From Hypertension to Heart Failure: What Have We Learned?

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Summary: Hypertension is associated with an increased risk for heart failure, stroke, and end-stage renal disease. The mechanisms involved in progression from hypertension to heart failure have been the focus of many recent studies. In addition, we have learned much from epidemiologic studies that have helped identify risk factors for hypertension and have thus provided insight into mechanisms that are involved in the pathogenesis of this disease. This paper will consider the epidemiology of both hypertension and heart failure and their relationship with left ventricular hypertrophy. In addition, results of recent clinical trials of antihypertensive agents will be reviewed.

Introduction

Hypertension is a major risk factor for severe cardiovascular problems.1,2 Almost one quarter of the U.S. population, about 50 million people, have some degree of hypertension,1, 3, 4, 5 which can lead to left ventricular hypertrophy (LVH) and heart failure.6 More aggressive efforts to identify and treat early hypertension, increase awareness, and improve pharmacologic therapy have reduced strokes and other complications but have had little effect on the increasing prevalence of heart failure.4, 5

Hypertension

The criteria used to define hypertension vary and affect estimates of incidence and prevalence, tempering our understanding of the epidemiology of hypertension. According to the World Health Organization (WHO) definition (i.e., systolic pressures equal to or greater than 160 mmHg or diastolic pressure greater than 95 mmHg), more than half of Americans over 50 years old have hypertension. This figure includes people already taking medication.

Rates of hypertension-associated complications, including coronary artery disease, stroke, claudication, and heart failure, all increase with increasing systolic blood pressure. Over the years, the recommended blood pressure to initiate therapy has decreased as we have learned more about hypertension-related complications.7

Pathophysiology and Genetics

Hypertension is associated with hyperinsulinemia, obesity, and dyslipidemia.2, 8 Patients with hyperinsulinemia have a twofold incidence of hypertension independent of weight.9 In addition, vascular hypertrophy and arterial resistance increase as part of the normal aging process.2 Hypertension clusters with other known risk factors including smoking, glucose intolerance, and elevated lipid levels, all of which have been implicated in intimal thickening and worsening afterload.10 Elevated hematocrit and plasma renin and norepinephrine levels are also common in people with hypertension.2

Hypertension also has an undefined hereditary component. Family groupings underscore the genetic predisposition to essential hypertension. Genetically derived causes of secondary hypertension include Liddle’s disease, pheochromocytoma, renal artery stenosis, and rare glucocorticoid and mineralocorticoid abnormalities.11, 12 Although the genes that predispose individuals to essential hypertension have not been identified, experts suspect that hypertension has a polygenic origin. Potential genetic candidates, such as the genes for angiotensinogen, angiotensin-converting enzyme (ACE), nitric oxide, and
endothelin, have shown promise but have been relatively unrevealing to date.\textsuperscript{11, 12} Perhaps in the near future, when the entire human genome has been sequenced, and with better ability to screen large populations, basic science will reveal the genetic basis of hypertension, which should facilitate the development of gene therapy.

**Hypertension Risk Factors**

Elevated blood pressure is the most common risk factor for cardiovascular and renal disease in the United States.\textsuperscript{6} Further, it is one of the most common factors for mortality worldwide.\textsuperscript{2} Even people with blood pressures in the high/normal range have an increased risk of heart disease and other related problems.\textsuperscript{13, 5}

The prevalence of hypertension increases in a predictable and linear manner from the third decade of life onward, such that the majority of elderly individuals have hypertension. Framingham statistics demonstrate that elderly patients experience mainly systolic hypertension; about 57\% of men and 65\% of women between the ages of 65 and 89 years old have isolated systolic hypertension (Fig. 1). Approximately 30\% have combined systolic and diastolic hypertension.\textsuperscript{1, 4, 5}

There is a substantial difference in the incidence of hypertension between the sexes. Younger women are less likely to have hypertension than age-matched men. With progressive aging, however, the prevalence of hypertension in women eventually matches and ultimately exceeds that of men.\textsuperscript{3, 14} These differences may be partly understood in light of the excess mortality of men at younger ages.\textsuperscript{5}

**Gender**

There are also significant differences in the type of hypertension experienced by men and women (Fig. 1). Men are more likely to have isolated diastolic hypertension (12.4\% versus 7.1\%), and women tend to have isolated systolic hypertension (65.2\% versus 57.3\%). The rates of combined systolic and diastolic hypertension, however, are nearly equivalent at 30.3\% for men and 27.7\% for women.\textsuperscript{6} These differences may be partly explained by the misconception that systolic hypertension poses no significant cardiovascular threat, leaving women less likely to receive treatment for hypertension.\textsuperscript{6, 14} This belief was altered by the Systolic Hypertension in the Elderly Program (SHEP) trial, which demonstrated the cardiovascular benefit of even a minor decrease (e.g., 12 mmHg) in isolated systolic hypertension. In that study, stepped-care treatment with low-dose diuretics and a beta blocker resulted in a substantial reduction in the risk for stroke (relative risk 0.63), myocardial infarction, and the development of heart failure.\textsuperscript{15}

**Race**

Racial differences also occur in hypertension. African Americans experience a substantially higher prevalence of hypertension, particularly with advancing age, compared with whites. Nearly three-quarters of African Americans over the age of 60 years have hypertension. In some studies, Hispanic populations also show a slightly increased prevalence compared with age- and gender-matched whites.\textsuperscript{5, 16} In other ethnic minorities, particularly certain Japanese and Filipino groups, the prevalence of hypertension is comparable to that in African Americans.\textsuperscript{16} All races, however, show a profound progression of hypertension with age.

**Trends in the Prevalence, Awareness, and Treatment of Hypertension**

According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of hypertension has decreased steadily over the past three decades.\textsuperscript{4, 5} In adults, the age-adjusted prevalence of hypertension (defined as 160/95 mmHg or above) declined from 20 to 14\% from the early 1970s to the late 1980s.\textsuperscript{4} At lower blood pressure levels (140/90 mmHg or below), the prevalence decreased more substantially from 36 to 20\%.\textsuperscript{4} This decline is likely attributable to improved screening and intervention. According to NHANES, from 1988 to 1991, more than half of people with hypertension were receiving antihypertensive medication and were controlled. Slightly less than 20\% were receiving medication but were uncontrolled, and approximately 10\% had uncontrolled hypertension and were not receiving medication. In addition, fewer than 20\% of patients have hypertension of which they remain unaware.\textsuperscript{4}

Women generally demonstrate greater tendency to be aware of their hypertension and are more likely to receive treatment than their male counterparts. They also tend to achieve blood pressure control on pharmacologic regimens more successfully than men.\textsuperscript{4, 5} Women face special risks from hypertension. Women predominate in cases of fibromuscular dysplasia, which, in turn, produces renal artery stenosis. Birth control pills with more progestins may increase blood pressure, and loss of estrogen at menopause has been shown to affect modulation of angiotensin negatively. Finally, an apparent association exists between women with a family history of hypertension and a salt-sensitive variety of hypertension.\textsuperscript{14}
Treatment

The standard recommendation from the Joint National Commission (JNC) on hypertension has been diuretics and beta blockers as first-line treatment.\textsuperscript{17} Thiazide diuretics, in particular, may be especially appropriate for women, as decreased excretion of calcium may provide some protection from osteoporosis.\textsuperscript{14} Thiazide diuretics are also especially effective in salt-sensitive hypertension and in African Americans.

Recent observations showed that about 47\% of patients with newly diagnosed hypertension were started on diuretics, whereas only about 8\% initially took beta blockers. Of the remainder, approximately 24\% were started on ACE inhibitors, almost 28\% first took calcium channel blockers, and 10\% were started on vasodilators. These numbers include patients started on more than one drug. Market pressures and physician discretion (giving consideration to patient tolerance, compliance, cost, and comorbid conditions) no doubt are partly responsible for these prescribing practices. Furthermore, some investigators suggest that moderate weight loss alone might obviate the need for antihypertensives in up to 50\% of cases.\textsuperscript{8}

Treatment Outcomes

Most large-scale studies of hypertension have been performed with beta blockers, diuretics, or both.\textsuperscript{15, 17} In a meta-analysis of long-term studies that assessed major disease endpoints as an outcome, these agents were shown to reduce the risk of hypertension-related disorders such as stroke and heart failure (Fig. 2).\textsuperscript{18} A variety of other medications are available, some of which have proved efficacious in preventing morbidity associated with hypertension. Among the antihypertensives, a probable link to increased mortality has been demonstrated with short-acting calcium channel blockers, whereas sustained-release preparations do not appear to have this property and appear to be beneficial.\textsuperscript{19, 20} More long-term studies with newer agents are needed.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH), the disproportionate overgrowth of muscle in the left ventricle, has historically been considered the natural evolution of hypertension.\textsuperscript{6} Assessing this abnormality, however, has been hindered by the wide variation in left ventricular mass among normal subjects.\textsuperscript{10} Other factors related to LVH include obesity and aging.\textsuperscript{8} As a general rule, left ventricular mass is disproportionately higher in men than women and in African Americans than whites.\textsuperscript{10} LVH associated with progressively increasing afterload may produce a vicious cycle that perpetuates the increase of left ventricle mass, even to the point of cardiac failure.\textsuperscript{10}

Left ventricular hypertrophy is usually determined by electrocardiography (ECG), but the ECG criteria have been found to be less sensitive than the echocardiogram, which is now being used more frequently.\textsuperscript{21, 22} In older studies, approximately 30\% of patients with hypertension were thought to have LVH.
but it is now estimated that the proportion of patients suspected of having ventricular abnormalities is much higher.22–26 Moreover, it is estimated that structural remodeling of the ventricular, brought on by hypertension, develops in about 70% of persons with sustained hypertension.25, 26

Pathophysiology of Left Ventricular Hypertrophy

Patients with mild hypertension have two to three times the risk of LVH, whereas those with severe hypertension have a tenfold increased risk.27 Some type of hypertrophy of the left ventricle occurs in the majority of hypertensive patients. The mechanism probably involves the relationship among peripheral resistance, the pulsatile nature of blood flow, and neurohormonal activation. Within cardiac muscle, fractional shortening may be reduced, and left ventricle dilatation may occur. Connective tissue abnormalities clearly play a role in the evolution and pathology of LVH, as hypertrophic cardiac muscle contains excess collagen and increased fibrosis. In arteries, intimal and medial thickening produce higher resistance. These vascular changes may be promoted by smoking, hyperlipidemia, glucose intolerance, and normal aging.6, 10, 28

Undoubtedly, genetic predisposition also plays a role in LVH, especially in youth.29 Contractile proteins in the myosarcomere have demonstrated genetic heterogeneity. The search for genetic causes of LVH holds some promise.10, 28, 29 The natriuretic peptides (atrial, B-type and C-type) have roles in myocyte response and function that remain to be fully elucidated.30

As in hypertension, the renin angiotensin system almost certainly plays a role in LVH, but studies of the ACE gene have resulted in equivocal findings.10, 12, 31 Hypertrophy of the arterial media and resultant stiffness and resistance may also be governed, in part, by angiotensin II.10, 31 This implies that reversal of LVH with ACE inhibitors may be partly due to effects on the arterial walls. Complete exploration of the effects of genetics in LVH will clearly be part of the coming millennium of research and may offer additional intervention in LVH.

