the start) a period of brief hospitalization and close observation during the initiation of ACEI therapy might be necessary.

Cough

Cough is one of the most common reasons for withdrawal of ACEIs. In general, the frequency of cough is between 5 and 10% in Caucasians; however, it has been reported to be higher (up to 20%) in oriental and Asian patients. It is important to recognize that many patients with HF may have concomitant bronchitis, upper respiratory tract infection, etc., which might be the main reason for their cough. Therefore, it is very important to establish that the cough is indeed directly related to the use of ACEI before discontinuing their use. It is also important to realize that worsening HF leading to decompensation can itself lead to cough due to peribronchial edema. Therefore, it is crucial to establish the link between the use of ACEI and cough before considering discontinuation of this life saving therapy in patients with HF. ACEI induced cough generally occurs within the first few weeks to months of therapy and is usually nonproductive, generally persistent, and sometimes associated with an annoying "tickle" in the back of the throat. ACEI induced cough generally disappears within 1–2 weeks of discontinuation of treatment and re-appears with ACEI re-challenge. In a number of studies of ACEI, cough, it was demonstrated that cough did not recur with rechallenge and was probably a coincidental finding. Unless the cough is severe and quite bothersome to the patient, clinicians should encourage patients to continue taking these drugs because of the well-demonstrated benefit on cardiovascular morbidity and mortality.

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Renal Dysfunction

Because of already reduced renal perfusion in many patients with HF, GFR is critically dependent on angiotensin mediated efferent arteriolar vasoconstriction. Therefore, ACEI might cause functional renal insufficiency by reducing the levels of angiotensin-II. The risk of renal dysfunction secondary to ACEI is greatest in patients who are dependent on renin angiotensin system (RAS) for support of renal homeostasis. It is, however, important to recognize that an increase in serum creatinine (e.g., > 0.3 mg/dL) is generally observed in 15–30% of patients with severe HF who are treated with ACEIs and in about 5–15% with mild to moderate HF. In most cases, this decline in renal function appears to be of little clinical significance. The risks are substantially greater if patient is taking NSAIDs or has baseline CKD and/or bilateral renal artery stenoses. In most cases, however, renal function usually returns to baseline or stabilizes at a new steady state despite continued treatment with the ACEI. Renal function usually improves after reduction in dosage of concomitantly administered diuretic, therefore, most patients can generally be managed without the need to withdraw treatment with ACEI. However, when clinically indicated discontinuing treatment or decreasing the dosage of the ACEI will rapidly resolve the renal dysfunction as well. In major clinical trials, the need for discontinuation of ACEI therapy because of renal impairment has been quite low (1–3%) and in some trials it was equivalent to that seen with placebo. The longer acting ACEIs, however, may be associated with a higher risk of renal dysfunction.

Hyperkalemia

Hyperkalemia can occur during ACEI therapy, and in some cases, it might be significant enough to cause cardiac conduction abnormalities. The risk of hyperkalemia is significantly higher in patients with baseline renal dysfunction and/or when renal dysfunction occurs as a result of ACEI use. Continued use of potassium sparing diuretics, potassium supplement, or salt substitute (which contains potassium) will obviously increase the risk of hyperkalemia and their use is generally prohibited. Concomitant use of aldosterone antagonists especially in presence of diabetes is also associated with increased risk of hyperkalemia and can be reduced by appropriate dose adjustments.

Angioedema

Angioedema is rare but a life threatening adverse effect that occurs only in less than 1% of patients taking ACEIs. It is now well established that angioedema occurs far more frequently in blacks. Because angioedema can be life threatening, any history or clinical suspicion of such reactions in the past should be considered a contraindication for ACEI therapy. Angiotensin receptor blockers can be considered as an alternative therapy as ARBs generally do not produce angioedema because

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they lack bradykinin potentiating effect. However, even therapy with ARBs be used with caution in patients with ACEI induced angioedema as there have been few reports of angioedema in patients treated with ARBs.

Angiotensin Receptor Blockers

Several RCTs have now shown that the renin angiotensin system can have partial escape during chronic therapy with ACEIs leading to increasing levels of angiotensin-II despite continued treatment with ACEIs. Such ACEI escape phenomenon occurs in part due to activation of alternative pathways for production of angiotensin-II in myocardial and vascular tissues (Fig. 4). These alternate pathways (especially chymase dependent) can be generally activated in the setting of myocardial injury secondary to infarction.