After LVH develops, the progression to more severe heart disease begins and, with it, a greater likelihood of heart failure.6, 10, 28 This occurs, in part, secondary to the increased oxygen demand in the thicker myocardium.6, 10, 28 The Framingham Study found a twofold to fivefold increase in the occurrence of myocardial infarction in patients with LVH, partly using criteria based on ECG findings.28 Along with the ischemic risks, hypertrophy carries a physiologic downside; as a result of excess cardiac muscle mass, ventricular filling and ejection fraction are decreased.24

Diagnosis of Left Ventricular Hypertrophy and Correlation With Hypertension

Identification of LVH in the clinical setting has been hampered to a degree by excessive reliance on ECG, which has a sensitivity as low as 50%. Fortunately, specificity is substantially higher, at approximately 90%.21, 22, 32 Even among African Americans, in whom LVH presents more commonly, the ECG has been shown to lack sensitivity.21 Thus, echocardiography now figures more prominently in the evaluation of LVH.

To some degree, the occurrence of cardiac dysfunction relates to the progression of hypertrophy. In one echocardiographic analysis of hypertensive patients, concentric remodeling was observed in 13% of patients; classic concentric hypertrophy was encountered in only 8%, with most patients displaying eccentric hypertrophy (27%).23 The remaining 52% of patients did not have any form of LVH. Significantly higher blood pressures appeared to be associated more with the classic concentric LVH than other types of LVH.

In addition to its correlation with hypertension, left ventricular mass is associated with overall body weight and height. Increased subscapular skin-fold thickness is also predictive of an enlarged left ventricle.33 Other than hypertension, the main factors that affect the left ventricular mass are age—presumably related to the duration of hypertension—and obesity.25

Left ventricular hypertrophy has been found in association with isolated systolic hypertension in men and women over 50 years of age.34, 25 One study found that 31% of men with isolated systolic hypertension had LVH, whereas only 12% of the normotensive group had LVH. In women, this difference was more pronounced. Fifty-seven percent of those with isolated systolic hypertension had LVH, and only 17% of the normotensive cohort exhibited LVH.35 These statistics may underestimate the prevalence of LVH; the work of Laufer and coworkers, through multivariate analysis, estimates the prevalence of LVH in the patients with sustained hypertension at 65 to 70%.26

In a study by Krumholz and associates of LVH in isolated systolic hypertension, the relative risk of LVH was 2.58 in men and 5.94 in women.34 This study also noted a difference between male and female subjects in the morphology of LVH. Women tended to develop concentric LVH, and men tended to develop an eccentric pattern of LVH. Other work has demonstrated a greater likelihood of concentric remodeling at higher blood pressures.23

Multiple studies show predictable progression of hypertrophy as systolic blood pressure increases.34, 33 The considerable effect of race on hypertension may contribute to a disparity in the rates of LVH. The Coronary Artery Risk Development in Young Adults (CARDIA) study demonstrated a statistically significant larger left ventricular mass in black men compared with white men and black women compared with white women.10, 33

Left ventricular hypertrophy facilitates the development of coronary artery disease. Many familiar factors play a role in this complication. The factors include compressive forces of myocardium on vessels, abnormalities that develop in endothelial excretion of stabilizing factor, and changes in the arterial media. The hypertrophied muscle exhibits increased myocardial oxygen consumption and demand, and mechanoceptors in the hypertrophied muscles may fail.36

For African Americans, the presence of LVH constitutes a stronger risk factor for coronary artery disease morbidity and mortality than any other risk factor.37 In other Framingham work by Levy and associates, patients underwent evaluation
for LVH with echocardiography. Relative risk of mortality for men with cardiovascular disease increased by 1.49 for each 50 gram/meter (related to height) increase in left ventricular mass. In women, the excess relative risk was even more pronounced, at 1.57.

Not surprisingly, in the same study, the increased incidence of cardiovascular death produced a relative risk of 1.73 in men and 2.12 in women. Death from all causes was similarly elevated with a relative risk of 1.49 for men and 2.01 for women, probably reflecting the fact that LVH may serve as a marker for other systemic disease, particularly hypertension and obesity. In the African American population, the presence of LVH produced a relative risk of 2.2 for cardiac death. The impact of LVH was stronger in African American women, and the relative risk of death was 3.2 compared with only 1.9 for men, regardless of whether coronary artery disease was present. In this population, beta blockers reduced this risk of death by one half. Of note, excess mortality may be anticipated simply from the increased incidence of serious dysrhythmias in patients with LVH, including ventricular tachycardia in up to 28% of patients.

**Treatment Options**

In light of the importance of LVH in cardiovascular physiology and patient prognosis, much consideration has been given to the use of therapies to reverse the process. Most antihypertensive medications have at least some beneficial effect in reducing left ventricular mass. Angiotensin-converting enzyme inhibitors have gained some prominence as the most potent drugs for reversal of LVH. Verapamil has also been associated with reduction of left ventricular mass and improved diastolic filling. Beta blockers and ACE inhibitors can be expected to prove cost effective in reducing LVH and concomitant risk, even if they had only about 30% of their expected impact on LVH and its associated poor outcomes.

In summary, LVH should be viewed as a step toward and harbinger of severe cardiac risk. It results in a 12-year mortality of greater than 50% after becoming apparent on ECG, and increases the risk for heart failure by 10 times.

**Heart Failure**

Heart failure comprises a physiologic state whereby the heart fails to pump sufficient blood to meet the oxygen requirements of the body. When this occurs, compensatory responses, aimed at maintaining tissue perfusion, increase peripheral resistance and heart rate. These reactions are regulated mainly by the renin angiotensin system and sympathetic outflow, as well as by some of the neurohormonal responses delineated in the discussion of LVH. In the long term, however, both of these responses strain the heart further, leading to decompensation.

Recent work from Framingham demonstrated hypertension to be the most common and one of the strongest risk factors for heart failure (Fig. 3). Stage 2 hypertension doubles their risk for heart failure in patients between 60 and 70 years old compared with normotensive aged-matched subjects. Factors as simple as increased heart rate also have been associated with an increased risk of heart failure. Heart failure can generally be defined clinically (Table I) and may be defined further with echocardiography. This discussion will ignore alcoholic and idiopathic cardiomyopathies, myocarditis, high-output failure, arrhythmias, and valvular abnormalities that contribute to heart failure, as they generally do not fall in the spectrum of the hypertension—LVH—heart failure progression.

**Pathogenesis of Heart Failure**

Although the entire pathway from hypertension to heart failure has not been clearly delineated, many factors—genetic, physiologic, and pathologic—contribute to its development. Specific consideration of myocyte neurohormonal modulation from extrinsic factors such as beta-

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**TABLE I Clinical signs and symptoms as diagnostic criteria for heart failure**

<table>
<thead>
<tr>
<th>Major criteria</th>
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<tr>
<td>Paroxysmal nocturnal dyspnea (PND)</td>
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<tr>
<td>Neck vein distention (JVD)</td>
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<tr>
<td>Acute pulmonary edema</td>
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<tr>
<td>Central venous pressure (CVP) &gt;16 cm H&lt;sub&gt;2&lt;/sub&gt;O</td>
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<tr>
<td>Hepatogjugular reflux (HJR)</td>
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<tr>
<td>Weight loss of more than 10 lb with therapy</td>
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<tr>
<td>Third heart sound (S3)</td>
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<table>
<thead>
<tr>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Bilateral ankle edema</td>
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<tr>
<td>Nocturnal dyspnea</td>
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<tr>
<td>Hepatomegaly</td>
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<tr>
<td>Pleural effusion</td>
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<tr>
<td>Decreased vital capacity (FVC)</td>
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<tr>
<td>Heart rate (100 bpm)</td>
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*Two major or one major and two minor criteria to make diagnosis.*
adrenergic signaling and transduction, R-G-adenylate cyclase pathways, and R-G-phospholipase C pathways predominate in our current understanding of biochemical aspects of the failing heart. 10, 28, 29, 44

Structural changes in the cytoskeleton, contractile proteins, and other bioenergetics are incorporated into the model of overall myocyte dysfunction. Extra strain may be placed on remaining myocytes when, perhaps by apoptotic mechanisms, replacement fibrosis occurs in the myocardium. 10, 25 Proteins involved in regulating calcium are also likely under genetic control changing in genetic activation in heart failure. ATP requirements may not be met in older myocardial cells, resulting in insufficient energy to meet the cardiac cycle needs. 10 In addition to these alterations, activation of the the renin angiotensin system results in long-term cardiac growth, remodeling, and hypertrophy. 28, 31 Aldosterone also acts as a putative agent of hypertrophic remodeling. 46 Norepinephrine and pressure-responsive atrial natriuretic peptide were found to increase progressively with heart failure in both Cooperative North Scandanavian Enalapril Survival Study (CONSENSUS) and Studies of Left Ventricular Dysfunction (SOLVD). 47–49

Prevalence of Heart Failure

Unlike other cardiovascular complications of hypertension, such as stroke, the incidence of heart failure has been increasing. It affects nearly 3 million Americans; 400,000 people develop heart failure annually. 50 More than 75% of patients with heart failure are over 65 years old. Annual incidence is 0.3% for men ages 50 to 59 years, but 2.7% for ages 80 to 89 years. For women, the comparable numbers are 0.2 and 2.2%. 51 Prevalence rises with aging. For women, an age-related prevalence, perhaps surprisingly, proves quite high, as the incidence in younger women equals that of young men, but older women experience higher rates (7.9%) than older men (6.6%). 51

It must be recognized that much of the excess heart failure encountered results from improved patient survival despite significant compromise of myocardium after acute myocardial infarction. With the epidemic of atherosclerotic heart disease and coronary artery disease, one would expect that the incidence of heart failure will increase with age. Almost 2% of adults over 65 have heart failure and new cases in patients over 75 years old occur with an incidence of about 2% annually. 1, 6, 50 In the near future, we can anticipate almost 500,000 new cases annually in the United States, and most will arise among the aging population. 51

This rising prevalence, along with more effective anti-hypertensive medications that prolong survival, has made heart failure the most commonly listed diagnosis at hospital discharge for Medicare patients. In 1993, 875,000 hospitalizations occurred for heart failure, and costs for treating this disease approached $10 billion. Individual costs for advanced heart failure average $20,000 per year. 52, 47 Reduced quality of life, missed work, and impact on family members inevitably add to unmeasured costs of the disease.

In addition to its costs, both direct and indirect, heart failure is associated with a very low survival rate; 1-year survival is 57% for men and 64% for women. 51 5-year survival is only 25% for men and 38% for women (Table II). 51 The median survival after diagnosis of heart failure is 1.37 years for men and 2.48 years for women. Given this, 69% of women and 76% of men will not survive 5 years after diagnosis, a statistic that compares poorly with cancer. 45, 53 These survival statistics, derived from Framingham data, did not change substantially between the 1940s and late 1980s.

Racial and gender differences are also apparent in heart failure mortality. African Americans experience a 40% greater mortality rate from heart failure compared with whites. Women experience certain advantages, perhaps arising from their prolonged estrogenic state along with better medical compliance; the mortality rate from heart failure is 25% higher in men compared with women. 53

Hypertension increases the risk for LVH, which in turn increases the risk for coronary heart disease and myocardial infarction. Microvascular compromise may impair myocardial perfusion, particularly in high-demand conditions. 28 According to Levy and associates, hypertension as a risk for heart failure incurs hazard ratios of 1.84 for men and 2.60 for women, even after adjusting for other risk factors. 35 Damage from myocardial infarctions may lead to regional wall motion deficits with compromised ejection fraction. 28 In the Framingham data, this risk (myocardial infarction) was particularly high in both sexes, even when adjusted for age and other risk factors (Fig. 4). 45

Vascular stiffness, associated with increasing age and related to medial and adventitial thickening, contributes to the development of LVH by increasing afterload. In the Framingham study, LVH was associated with a heart failure hazard ratio of 1.97 for men and 2.80 for women. 46 Other “noncardiac” considerations—such as reduced glomerular filtration, lung or breathing disorders, and electrolyte abnormalities—also may contribute to heart failure.

Even in the absence of hypertension, cardiac muscle itself stiffens with aging, owing to hypertrophy, myocyte loss, delayed relaxation, and calcium-uptake abnormalities. Myocyte stretch becomes compromised, and the Frank-Starling mechanism may become limited. 19 Myocardial fibrosis may play a

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**Table II** Five-year mortality for cardiac failure according to underlying pathology: Framingham Study

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<tr>
<th>Disorder</th>
<th>5-year mortality (%)</th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>CAD</td>
<td>73</td>
<td>65</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>89</td>
<td>66</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68</td>
<td>55</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>90</td>
<td>48</td>
</tr>
<tr>
<td>Overall</td>
<td>75</td>
<td>62</td>
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particularly important role in the excess risk of diabetics for developing heart failure, even when adjusted for other factors. Levy and associates reported a heart-failure hazard ratio in hypertensive diabetics of 1.78 for men and 3.57 for women.45

**Diastolic Dysfunction**

Normal or supranormal left ventricular systolic function is present in up to 40% of patients with heart failure.28, 54 Diastolic dysfunction constitutes a high percentage of heart failure in the population, underlining the need for accurate identification of the cause of heart failure. Diastolic dysfunction results primarily from LVH, which decreases ventricular compliance.28 In diastolic dysfunction, slowing heart rate and regressing left ventricular size require primary consideration.41, 55

Diastolic dysfunction is observed less frequently in patients younger than 65 years old with heart failure, occurring in approximately 6% of men and 12% of women; however, it becomes substantially more prevalent in those over the age of 65 years (approximately 34% for men and 30% for women).16 Diastolic dysfunction occurs approximately 6 years later in life than typical systolic dysfunction. Annual mortality for diastolic dysfunction remains significantly lower than in systolic heart failure, at about 10%, except when valvular disease is the underlying disease.16

The presence of coronary artery disease reduces the likelihood of diastolic dysfunction because many of these patients have wall-motion abnormalities and compromised ejection fractions.54 Therapy with rate-altering agents, such as beta blockers, may provide more filling time and more potential relaxation of myomeric units.54 In this instance, calcium channel blockers may be appropriate for heart failure.54 Reduction of LVH can be reasonably pursued in diastolic dysfunction with ACE inhibitors as well.41 Definitive studies to determine the best medical therapy for the entity remain in the future.  

Recent studies have examined intervention in the burgeoning and devastating problem of systolic heart failure. Substantial risk reduction for heart failure was encountered incidentally in the SHEP studies, and the overall relative risk of left ventricle failure was 0.46 in the treatment group.15 The primary medication was a diuretic; patients who did not meet the blood pressure goal with one medication received a beta blocker.15 The CONSENSUS trial demonstrated a 40% reduction in mortality among patients with heart failure using enalapril, but sudden cardiac death was not lowered by therapy.48

The SOLVD trial studied the effects of enalapril on mortality and hospitalization among patients with chronic heart failure. As in CONSENSUS, patients experienced less progression of heart failure, fewer patients were hospitalized or died, but arrhythmias were not reduced.56 Quality of life was improved modestly in the active therapy group.57 Echocardiographic evaluation of SOLVD participants showed that left ventricle dilatation and hypertrophy were reduced in those receiving enalapril.40, 58 Finally, in the postmyocardial infarction setting, the Survival and Ventricular Enlargement (SAVE) trial demonstrated that, in the presence of left-ventricular dysfunction, captopril could limit morbidity and mortality.59 These results, probably attributable to the ability of captopril to reduce afterload and its beneficial effects on ventricular remodeling, changed the management of myocardial infarction in many patients.

Digoxin, long a mainstay of heart failure therapy, has come under closer scrutiny in recent years, and, in general, the use of...
digoxin in moderate doses is still widely practiced. In the Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) trial, patients withdrawn from digoxin therapy showed near universal worsening of their disease. This decompensation was characterized by worse exercise capacity and increased treatment failures, among other parameters.60 The Randomized Assessment of the effect of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) trial looked at the same question among patients already receiving ACE inhibitors. Those withdrawn from digoxin suffered more treatment failure as well as higher heart rates and worse ejection fractions.61

Beta blockers have been used successfully for many years in the treatment of heart failure but have only now started to receive wider acceptance.62, 63 Carvedilol and metoprolol are the most commonly prescribed and best-documented agents at this time.62 In the Metoprolol in Dilated Cardiomyopathy study, considerably fewer patients progressed to heart transplant, and wedge pressure decreased compared with placebo.60 The recently concluded CIBIS trial used the beta blocker bisoprolol and also demonstrated improved functional benefit in patients with heart failure.64

Although diuretics remain a mainstay of treatment for heart failure, they serve a very limited role in reducing morbidity or mortality of heart failure, except in obviating acute failure. As emphasized in a recent review by Brater, these medications may be used in a stepwise manner, progressive from thiazides to loop diuretics, and ultimately adding acetazolamide for synergistic effect with the loop diuretic.

Nitrates and hydralazine may be substituted in patients who cannot tolerate ACE inhibitors. Medication aimed at reducing thrombotic events also plays a role in the treatment of a dyskinetic heart. Either aspirin, other platelet inhibitors, or coumadin may be required, depending on the degree of failure.65

Conclusion

The spectrum of hypertension, LVH, and heart failure represent an underdiagnosed and undertreated problems. Too few patients have their blood pressure under good control, and too many progress to heart failure. Given what we know, the need for echocardiography to assess the degree of hypertrophy in hypertensives over the age of 65 should be considered. Combined regimens, considering agents with different modes of action, may act optimally in patients with moderate to severe hypertension. Certainly the prominence of angiotensin in the pathophysiology of all the entities considered here lends credence to the consideration of ACE inhibitors as first-line therapy in hypertension. Practitioners also need to realize that hypertension is typically accompanied by other CVD risk factors, especially dyslipidemia and hyperglycemia, and that optimal care of these other factors will affect vascular disease incidence. Finally, the metabolic and genetic underpinnings of hypertension require further research, and the importance of improved therapy for hypertension and cardiac failure needs to be stressed.

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Prevention of Sudden Cardiac Death with Beta Blockers

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Summary: Beta blockers have been shown to reduce the risk of sudden cardiac death in more than 50 randomized trials involving more than 55,000 patients. Relative reductions (vs. placebo) in cardiac death in some of these trials ranged from 30 to 50%. These reductions are substantially greater than trials of other drug classes including angiotensin-converting enzyme inhibitors. However, not all beta blockers confer equal benefit to patients at risk of sudden cardiac death. Results from various trials suggest that lipophilic beta blockers—such as timolol, metoprolol, propranolol, bisoprolol, and carvedilol—may be more beneficial than hydrophilic beta blockers. Results of animal studies have indicated that sudden cardiac death is mediated, at least in part, by the central nervous system, which may account for why lipophilic agents have more pronounced clinical effects.

Based on the results of numerous clinical and mechanistic studies, it is suggested that beta blockers should be given to all patients at risk for sudden cardiac death, including those patients with previous myocardial infarction, hypertension, or congestive heart failure.

Key words: beta blockers, sudden cardiac death, trials

Introduction

It is known that about half of all deaths among patients with ischemic heart disease is due to sudden cardiac death. Sudden cardiac death is responsible for about 300,000–400,000 deaths each year in the US. In the majority of cases, the cause of sudden death is thought to be ventricular fibrillation shortly after onset of acute ischemia. In some patients ventricular fibrillation occurs without any prior symptoms. To reduce the incidence of sudden cardiac death, patients at risk of developing sudden cardiac death should be identified; therapies with proven effects on sudden cardiac death have to be identified; and such therapies ought to be given to all patients at risk, considering contraindications and side effects.