Because ARBs provide direct blockade of angiotensin II type-1 (AT1) receptors they have been utilized to counteract effects of angiotensin-II on tissues regardless of the site of origin of angiotensin II (Fig. 4). In addition, this effect is achieved without accumulation of bradykinin, which is primarily responsible for some adverse reactions associated with the use of ACEIs, such as persistent cough, angioedema, and significant hypotension.

Theoretically, the use of these drugs should be associated with beneficial effects on clinical outcomes similar to those observed with ACEI therapy and generally with fewer side effects. The ARBs have produced favorable hemodynamic effects during short- and long-term administration. Also, RCTs comparing ARBs with ACEIs have generally shown equivalent or enhanced benefits.

Several ARBs have been evaluated in the setting of HF and are available for clinical use (Table 2). Overall, placebo RCTs have demonstrated that long-term therapy with ARBs is associated with beneficial effects on hemodynamic, neurohormonal, and clinical parameters that are expected with RAS blockade. However, it is important to note that the overall experience with ARBs in large RCTs in HF is significantly less than that with ACEIs. Based on the clinical trials experience presently only 3 ARBs are approved for treatment of patients with HF (Table 2). Although these ARBs can be considered as an alternate RAS blocking therapy it is important to emphasize that treatment with ACEIs remain the first choice for inhibition of RAS in patients with HF. The use of ARBs should generally be reserved as an alternate therapy in patients who are intolerant to treatment with ACEI. The benefit of alternative therapy with an ARB was well demonstrated (Fig. 5) with candesartan in the candesartan in HF: assessment of reduction in mortality and morbidity (CHARM) alternative trial.[10]

Practical Considerations Regarding Use of ARBs

Similar to the use of ACEIs treatment with an ARB, when appropriate, should be started at the low doses (Table 2). In general, as discussed earlier, most considerations

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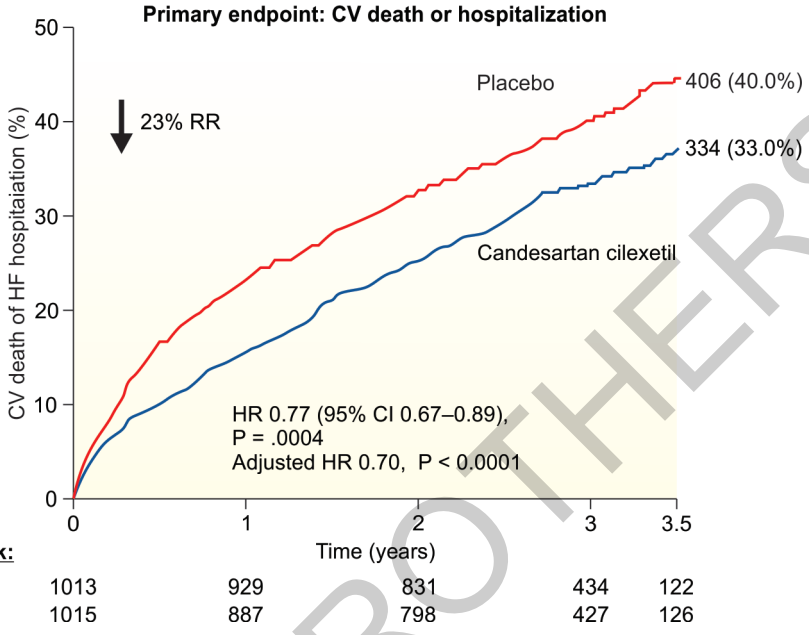

Figure 5: Results of CHARM alternative study showing efficacy of candesartan versus placebo in patients with systolic heart failure. CHARM, Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity; CV, cardiovascular; RR, relative risk; HF, heart failure; HR, hazard ratio; CI, confidence interval.

Source: *Adapted from* Granger CB, McMurray J, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362:7726.

regarding the use of ARBs are similar to those with ACEIs. Close monitoring of blood pressure, renal function, and serum K^+ is recommended starting at 1–2 weeks after initiation of ARB therapy and as needed subsequently. Titration of ARB doses is generally achieved by doubling doses every 2 weeks until the target dose is achieved or patient develops intolerance. The overall side effects related to the use of ARBs on renal function and serum potassium level are similar to those described above with ACEIs. However, angioedema (although reported in the literature) occurs rarely with ARBs.

BETA ADRENERGIC BLOCKERS

Activation of sympathetic adrenergic nervous system in response to cardiac dysfunction leads to higher levels of plasma catecholamines which are associated with deleterious effects on the heart (Fig. 3). Sympathetic activation causes profound vasoconstriction leading to increased afterload which subsequently increases ventricular pressures and volumes perpetuating the process of cardiac

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remodeling. In addition norepinephrine can itself induce cardiac hypertrophy and worsen myocardial ischemia in those with underlying CAD. Activation of SNS also impairs sodium excretion by kidney as well as it promotes release of aldosterone which also results in salt and water retention. Enhanced sympathetic activity can also provoke arrhythmias by increasing the automaticity of myocytes, increasing trigger activity in the heart, and promoting electrolyte imbalance. High levels of norepinephrine also potentiate the actions of the RAAS. Finally, norepinephrine can also trigger cardiac apoptosis by stimulating growth and increasing oxidative stress in terminally differentiated cells (Fig. 3). It is because of these deleterious effects of the SNS activation in patients with HF that treatment with beta blockers was considered useful in HF despite their well-known negative inotropic effects. Beta blockers work primarily by preventing the adverse consequences of enhanced SNS activity in patients with HF and these beneficial effects far outweigh their negative inotropic effects. As a matter of fact, long-term studies with beta blockers have shown that continued use of beta blockers is associated with positive cardiac remodeling which leads to significant improvement in LV performance associated with increased LVEF. There are several additional beneficial effects of beta blockers at the cellular level which are beyond the scope of this review.

It is important to note that so far only three beta blockers (carvedilol, bisoprolol, and sustained release metoprolol succinate) have been shown to be effective (Fig. 6) in patients with chronic HF.[11-14] It is important to realize that beneficial effects demonstrated with these three beta blockers are not indicative of a beta blocker class effect, as shown by the lack of effectiveness of bucindolol and lack of effectiveness of short acting metoprolol in clinical trials.[15-16]

Beta blockers have now been evaluated in numerous placebo controlled RCTs in HF patients with reduced LVEF (< 35–45%) who where already receiving treatment with diuretics and ACEIs, with or without digitalis. The aggregate experience from these trials indicates that long-term treatment with beta blockers reduced the symptoms of HF, improved the clinical status and reduced the risk of hospitalization for HF. More importantly, in all trials, treatment with beta blocker was associated a significant improvement (Fig. 6) in survival.[11-14] These benefits of beta blockers were seen in all subgroups of patients including those with milder or more severe HF, those with or without underlying CAD, those with or without DM, as well as in black and female patients.

Practical Considerations

Based on the consistent efficacy and significant survival benefit of the three beta blockers approved for treatment of HF, they are now recommended for all patients with chronic HF with reduced LVEF unless there is a contraindication or a history of intolerance. Because their significant favorable effect on cardiac remodeling, disease

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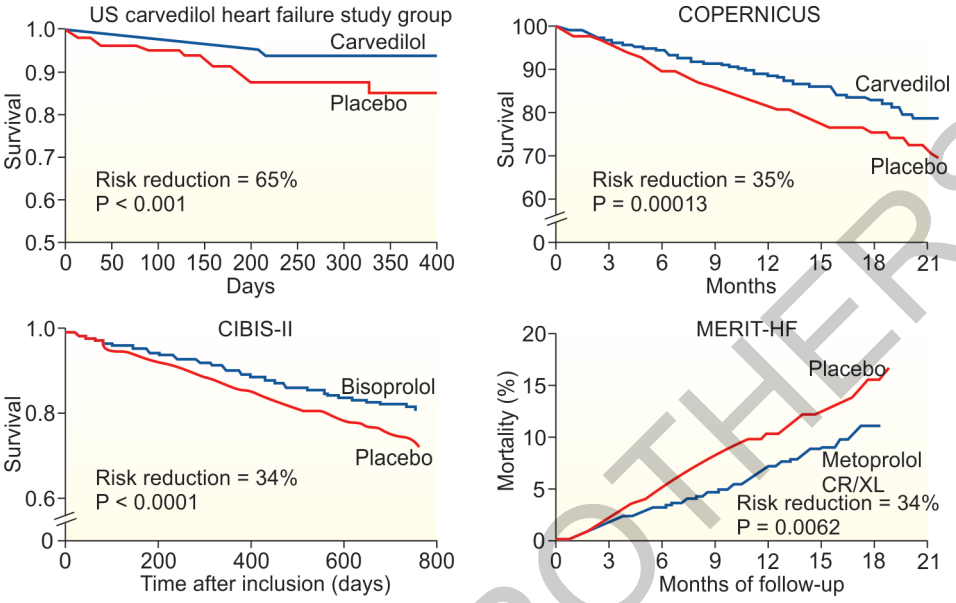