During the past two decades, several treatments have been found to reduce mortality in patients with ischemic heart disease, including coronary artery revascularization and administration of beta blockers, aspirin, thrombolytic agents, and angiotensin-converting enzyme (ACE) inhibitors. In selected groups of patients, these therapies have been found to reduce total mortality significantly. On the other hand, other groups of drugs, including antiarrhythmic agents, calcium antagonists, and nitrates, have failed to reduce mortality in patients with ischemic heart disease. Only one group of drugs, beta blockers, has been found to have an even more marked effect on sudden cardiac death than on other modes of death.

Myocardial Infarction

In 1981, three placebo-controlled trials, the Norwegian Timolol,3 the Beta-Blocker Heart Attack Trial (BHAT),4 and the Göteborg Metoprolol5 trials, were published. They showed for the first time that medical treatment started after onset of myocardial infarction reduced total mortality. The two studies on timolol and propranolol were started 1–2 weeks after onset of acute myocardial infarction with a follow-up time of about 2 years. Total mortality was reduced by 36 and 26%, respectively. In the Metoprolol Trial, the beta blocker was given to patients with suspected acute myocardial infarction shortly after arrival in hospital with 3 months follow-up, and mortality was reduced by 36%. A large number of other small studies has been published, and there are 24 long-term trials today that have included about 25,000 patients. The average reduction in mortality was about 20% over about 2 years of follow-up (Table I).

Two even larger trials, Metoprolol in Acute Myocardial Infarction (MIAMI)6 and First International Study of Infarct Survival (ISIS-1),7 including about 6,000 and 16,000 patients, respectively, assessed the possibility of reducing mortality within 1–2 weeks of myocardial infarction when beta blockers metoprolol and atenolol were administered within the first 24 hours of the incident. The ISIS-1 Trial reduced cardiovascular mortality by 14% after 7 days and the MIAMI Trial showed a 13% nonsignificant difference of 15 days total
Pool all early intervention trials starting with intravenous administration of a beta blocker, there are 28 trials including more than 27,000 patients. The pooled data showed a significant 13% reduction in total mortality (Table I).

In 16 of the postinfarction trials, sudden cardiac death—mostly deaths within 1–24 h after onset of symptoms—has been reported (Tables I, II). In the BHA T Trial, death occurring within 1 h after onset of symptoms was reduced by 28%, while in the trials on timolol and metoprolol sudden death defined as death within 24 h after onset of symptoms was reduced by 40–50% (Table II). It is of interest to note that the Sotalol Trial from the United Kingdom showed no effect at all on sudden cardiac death despite the fact that the study was large enough to demonstrate a significant reduction in reinfarction rate and had a favorable trend toward total mortality (14%). Sotalol is the only beta blocker which, in a larger study, has not shown a favorable effect on sudden death that has not been more marked than the effect on total mortality. In the two large trials, ISIS-1 and MIAMI, there were no reports on sudden cardiac death defined as death within 1–24 h after onset of symptoms. Both studies, however, reported a major effect on early cardiac rupture within 24 h, which could also be a cause of sudden cardiac death, especially during the short-term follow-up after acute myocardial infarction.

The cause of death is thought to be due to ventricular fibrillation in the majority of patients. Animal studies on experimental infarction have clearly demonstrated that some beta blockers can prevent ventricular fibrillation following coronary artery ligation. In two clinical studies, beta blockers have been found to reduce the incidence of ventricular fibrillation in patients suffering an acute myocardial infarction. These studies were the Göteborg Metoprolol Trial and a study on propranolol from New Zealand. In these trials, beta blockers

<table>
<thead>
<tr>
<th>No. of deaths/patients</th>
<th>Control</th>
<th>Beta blocker</th>
<th>Reduction (%)</th>
<th>p Value</th>
</tr>
</thead>
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<tr>
<td>Total mortality</td>
<td></td>
<td></td>
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<tr>
<td>All long-term studies (n = 24)</td>
<td>1,199/12,431</td>
<td>1,027/13,815</td>
<td>20</td>
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<td>All short-term studies (n = 28)</td>
<td>586/13,721</td>
<td>513/13,815</td>
<td>13</td>
<td>&lt;0.02</td>
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<tr>
<td>Sudden deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All studies (n = 16)</td>
<td>480/9,441</td>
<td>333/9,887</td>
<td>34</td>
<td>&lt;0.001</td>
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*Two-year follow-up.

<table>
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<th>Reduction (%)</th>
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<tr>
<td>Norwegian Multicenter Study (timolol)</td>
<td>95/939</td>
<td>47/945</td>
<td>51</td>
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<tr>
<td>BHAT (propranolol)</td>
<td>89/1,921</td>
<td>64/1,916</td>
<td>28</td>
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<tr>
<td>All metoprolol (5 studies)</td>
<td>104/2,721</td>
<td>62/2,753</td>
<td>41</td>
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<tr>
<td>APSI (acebutolol)</td>
<td>9/309</td>
<td>6/298</td>
<td>30</td>
</tr>
<tr>
<td>United Kingdom (sotalol)</td>
<td>27/583</td>
<td>41/873</td>
<td>−7</td>
</tr>
<tr>
<td>All other (7 studies)</td>
<td>156/2,968</td>
<td>113/3,102</td>
<td>30</td>
</tr>
</tbody>
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Abbreviations: APSI = Acebutolol Prévention Secondaire de l’Infarctus; BHAT = Beta Blocker Heart Attack Trial.

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![Fig. 1](image) Cumulative number of sudden cardiac death from pooled results of five double-blind placebo-controlled postinfarction trials. Solid line shows sudden death in the placebo group (n = 2,721) and the dotted line sudden death in the metoprolol group (n = 2,753). The effect was highly significant (p = 0.002).
reduced ventricular fibrillation markedly by prophylactic use of metoprolol (Fig. 2) and propranolol.

**Primary Prevention**

The Framingham heart study demonstrated that hypertension is a highly significant risk factor for development of coronary artery disease and sudden cardiac death. The impact of treating hypertension has been assessed in many prospective clinical trials, and diuretics and beta blockers have been found to reduce morbidity and mortality. The most marked effect has been found on prevention of cerebrovascular events. Effects of ACE inhibitors, calcium antagonists, and alpha blockers have not yet convincingly demonstrated effects on mortality and morbidity. The only study that has demonstrated a significant effect on sudden cardiac death in patients with hypertension is the Metoprolol Atherosclerosis Prevention in Hypertension Trial (MAPHY). In this study, with a mean 5-year follow-up of middle-aged men with hypertension, metoprolol was found to reduce total mortality more markedly than did thiazide diuretics. There was a marked difference in the incidence of sudden cardiac death between patients treated with metoprolol and diuretics (Fig. 3). Subgroup analyses from other studies on hypertension have also shown favorable effects of beta blockers on sudden cardiac death. Besides the beta blockers, none of the other agents used for the treatment of hypertension have been found to reduce sudden cardiac death.

**Congestive Heart Failure**

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) was the first to show that the ACE inhibitor enalapril reduced total mortality in patients with severe congestive heart failure. The major effect was due to a prevention of progressive heart failure causing death, while there was no effect on sudden cardiac death. Similar effects with a reduction of total mortality and less clear effects on sudden cardiac death were also found in other placebo-controlled trials including the Studies of Left Ventricular Dysfunction (SOLVD). The effect on sudden cardiac death observed in some studies with ACE inhibitors seems to be indirectly due to prevention of remodeling, a progression of the disease. In the CONSENSUS II Trial of about 6,000 patients, there were more than 200 cases of sudden cardiac death during the first 6 months after myocardial infarction and there was no difference between enalapril and placebo. This study included patients both with and without congestive heart failure and no effect was seen on sudden death even in subgroups.

Very recently, two large studies on beta blockers in patients with mild to severe heart failure have also shown a significant reduction in sudden cardiac death. The Cardiac Insufficiency Bisoprolol Study (CIBIS) II, including 2,647 patients (class III–IV) reported a 34% reduction in total mortality and an even more marked effect on sudden cardiac death, that is, 44%. In the Metoprolol Randomised Intervention Trial in Heart Failure (MERIT-HF) including 3,991 (class II–IV) patients with congestive heart failure, metoprolol CR/XL reduced total mortality, also by 34%, and sudden death by 41% compared with placebo. Also, in the US Carvedilol program, retrospectively pooling four different studies in patients with heart failure, there was a significant reduction in total mortality, and on both sudden cardiac death and progressive heart failure.

**Possible Mode of Action**

Three beta blockers, timolol, metoprolol, and propranolol, have been found to reduce sudden cardiac death significantly by about 30–50%. These beta blockers have two properties in common: beta1-receptor blockade and a higher degree of lipophilicity. In this context it can be stated that the beta blockers carvedilol and bisoprolol also reduced sudden cardiac death by 40–50% in patients with congestive heart failure. Carvedilol and bisoprolol also reduced sudden cardiac death by 40–50% in patients with congestive heart failure.
vedilol has several different properties of action, but the two factors in common for timolol, metoprolol, propranolol, beta1-blockade, and a higher degree of lipophilicity, are also properties of carvedilol. It is well known that beta1-receptor blockade reduces the sympathetic overstimulation of the ventricular myocardium and the metabolic demand, mainly by a reduction of heart rate work and prolongation of diastolic perfusion time. The high sympathetic activity per se has been found to reduce the ventricular fibrillation threshold, which is also the effect of myocardial ischemia. It is likely that these mechanisms are involved in the prevention of ventricular fibrillation and sudden cardiac death.

A probable role of a higher degree of lipophilicity of beta blockers has been brought up during the last decade. Parker et al. reported that injection of propranolol into the brain markedly reduced the risk of ventricular fibrillation in pigs after coronary artery ligation. This was found despite the fact that with this mode of administration of the beta blocker there was very little direct effect of the beta blocker on the myocardium. The intracerebral injection was far more effective than intravenous administration of propranolol to pigs, despite the fact that in this situation there was a marked effect directly on the ischemic myocardium. The authors propose that there have to be central nervous mechanisms involved in the prevention of ventricular fibrillation by beta blockade. Åblad et al. studied this hypothesis in a rabbit model, in which the animals were pretreated with beta blockers [metoprolol (lipophilic) or atenolol (hydrophilic)] using osmotic pumps during 3 weeks prior to coronary artery occlusion under anesthesia. After coronary artery occlusion, death from ventricular fibrillation occurred in most controls and also in atenolol-treated animals, whereas metoprolol markedly reduced the risk of ventricular fibrillation. In this study the degree of myocardial ischemia, assessed by ST-segment elevation, heart rate, and systolic blood pressure, was reduced similarly by the two beta blockers. In contrast, the level of vagal tone as measured by heart rate variability was significantly higher in the metoprolol group than in the atenolol group and in controls. Assessment of vagal activity by using cholinergic antagonists demonstrated that vagal tone was better maintained in this situation of stress and acute coronary ligation in animals treated with metoprolol than in treatment with atenolol. It was thus proposed that metoprolol, as it is more lipophilic, penetrates into the brain and thereby causes better maintenance of vagal activity during stress in contrast to the hydrophilic atenolol.