Figure 6: Results of RCTs demonstrating effects of selected beta blocker therapy in patients with HF secondary to LV systolic dysfunction. RCT, randomized controlled trials; HF, heart failure; LV, left ventricular; COPERNICUS, carvedilol prospective randomized cumulative survival study; CIBIS-II, cardiac insufficiency bisoprolol study II; MERIT-HF, metoprolol CR/XL randomized intervention trial in congestive heart failure.

Source: Based on data adapted from references 11-14.

progression, and survival, treatment with beta blockers should be initiated as soon as evidence of LV dysfunction is detected regardless of the lack and/or severity of symptoms. Treatment with beta blocker should be continued and optimized to reduce the risk of progressive LV dysfunction, further clinical deterioration, and prevent the risk of sudden cardiac death. The benefits of beta blocker therapy are evident even when the patient is not taking high doses of ACEIs. As a matter of fact when both drugs cannot be used in maximal doses the use of beta blocker has been shown to produce greater improvement in symptoms and reduction in risk of death in patients who are taking low dose ACEI. Therefore, it seems prudent to optimize the dosage of beta blockers rather than maximizing the dose of ACEIs especially in patients who develop symptomatic hypotension with higher doses of both classes of drugs.

Helpful Hints Regarding Use of Beta Blockers in Heart Failure

Beta blocker therapy should only be initiated when patient is stable and it is best to delay starting beta blockers during decompensated state. Recent data show that beta blocker therapy can be started safely before discharge even in patients

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hospitalized with HF who did not require intravenous therapy for HF. Treatment with a beta blocker should be initiated at very low dose (Table 2). If a lower dose has been well tolerated then dose should be increased gradually, usually doubling the dose at 2 weeks intervals. Careful monitoring of heart rate, blood pressure, and HF symptoms is needed during the initial period as well as during the entire up titration phase. All patients with current evidence or prior history of fluid retention should be on a diuretic before starting beta blocker therapy because diuretics are often needed to maintain sodium and fluid balance and prevent excessive fluid retention. Initiation of treatment with beta blocker can cause fluid retention, and lead to decompensated HF. Because of this, patients should be advised to weigh regularly on a daily basis and manage any weight increase by increasing the dose of diuretic to maintain the pretreatment weight. In presence of significant fluid retention, planned increment in the dose of beta blocker should be delayed until the patient's clinical condition has been stabilized. Utilizing such careful approach, most patients will tolerate the increase in dosing to the recommended target dosage.

The optimal dose of beta blocker is the target dose achieved in the clinical trial. The target dose in the RCTs was not based on the patients' therapeutic response but rather dependent on prespecified target dose. Lower doses were only used in these trials if the target dose could not be tolerated and most of these trials did not evaluate if lower dose would be as effective. Thus, clinician should make every effort to achieve the target dose of beta blocker shown to be effective in the clinical trials to ensure the maximal survival benefit. Once the target dose has been reached, most patients can continue long-term therapy without difficulty. It is important to educate the patient that the clinical response to beta blocker therapy is generally delayed and may require many months of treatment before improvement is noted. Even when symptoms do not improve, long-term therapy with beta blocker should be maintained to reduce the risk of cardiac and sudden death. Abrupt withdrawal of beta blocker therapy is to be avoided because it can lead to clinical deterioration and beta blocker withdrawal syndrome. Because long-term treatment with beta blocker reduces the risk of worsening HF, discontinuation of treatment with these drugs after an episode of decompensated HF will not diminish, and in fact might increase the subsequent risk of clinical decompensation. Therefore, even when patients develop fluid retention with or without worsening symptoms, it is advisable to continue beta blocker therapy and adjust the dose of diuretics. Only when the clinical deterioration is accompanied by hypoperfusion and/or requires use of intravenous inotropic agents, it may be necessary to decrease the dose or in rare cases hold beta blocker therapy temporarily until the clinical status is stabilized. Beta blocker should be reintroduced once patient is stable to reduce the risk of worsening HF and adverse clinical outcome.