**Selection of Patients**

Patients with depressed cardiac function and more widespread coronary artery disease are at higher risk of ventricular fibrillation. It was reported from the BHAT Trial that propranolol given to patients after myocardial infarction had a more marked effect on reduction of total mortality as well as on sudden cardiac death in patients with compared with those without congestive heart failure at onset of treatment (Fig. 4). The patients with congestive heart failure had about twice as high total mortality as well as sudden death compared with patients without heart failure. Propranolol reduced sudden cardiac death by 47% in patients with congestive heart failure. In the two early intervention trials with metoprolol, the Göteborg Metoprolol and the MIAMI trials, it was found that mortality reduction was more marked in patients at high risk.

In a recent analysis of patients who have congestive heart failure prior to randomization in the Göteborg Metoprolol Trial, metoprolol reduced total mortality by 50% at 3 and 12 months after myocardial infarction. Patients with diabetes after myocardial infarction are known to be at high risk of death, and in several studies beta blockade has reduced short- and long-term mortality by as much as 50%.

Thus patients at higher risk of death—and most likely of sudden cardiac death—will benefit most from postinfarct prophylactic treatment with a beta blocker.

**Conclusion**

In more than 50 randomized controlled trials including about 55,000 patients, beta blockers have been found to reduce total mortality, and even more markedly, sudden cardiac death. The effect on sudden cardiac death in some of these studies is 30–50%. Also, in patients with hypertension, some beta block-
ers have been reported to reduce sudden cardiac death. Very recently, two large trials in patients with congestive heart failure have shown a 34% reduction in total mortality and 41–44% reduction in sudden cardiac death. There is no other therapy with such marked and well documented effect on sudden cardiac death as the beta blockers. An important question is whether all beta blockers have similar favorable effects on sudden cardiac death. The beta blockers that have been reported to reduce sudden cardiac death are both beta1-selective and nonselective agents, but they have two properties in common: beta1-receptor blockade and a higher degree of lipophilicity (timolol, metoprolol, propranolol, bisoprolol, and carvedilol). It has been suggested from animal experimental observations that reduction in sudden cardiac death is at least in part mediated through central nervous system mechanisms that might explain the importance of a higher degree of lipophilicity. It can be concluded that beta blockers with proven clinical effect should be given to patients at risk of sudden cardiac death, including those with previous myocardial infarction, hypertension, and congestive heart failure.

References

The Cellular and Physiologic Effects of Beta Blockers in Heart Failure

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Summary: Enhanced and sustained cardiac adrenergic drive occurs in heart failure (HF) and contributes, in part, to the progression of left ventricular (LV) dysfunction and remodeling that are characteristic of this disease state. Enhanced sympathetic drive in HF can lead to downregulation and desensitization of cardiac beta-adrenergic receptors with a consequent impairment of myocardial reserve and exercise tolerance. This sympathoadrenergic maladaptation can also lead to cellular abnormalities in the failing heart, manifested by defects in calcium handling of the sarcoplasmic reticulum, by defects in myocardial energetics, and by ongoing loss of cardiomyocytes through necrosis or apoptosis. Chronic treatment with beta blockers in patients with HF and in animals with experimentally induced HF has been shown to reverse, prevent, or, at the least, arrest many, if not all, of these adverse processes. Beta blockers improve function of the failing LV, prevent or reverse progressive LV dilation, chamber sphericity, and hypertrophy, and consequently have positive impact on cardiac remodeling. Beta blockers also reduce heart rate and LV wall stress, leading to reduced myocardial oxygen consumption, a clear benefit to the failing heart. Beta blockers can also improve the intrinsic contractile function of cardiomyocytes and have also been shown to improve myocardial energetics in HF, possibly through desirable changes in substrate utilization. Recent studies from our laboratories have also shown that beta blockers can attenuate cardiomyocyte apoptosis in HF. These benefits provide strong reinforcement to the clinical findings that beta blockers are highly beneficial for the management of patients with chronic HF and, when properly used, afford unequivocal reductions in mortality and morbidity in this patient population.

At present, there is general agreement that increased cardiac sympathetic drive occurs in HF and may potentially be an important contributor to the progression of LV dysfunction and chamber remodeling that is characteristic of this disease state. Experimental studies in animal models of HF as well as clinical studies in patients with HF have suggested that chronic therapy with beta blockade is effective in preventing the progression of LV dysfunction and remodeling, the latter evidenced by reversal and/or prevention of progressive LV dilation and chamber sphericity. Results of recent multicenter clinical trials support these findings and have made it abundantly clear that long-term therapy with beta blockade inhibits clinical progression and has a major impact on mortality and morbidity in patients with HF that is at least as favorable, if not better, than that observed with angiotensin-converting enzyme (ACE) inhibitors. Beta blockers improve mortality and morbidity in HF and also improve LV ejection fraction (EF), a beneficial feature that, until recently, has only been attributed to positive inotropic agents.

Key words: heart failure, beta blockade, mortality, morbidity

Abnormalities of the Beta-Adrenergic Receptor Pathway in Heart Failure

To appreciate the benefits derived from long-term beta blockade in HF fully, one should appreciate the adverse effects that a sustained increase of adrenergic drive can have on the failing heart. Over the years, several abnormalities of the cardiac beta-adrenoceptor pathway have been uncovered in the setting of HF and have previously been reviewed in detail. These abnormalities include downregulation of cardiac beta1-receptors, uncoupling of beta2-receptors, possibly mediated through an increase in the functional activity or amount of inhibitory guanine nucleotide binding protein (Gi protein), uncoupling of beta1-receptors observed only in patients with ischemic cardiomyopathy, upregulation of beta-adrenergic-receptor kinase (ßARK) which can lead to beta1 and beta2 phosphorylation and contributes to receptor uncoupling, and downregulation in the function and possibly amount of adenylyl cyclase observed primarily in HF secondary to pressure overload.
Consequences of Enhanced Beta-Adrenergic Drive in Heart Failure: Effects of Receptor Downregulation and Desensitization and Modulation by Beta Blockade

Abnormalities of enhanced and sustained sympathetic drive impact the failing heart in two major ways. First, it results in desensitization of beta-adrenergic signal transduction system evidenced by decreased responsiveness to beta-agonist stimulation. The marked attenuation in inotropic response is readily apparent during exogenous infusion of the beta-agonist dobutamine.14, 15 This blunted inotropic response can contribute to a decline in myocardial reserve14 and to a reduction in exercise capacity.16 A close relationship between the decrease in total cardiac beta-adrenergic receptor density and impaired maximal exercise response has been shown in patients with idiopathic dilated cardiomyopathy.16 In the setting of HF, beta-receptor density was shown to be the only measurable parameter predictive of maximal exercise response.8, 16 Long-term treatment with so-called second-generation beta1-selective antagonists such as metoprolol CR/XL, but not third-generation mixed beta1 and beta2 antagonists such as carvedilol, have been shown to upregulate cardiac beta1-adrenergic receptors and increase cardiac responsiveness to exogenous catecholamines in patients with heart failure.2, 17–20 Second-generation agents also have been shown to recouple uncoupled beta2 adrenoceptors.18 Consistent with these observations, several studies have shown that therapy with the beta1-selective receptor blocker metoprolol CR/XL is associated with improvements in exercise capacity in patients with congestive heart failure (CHF).2, 21–23

Consequences of Enhanced Beta-Adrenergic Drive in Heart Failure: Adverse Biologic Effects and Modulation by Beta Blockade

A second path by which a sustained increase of sympathetic drive impacts the failing heart is through a direct adverse effect on the functional cardiac unit itself: the cardiomyocytes.8 The adverse biologic effects are manifested through alterations in calcium handling at the level of the sarcoplasmic reticulum (SR),24, 25 through cardiac myocyte cell death by necrosis or apoptosis,26–28 and by an effect on high-energy phosphate generation or metabolic substrate utilization.29, 30 All of these abnormalities are subject, directly or indirectly, to sympathoadrenergic regulation,8 and all potentially play key roles in the progression of LV dysfunction and remodeling.

Abnormalities of Sarcoplasmic Reticulum Calcium Handling

Cardiac myocytes isolated from explanted failed human hearts as well as from hearts of animals with experimentally induced HF manifest diminished systolic shortening.31–33 The contractile response of isolated failed myocytes to increasing concentrations of calcium is also severely blunted compared with cardiac myocytes isolated from normal hearts.32 Studies from our laboratories and others also showed that contrary to normal myocytes, myocytes isolated from failing hearts exhibit altered shortening–frequency response,31 a finding consistent with the characteristic inverse force–frequency relation observed in the failing heart.34 Thus, instead of increasing force of contraction with increasing heart rates in the chronically failing myocardium, the contractile performance declines with increasing heart rates.34 Associated with these functional abnormalities are biochemical abnormalities of calcium mobilization in the SR of the failing heart. We and others have shown that the activity and expression of Ca2+-adenosine triphosphatase (ATPase) are reduced in HF;35 as is the rate of Ca2+ uptake into the SR.36 At the same time, the cardiac sarcoplasmal Na+-Ca2+ exchanger is increased in both function and expression in end-stage human HF.36, 37 These alterations can lead to decreased diastolic uptake of Ca2+ into the SR with subsequent reduced calcium release during systole, resulting in reduced contractile performance. At the same time, increased capacity of the Na+-Ca2+ exchanger extrudes intracellular calcium ions to the extracellular space, thereby rendering these ions unavailable for the contractile cycle.36 In addition to their sympathoadrenergic inhibition, all beta blockers reduce heart rate. For any given patient with HF, a reduction of heart rate can cause a leftward shift along the intrinsic force–frequency relation curve, with resulting improvement in the force of contraction. A reduction in heart rate with the use of beta blockers can also prolong the diastolic period allowing a longer time for the depressed Ca2+ -ATPase pump38 to continue loading calcium into the SR, which, in turn, can be used for contraction during systole. Unfortunately, things are not as simple as they seem. Although reducing heart rate with beta blockers in patients with HF is important, a direct cause and effect relationship between reduction of heart rate and improvement of LV function remains difficult to establish.

Ongoing Cardiac Myocyte Death

It has been long recognized that high concentrations of catecholamines can produce myocardial necrosis. Studies in rats in which isoproterenol was administered subcutaneously at a dose of 1 mg/kg for several days showed considerable cardiomyocyte necrosis evidenced by in vivo labeling with antimyosin antibody.39 Studies by Mann et al.40 showed that norepinephrine can be cytotoxic to cultured cardiac myocytes at concentration (10–100 nM) present in the failing human heart. The observation that beta-adrenergic receptor desensitization can ameliorate catecholamine-induced cardiomyocyte toxicity41 provides further support to this concept of cardiac myocyte death in HF secondary to enhanced and sustained sympathoadrenergic drive. Based on these observations, one can safely assume that drugs that attenuate sympathetic drive such as beta blockers are likely to attenuate this form of cell death.

Loss of cardiac myocytes in HF can also occur as a result of programmed cell death or apoptosis.27, 28 Whereas cell necrosis occurs in response to lethal injury, apoptosis is an active,
energy-requiring process that appears to be under genetic control. Apoptosis differs from necrosis in that cell death occurs in the absence of cell membrane rupture and inflammation and is characterized by nuclear DNA fragmentation. Although factors that trigger cardiomyocyte apoptosis in the failing heart are not fully understood, there is some evidence to suggest that certain pathophysiological conditions common to the heart failure state may contribute to or play an important role in promoting cardiac myocyte apoptosis. Some of the triggers of cardiac myocyte apoptosis can be modulated by beta blockade and include increased cytosolic calcium concentration, exposure of cardiac myocytes to hypoxia, and excess levels of norepinephrine, all of which are common features of the failing heart. As eluded to earlier, beta blockers can limit calcium overload by positively altering the dynamics of calcium transport. Beta blockers can also have a positive impact on myocardial hypoxia, given their well-recognized capability to reduce myocardial oxygen consumption. In a recent study, Communal et al. showed that exposure of adult rat ventricular myocytes to norepinephrine leads to apoptosis. When cells were incubated with norepinephrine in the presence of the beta blocker, propranolol, the rate of myocyte apoptosis was substantially attenuated, leading, in part, to the conclusion that beta blocker, propranolol, the rate of myocyte apoptosis was substantially attenuated, leading, in part, to the conclusion that beta blockade causes a shift in myosin isoform gene expression to alpha-myosin heavy chain with downregulation of the beta-myosin heavy chain. Downregulation of alpha-myosin heavy chain in the failing heart may be related to the repression of systolic performance characteristic of this disease state. Of interest, increased LV wall stress may play a key role in the regulation of alpha-myosin heavy chain.

Limited oxygenation of the myocardium or localized hypoxia has received considerable interest in recent years. In dogs with chronic HF produced by intracoronary microembolizations, we have shown that accumulation of collagen in the cardiac interstitium or “reactive interstitial fibrosis” can lead to hypoxia of the collagen-encircled cardiomyocytes. This concept was based on evidence of decreased capillary density, increased oxygen diffusion distance, and increased myocyte lactate dehydrogenase activity in myocardial regions manifesting severe interstitial fibrosis compared with myocardial regions with little or no fibrosis. Furthermore, studies in our laboratories in both patients and dogs with HF showed that the highest incidence of cardiac myocyte apoptosis occurred in myocardial regions that bordered old infarcts, where interstitial fibrosis tends to be most severe. In a recent study in dogs with HF treated long-term with the beta1-selective blocker metoprolol CR/XL, we showed significant attenuation of cardiomyocyte apoptosis. In this study, apoptosis was significantly reduced in myocardial regions bordering old infarcts as well as in regions remote from any infarcts. We also observed an upregulation in the expression of the Bcl-2 protein—an inhibitor of apoptosis—in dogs treated with metoprolol CR/XL compared with untreated dogs. The increase of Bcl-2 in metoprolol CR/XL-treated dogs occurred in the absence of any changes in Bax, a promoter of apoptosis. The increase in Bcl-2 in untreated dogs with HF may have limited the formation of Bax homodimers. These data suggest the possibility that metoprolol CR/XL induces expression of Bcl-2 independent of HF and that this independently confers protection. Furthermore, the observed increase in the Bcl-2 to Bax ratio, the so-called “death switch,” favors cell survival over cell death, a finding consistent with marked attenuation of myocardocyte apoptosis in dogs treated with metoprolol CR/XL. Another factor intimately involved in promoting apoptosis is the interleukin-converting enzyme (ICE) family of cysteine proteases also known as caspases. Bcl-2 expression has been shown to prevent activation of the ICE protease cascade.

### Abnormalities of Myocardial Energetics

In chronic HF, a state of high myocardial metabolic load exists despite low mechanical output. The syndrome is often characterized by limited aerobic function of the myocardium and limited ATPase production by mitochondria that lead to a state of so-called energy depletion. Long-term treatment with beta blockers counteracts these abnormalities of myocardial energetics. Studies with metoprolol CR/XL in both patients and animals with HF have shown a reduction in myocardial oxygen consumption along with reductions of heart rate and LV wall stress, both of which are primary determinants of myocardial oxygen consumption. In a randomized trial of patients with dilated cardiomyopathy, Eichhorn et al. showed that metoprolol CR/XL, in fact, can improve myocardial efficiency of the failing heart. These benefits of beta blockade are difficult to justify as merely the consequences of reduced oxygen consumption. It has recently been suggested that beta blockade causes a shift in myosin isoform gene expression to alpha-myosin heavy chain with downregulation of the beta-myosin heavy chain. Downregulation of alpha-myosin heavy chain in the failing heart may be related to the repression of systolic performance characteristic of this disease state. Of interest, increased LV wall stress may play a key role in the regulation of alpha-myosin heavy chain.

Another possible explanation for the improvement in function and efficiency of the failing heart after long-term therapy with beta blockade may be related to alterations in energy substrate utilization. The hyperadrenergic state that exists in HF can lead to hypermetabolic state due to increased blood levels and utilization of fatty acids resulting from norepinephrine stimulation of lipolysis in both fat and other cells. This can lead to fatty acid-induced “ATPase wastage” and limit ATPase availability that, in turn, compromises myocardial performance. Metoprolol CR/XL has been shown to correct this hypermetabolic state by increasing dependency on carbohydrate utilization and away from fatty acid oxidation. In a recent study of dogs with HF, we observed a significant reduction in carnitine palmitoyl transferase I (CPT-I) activity in dogs treated long-term with metoprolol CR/XL compared with untreated dogs. Carnitine palmitoyl transferase-I is the enzyme that controls the rate of fatty acid transport into mitochondria. Studies by Rupp et al. showed that inhibition of CPT-I by etomoxir in spontaneously hypertensive rats (SHR) increases the rate of SR Ca2+ uptake. Increase in SR Ca2+ uptake can mediate improvements in both systolic and diastolic cardiac performance.
Conclusion

Available studies to date support the conclusion that, in the setting of HF, beta blockers elicit substantial physiologic and cellular benefits. Available data point to a multiplicity of mechanisms through which beta blockers elicit these beneficial effects. Each of the many possible mechanisms is plausible and all appear to be closely interrelated so that the emergence of a single predominant mechanism is becoming less likely. What is certain is the undeniable fact that beta blockers are highly beneficial in the management of patients with chronic HF and, when properly used, afford unequivocal reductions in mortality and morbidity in this patient population.

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Experience with Beta Blockers in Heart Failure Mortality Trials

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Summary: Recent investigations have indicated that chronic heart failure can be reversed with agents that inhibit the renin-angiotensin-aldosterone or sympathetic nervous system, such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers. A meta-analysis of clinical trials of ACE inhibition in chronic heart failure reported reductions in mortality ranging from 13 to 33%, but as ACE inhibitors do not block chronic noradrenergic stimulation of the heart, mortality remains unacceptably high. Beta blockers have been shown to increase left ventricular ejection fraction, reduce end-systolic and end-diastolic cardiac dimensions, improve quality of life, and reduce mortality. All-cause mortality in the US Carvedilol trial was reduced 65%, and in MERIT-HF there was a 49% reduction in mortality from heart failure among patients receiving metoprolol CR/XL. MERIT-HF was ended early because of evidence of survival benefit. Although certain effects of beta blockers may be considered class effects, it is not yet clear whether there are differences between beta1-selective antagonists and nonselective agents. The benefits conferred across differences in disease severity, race, and age should be answered as large ongoing and planned clinical trials of beta blockers are completed.

Key words: chronic heart failure, beta blockers, angiotensin-converting enzyme inhibitors, mortality reduction

Introduction

Chronic heart failure affects more than 5 million persons in the United States and accounts for approximately 43,000 deaths per year. Until recently, clinical management, outside of heart transplant, was largely palliative. Treatment with drugs, such as positive inotropes, vasodilators, and digoxin, often improved hemodynamic abnormalities and enhanced short-term functional status, but had negative or little effect on long-term survival. As our understanding of the pathophysiology of heart failure has grown, we have begun to consider agents such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers for treatment of heart failure.

As recently as 10 years ago, heart failure was viewed as a mechanical disease in which progressive efforts to compensate for pump dysfunction lead inexorably to further pump failure. In this model of hemodynamic dysfunction, treatment with beta blockers would be theoretically contraindicated because of their negative inotropic action. However, now as we have refined our model of heart failure to reflect the deleterious effects of chronic neurohormonal stimulation on remodeling and myocyte destruction, treatments aimed at blocking the action of norepinephrine and angiotensin II appear promising (Fig. 1).