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Safety and Adverse Experience

As discussed earlier, initial therapy with beta blocker can cause fluid retention in some patients. Such fluid retention is generally asymptomatic but can occasionally lead to worsening of HF symptoms. Patients with fluid retention prior to treatment are at higher risk of retaining fluid during treatment with beta blockers and thus the clinician should be certain that patients are euvolemic before initiating beta blocker therapy. As described above, any increase in weight or worsening signs and symptoms of HF should be quickly managed with increased dosage of diuretic. However, the occurrence of fluid retention or decompensation of HF is generally not a reason for permanent withdrawal of beta blocker treatment.

Treatment with beta blocker can be associated with general fatigue and tiredness, therefore, it is important to educate the patients about such side effects in advance and ask them not to discontinue beta blocker therapy. Patient should be reassured that fatigue is generally short lasting and resolves within a few weeks of initiation of beta blocker therapy. In some cases, the fatigue may be significant enough to limit further increase in dose and rarely may require a reduction if symptoms are severe. But treatment should not be discontinued unless there is evidence of hypoperfusion.

Bradycardia and slowing of AV nodal conduction is an expected effect of beta blockers. In most patients, bradycardia is asymptomatic and requires no treatments. However, if high grade (2nd or 3rd degree) AV block develops, the dose of beta blocker should be reduced and careful evaluation should be made regarding other conditions or agents that can cause bradycardia or heart block. In some cases where bradycardia or AV block persists and when significant, pacemaker placement should be considered to permit continued use of beta blocker therapy.

Although hypotension can occur with beta blocker therapy (especially with carvedilol due to its alpha blocking action), it is usually asymptomatic. When hypotension is associated with dizziness, lightheadedness, or blurred vision, it might be necessary to reduce the dose and/or change the beta blocker to a non-alpha blocking agent. The risk of hypotension can also be minimized by administering beta blockers and ACEIs/ARBs at different times of the day. If hypotension still persists, a decrease in the dose of ACEI/ARB might be necessary, and in some cases, the dose of diuretic might need to be reduced in patients who are volume depleted.

CLINICAL APPLICATION OF GUIDELINE-BASED THERAPY

Despite the overwhelming evidence of benefits with evidence-based therapy utilizing RAAS blocking drugs and beta blocking agents in patients with HF and LV systolic dysfunction, their application in clinical practice is less than ideal. The burden of HF is enormous and increasing across the world. Heart failure remains a leading cause of hospitalization in the United States. In addition, the patients with HF suffer from significant morbidity and mortality. All of these consequences of

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Table 3 **Relative benefits of various evidence-based drug therapies for heart failure**

Guideline-suggested therapy	*RRR (%) (RCT)*	*RRR (%) (meta-analyses)*
ACEI/ARB	17	20
Beta-Blocker	34	31
Aldosteone antagonist	30	25
Hydralazine/nitrate	43	NA

RRR, relative risk reduction; RCT, randomized clinical trials; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; NA, not applicable.

Source: *Adapted from* Fonarow GC, Yancy CW, Hernandez AF, et al. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. Am Heart J. 2011;161:1024-30.e3.

HF can be substantially reduced by adequate implementation of evidence-based guideline recommended therapy.[17] A recent analysis emphasized the degree of benefit in reducing mortality that can be achieved with the use of evidence-based therapy in patients with HF (Table 3).[18] This analysis emphasized that optimal implementation of evidence-based therapies with ACEIs/ARBs, beta blockers, aldosterone antagonists, and hydralazine-nitrate combination could potentially prevent as many as 47,500 deaths per year in the United States. These data clearly emphasize that considerable opportunity exists for implementation of evidence-based guideline recommended therapy in patient with HF due to LV systolic dysfunction to improve the associated adverse prognosis.

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