Recently, numerous animal models and clinical studies have demonstrated that beta blockers and ACE inhibitors improve ejection fraction, reduce ventricular volumes, increase developed pressures, and normalize the force–frequency relationship that is altered in heart failure. In addition, restoration of ventricular chamber and myocyte contractile function has been shown in canine models. The theoretical application of these findings to increase survival appears promising. Angiotensin-converting enzyme inhibitors are associated with a 24% (13–33%) reduction in mortality in the 39 published trials of patients with heart failure (total n = 8,308). Despite the survival benefits of ACE inhibitors, these agents do little to block chronic noradrenergic stimulation of the failing heart, and mortality still remains high. Until recently, the addition of a beta blocker to heart failure therapy remained controversial because of a lack of definitive survival data. Although numerous pilot studies have demonstrated the positive long-term effects of beta blockers on hemodynamic function, only a few large, well-controlled survival studies have been completed with all-cause mortality as a primary endpoint (Table I).
Effects on Left Ventricular Ejection Fraction

Beta blockade results in a transient decline in hemodynamics due to its negative inotropic effect, but by 3 months, left ventricular ejection fraction (LVEF) is consistently increased compared with placebo. This late benefit suggests a gradual, secondary biologic effect of beta-blocker therapy. Among the large clinical trials, the Metoprolol in Dilated Cardiomyopathy (MDC), the Australia/New Zealand Heart-Failure Research Collaborative Group (ANZ), and the US Carvedilol MOCHA and PRECISE protocols reported LVEF outcomes; all showed significant improvements in LVEF with beta-blocker therapy (Table II). The increase in LVEF is seen consistently across these studies even though subjects had different cardiac etiologies (ischemic vs. idiopathic cardiomyopathy vs. mixed) and were treated with different beta blockers (metoprolol CR/XL vs. carvedilol). This suggests that improvement in LVEF is a beta-blocker class outcome (as long as the beta1-receptor is blocked), which is independent of heart failure etiology. The magnitude of this effect appears to be dose dependent as seen in the MOCHA trials, in which significant increases in LVEF occurred with increases in the dose of carvedilol to a maximum of 25 mg/day (p < 0.001).

A recent meta-analysis by Lechat et al. pooled primary data from 18 published double-blind, placebo-controlled, parallel-group trials of beta blockers in heart failure. Unweighted analyses of this pooled data demonstrated a significant (p < 10^{-9}) increase in LVEF from 23 to 31% (29% relative increase) with beta-blocker therapy. No significant difference was found between the LVEF outcome of studies employing selective or nonselective beta blockers.

In addition to the functional improvements seen with beta-blocker therapy in LVEF, the ANZ study demonstrated that treatment with carvedilol resulted in significant reductions

TABLE I Large clinical trials of beta-blockade

<table>
<thead>
<tr>
<th>Trial name (Ref. No.)</th>
<th>Number of patients</th>
<th>Agent(s) used</th>
<th>NYHA class</th>
<th>LVEF</th>
<th>Mean follow-up (months)</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol in Dilated Cardiomyopathy (MDC) (26,27)</td>
<td>383</td>
<td>Metoprolol/ placebo</td>
<td>I–IV</td>
<td>&lt;40%</td>
<td>18</td>
<td>Death or need for transplantation</td>
</tr>
<tr>
<td>Australia/New Zealand Heart-Failure Research Collaborative Group (ANZ) (12,28)</td>
<td>415</td>
<td>Carvedilol/ placebo</td>
<td>I–III</td>
<td>&lt;45%</td>
<td>20</td>
<td>LVEF changes or exercise duration</td>
</tr>
<tr>
<td>US Carvedilol Program (29,30,37)</td>
<td>1,094</td>
<td>Carvedilol/ placebo</td>
<td>II–IV</td>
<td>&lt;35%</td>
<td>6.5</td>
<td>Safety</td>
</tr>
<tr>
<td>CIBIS-I (32,34)</td>
<td>641</td>
<td>Bisoprolol/ placebo</td>
<td>III–IV</td>
<td>&lt;35%</td>
<td>23</td>
<td>Total mortality</td>
</tr>
<tr>
<td>Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) (35)</td>
<td>2,647</td>
<td>Bisoprolol/ placebo</td>
<td>III–IV</td>
<td>&lt;35%</td>
<td>14</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Metoprolol Randomized Intervention Trial in Heart Failure (MERIT-HF) (36)</td>
<td>3,993</td>
<td>Metoprolol/ placebo</td>
<td>II–IV</td>
<td>&lt;40%</td>
<td>12</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Beta-Blocker Evaluation of Survival Trial (BEST) (47)</td>
<td>2,708</td>
<td>Bucindolol/ placebo</td>
<td>III–IV</td>
<td>&lt;35%</td>
<td>23</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS)</td>
<td>2,500</td>
<td>Carvedilol/ placebo</td>
<td>IIIb–IV</td>
<td>&lt;25%</td>
<td>36</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Carvedilol or metoprolol (COMET)</td>
<td>3,073</td>
<td>Carvedilol or metoprolol</td>
<td>II–IV</td>
<td>&lt;35%</td>
<td>36</td>
<td>All-cause mortality</td>
</tr>
</tbody>
</table>

Abbreviations: NYHA = New York American Heart class, LVEF = left ventricular ejection fraction.
Further evidence for remodeling after treatment with bisoprolol comes from the Cardiac Insufficiency Bisoprolol Study (CIBIS)-I trial. Left ventricular (LV) end-systolic diameter (ESD) significantly decreased and LV fractional shortening significantly increased in the bisoprolol group compared with the placebo group.32

These data, together with the increases in LVEF, demonstrate that beta blockade not only halts the progression of deleterious remodeling, but also significantly reverses the pathologic changes associated with heart failure. Although LVEF and LV size appear to be attractive short-term endpoint surrogates for morbidity/mortality in heart failure, we must still await the survival data from the current large beta-blocker trials in order to evaluate the predictive value of reversal of pathologic LV remodeling further.

### Effects on Exercise Tolerance

Exercise capacity is a good measure of clinical status, but it has not been a useful predictor of long-term morbidity or mortality in heart failure (e.g., positive inotropes and nitrates increase exercise tolerance but fail to decrease mortality). Exercise tolerance has been used as a short-term endpoint in numerous beta-blocker trials (Table III).

Exercise capacity was measured by the Naughton treadmill protocol in the ANZ and North American MDC study centers and by bicycle exercise protocol in the European MDC study centers. Only the MDC study, which pooled its North American Naughton data with its European bicycle data, showed a significant increase in exercise tolerance with metoprolol therapy compared with placebo (p < 0.05).26, 27 Although the ANZ also employed the Naughton protocol, no significant differences in exercise tolerance were seen between carvedilol treatment and placebo.28

It is not clear whether the discrepancy in findings between the MDC and ANZ reflects the variance in protocol or the choice of beta blocker. Theoretically, metoprolol, a highly beta1-selective beta blocker, may allow for greater increases...

Effects on New York Heart Association Class or Quality of Life/Symptom Improvement Measures

Most of the studies have evaluated the effect of treatment on New York Heart Association (NYHA) class as an indication of clinical improvement. Patients’ perception of quality of life also was assessed with various instruments that evaluated emotional and physical symptomology. At least one study has shown a significant correlation between the evaluation of patients with heart failure by quality of life (QOL) and their physician-attributed NYHA class. The MDC and the CIBIS trials, which employ beta₁-selective beta blockers, both demonstrated significant improvements in QOL and NYHA class after long-term (18–23-month) follow-up. However, the results of patient and physician global assessments and NYHA functional class ranking were improved in those studies. The ANZ trials, after an initial carvedilol-related decline of 6 months duration, showed no significant effect on symptoms or NYHA class at 12-month follow-up. However, these patients had very mild symptomatology at baseline and so were least likely to notice much improvement.

The PRECISE protocol of the US Carvedilol trial also demonstrated no difference between the two treatment groups at 6-month follow-up in QOL scores, assessed either as a total score or separately for the physical and emotional dimensions. However, carvedilol produced a significant improvement in NYHA functional class, as indicated by a shift in the distribution of patients from greater to lesser severity of heart failure (p = 0.014), as well as significant improvement in patient and physician global assessments (p < 0.002).
Effects on Morbidity

The primary endpoints of the earlier large clinical trials (MDC, ANZ, and US Carvedilol) were progression of heart failure as evidenced by hospitalization, need for transplantation, or decreased exercise tolerance. Death or first event combinations (death and hospitalization and/or transplantation) were secondary endpoints. More recent studies [e.g., CIBIS-I, CIBIS-II, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), Beta Blocker Evaluation Survival Trial (BEST), and Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS)] used mortality as a primary endpoint, with combinations of morbidity outcomes as secondary endpoints. All these reports for which we have data indicate that beta-blocker therapy significantly decreases morbidity (Table IV).

The MDC trial randomized patients with idiopathic dilated cardiomyopathy heart failure to immediate release of metoprolol or placebo. This trial demonstrated a significant decrease in mean hospital readmissions per patient.26, 27 Furthermore, a 34% [95% confidence interval (CI) –6–62%, p = 0.058] reduction in the combined endpoint of death or need for transplantation was seen with immediate release metoprolol treatment26, 27 (Fig. 4).

The CIBIS-I and CIBIS-II trials also evaluated treatment with a selective beta blocker, bisoprolol. CIBIS-I had significantly decreased episodes of decompensation leading to hospitalization (p<0.01) and significantly decreased episodes of non-lethal events (p<0.0001).32, 34 Fewer patients in the bisoprolol group (31% reduction) had at least one episode of heart failure decompensation requiring hospitalization. The CIBIS-II trials also demonstrated a 32% decrease in hospital admissions for heart failure decompensation.35

The carvedilol studies, ANZ and US Carvedilol protocols, demonstrate similar decreases in morbidity with treatment. The US Carvedilol mild heart failure trial had clinical progression as its endpoint, which was defined as either death due to heart failure, hospitalization due to heart failure, or a sustained increase in heart failure medications.36 There was a 48% reduction in clinical progression as defined above [relative risk (RR) = 0.52, (95% CI = 0.32–0.85); p = 0.008]. Furthermore, the ANZ study demonstrated a 26% reduction in risk of the combined endpoint of death or hospital admission among patients treated with carvedilol [RR = 0.74 (95% CI = 0.57–0.95); p = 0.02].28 For hospital admission alone there was a 23% reduction in risk [RR = 0.77 (95% CI = 0.59–1.0); p = 0.05]. The US Carvedilol MOCHA protocol also reported decreased morbidity (hospitalizations per patient) with carvedilol in a dose-dependent manner.29

Table IV Effect of beta blockers on morbidity or morbidity/mortality mixed endpoints

<table>
<thead>
<tr>
<th>Trial name (Ref. No.)</th>
<th>Number of patients</th>
<th>Etiology of heart failure</th>
<th>Agent(s) used</th>
<th>Results</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC (26,27)</td>
<td>383</td>
<td>IDCM</td>
<td>Metoprolol/ placebo</td>
<td>Decreased mean number of heart failure readmissions/patient</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34% decrease in combined risk of death or need for transplant combined</td>
<td>0.058</td>
</tr>
<tr>
<td>ANZ (28)</td>
<td>415</td>
<td>IHD</td>
<td>Carvedilol/ placebo</td>
<td>Decreased risk of all hospital admissions by 23%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased combined death or hospitalization risk by 26%</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>US Carvedilol Program (29, 30, 37)</td>
<td>1,094</td>
<td>IHD or IDCM</td>
<td>Carvedilol/ placebo</td>
<td>Time to first event analysis showed combined risk of CHF hospitalization or death decreased from 24.6 to 15.8% (38% reduction in risk)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CIBIS-I (32,33)</td>
<td>641</td>
<td>Mixed</td>
<td>Bisoprolol/ placebo</td>
<td>Decreased episodes of decompensation leading to hospitalization</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased episodes of non-lethal events 32% decrease in hospital admissions for heart failure decompensation</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CIBIS-II (35)</td>
<td>2,647</td>
<td>Mixed</td>
<td>Bisoprolol/ placebo</td>
<td>NR</td>
<td>0.0001</td>
</tr>
<tr>
<td>MERIT-HF (39)</td>
<td>3,993</td>
<td>Mixed</td>
<td>Metoprolol/ placebo</td>
<td>Hospitalizations for CHF decreased from 17.1 to 9.6% (41% reduction in risk)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Meta-analysis of double-blind, placebo-controlled, randomized trials (31)</td>
<td>3,023</td>
<td>Mixed</td>
<td>Beta blockers/placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** CHF = congestive heart failure. Other abbreviations as in Table III.
The MOCHA group also analyzed total hospitalizations. Almost a quarter of the patients (23.8%) were randomized into the placebo group, while 13.2, 18.0, and 13.5% were randomized into groups receiving the three increasing carvedilol doses, respectively (p = 0.16 by linear trend).29 The mean number of hospital days per patient was reduced by carvedilol (placebo 3.1, carvedilol increasing doses 1.1, 1.5, and 1.3, respectively, p = 0.01).29 Although there was no clear dose-dependent effect on these parameters, there was a dose-related reduction in mean number of hospitalizations per subject (p = 0.01). In all hospitalization categories, combining the carvedilol dosing groups, there was a significant reduction (p ≤ 0.05) in favor of carvedilol treatment.29 The PRECISE protocol also demonstrated significant reductions in morbidity; 24.4% of the placebo group, but only 14.5% of the carvedilol group experienced a cardiovascular hospitalization (p = 0.029).30 When deaths and cardiovascular hospitalizations were combined in a time-to-first-event analysis to account for competing risks, the probability of a major fatal or nonfatal event was reduced by carvedilol from 31.0 to 19.6% (p = 0.029).30 Lechat et al.’s meta-analysis of beta-blocker therapy demonstrates a 41% reduction in risk of hospitalization for heart failure (p < 0.0001).31 This indicates that decreased hospitalization is consistently seen with therapy in beta-blocker trials, and suggests a beta-blocker class effect on morbidity.

Effects on Mortality

Mortality data were collected retrospectively in all the large clinical trials, but it was not until CIBIS-I that mortality was assigned as a primary endpoint (Table V). The CIBIS trial randomized 641 patients with moderate heart failure to the beta-1-selective agent bisoprolol or placebo.34 Although this trial was underpowered, and only half of the patients were titrated to target dosage, there was a 20% reduction in mortality with bisoprolol [RR = 0.80, (95% CI = 0.56–1.15); p = 0.22], but this did not reach statistical significance.34 The US Carvedilol Trial was a prospectively designed, stratified program with four component protocols under a single Data and Safety Monitoring Board.29, 30, 36, 37 When the Board examined the data of all four component protocols together, there was a 65% reduction in all-cause mortality with carvedilol [RR = 0.35, (95% CI = 0.20–0.61); p ≤ 0.001].37 This finding of a mortality benefit of carvedilol has been surrounded by controversy because of the pooling of the four protocol components, the short follow-up, the few deaths, and concern about the study bias created by the open-label run-in period. However, some experts have argued that none of these issues can significantly detract from the survival benefit of carvedilol.38 Furthermore, each individual protocol had findings consistent with the survival benefit.29, 30, 36 The MOCHA protocol demonstrated that 6-month mortality among treatment groups was dose dependent.29 MOCHA showed a dose-related, statistically significant linear reduction in mortality (p ≤ 0.001) in the carvedilol-treated groups, with respective mortality rates of 6.0% [RR = 0.356 (95% CI, 0.127–0.998); p ≤ 0.05], 6.7% [RR = 0.416 (95% CI, 0.158–1.097); p = 0.07], and 1.1% [RR = 0.067 (95% CI, 0.009–0.512; p ≤ 0.001)] for the carvedilol doses of 6.25 mg twice daily, 12.5 mg twice daily, and 25 mg twice daily, respectively.

Whereas many of the above trials suggested that beta blockers decrease mortality, there were no large prospective, randomized, controlled clinical trials that definitively answered the question of whether or not these agents prolong survival in patients with heart failure. Thus, the CIBIS-II and MERIT-HF
trials, with primary endpoints of mortality, were expected to define the future role for beta1-selective blockers in heart failure. Both of these studies were stopped early because of evidence for a survival benefit. In MERIT-HF, extended release metoprolol CR/XL therapy led to a 34% reduction in all-cause mortality, 41% decrease in sudden deaths, and a 49% decrease in heart-failure deaths.39 These data are consistent with the recently published CIBIS-II data.35 That trial was also stopped early because all-cause mortality was significantly less in the bisoprolol group than in the placebo group (p < 0.0001).35 The estimated annual mortality rate was 8.8% in the bisoprolol group and 13.2% in the placebo group [hazard ratio 0.66 (95% CI = 0.54-0.81)].35 There were significantly fewer cardiovascular deaths in patients receiving bisoprolol than in those receiving placebo (p = 0.0049).

Mortality and admissions to hospital did not differ significantly between groups for any etiology subgroup of heart failure or NYHA class of disease severity (Fig. 5). The greatest effect, however, was seen in patients with ischemic heart disease who were in NYHA class III at baseline.35 It should be noted that on the whole patients in the CIBIS II and MERIT-HF trials had mild-to-moderate heart failure symptoms. Thus, the mortality benefit of beta blockers cannot yet be extended to patients with advanced symptomatology. However, there are two ongoing trials in advanced heart failure using nonselective agents to test this hypothesis (BEST and COPERNICUS).

The magnitude of the treatment effect seen in CIBIS-II and MERIT-HF are in agreement with findings from meta-analyses of previous randomized, placebo-controlled trials, in which beta-blocker treatment reduced mortality by 32% in patients with mild-to-moderate heart failure.31

**Future Directions**

Some evidence suggests that beta1-selective antagonists are not as protective against sudden death as nonselective beta blockers.38,41 However, both MERIT-HF and CIBIS II showed a decrease in sudden death with beta blocker compared with placebo. An ongoing trial, the Carvedilol or Metoprolol trial (COMET) will examine the effects of carvedilol and metoprolol in a head-to-head comparison mortality trial. Meanwhile, there are conflicting data that either show beta1-selective antagonists as more protective,42 no different,40 or less protective31, 43 than nonselective beta blockers in all cause mortality. Preliminary evidence suggests that there is no difference between the biologic effect of beta1-selective antagonists and the nonselective beta blockers. Carvedilol and metoprolol have not differed in their effect on LVEF in many small pilot studies33 (Fig. 6).

Data from a small mechanistic trial indicated no significant differences in exercise capacity, LVEF, and lipid peroxidation measures between carvedilol or metoprolol CR/XL treatment groups.44 Whether this lack of difference in biologic parameters will translate into equivalent mortality rates remains to be seen.

### Table V: Effect of beta blockers on mortality

<table>
<thead>
<tr>
<th>Trial name (Ref. No.)</th>
<th>Number of patients</th>
<th>Etiology of heart failure</th>
<th>Agent(s) used</th>
<th>Result</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC (27)</td>
<td>383</td>
<td>IDCM</td>
<td>Metoprolol/placebo</td>
<td>No change in the number of deaths</td>
<td>&lt;0.69</td>
</tr>
<tr>
<td>ANZ (28)</td>
<td>415</td>
<td>IHD</td>
<td>Carvedirol/placebo</td>
<td>No change</td>
<td>NR</td>
</tr>
<tr>
<td>US Carvedilol Program (29, 30, 37)</td>
<td>1,094</td>
<td>IHD or IDCM</td>
<td>Carvedirol/placebo</td>
<td>Decreased from 7.8 to 3.2% (65% reduction in risk of death)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CIBIS-I (32, 33)</td>
<td>641</td>
<td>Mixed</td>
<td>Bisoprolol/placebo</td>
<td>Decreased from 17.3 to 11.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CIBIS-II (35)</td>
<td>2,647</td>
<td>Mixed</td>
<td>Bisoprolol/placebo</td>
<td>[estimated annual mortality rate hazard ratio 0.66 (95% CI = 0.54-0.81)]</td>
<td>NR</td>
</tr>
<tr>
<td>MERIT-HF (39)</td>
<td>3,993</td>
<td>Mixed</td>
<td>Metoprolol/placebo</td>
<td>34% reduction in overall death rate; 49% reduction in cardiac death rate</td>
<td></td>
</tr>
<tr>
<td>Meta-analysis of double-blind, placebo-controlled, randomized trials (31)</td>
<td>3,023</td>
<td>Mixed</td>
<td>Beta blockers/placebo</td>
<td>Decreased from 11.9 to 7.5% (32% reduction in risk of death)</td>
<td>&lt;0.003</td>
</tr>
</tbody>
</table>

**Abbreviation:** CI = confidence interval. Other abbreviations as in Table III.

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**Fig. 5** Relative risk of treatment effect on mortality by etiology and functional class at baseline (horizontal bars represent 95% confidence interval). Reprinted from Ref. No. 35 with permission.
Another concern is that the current data do not address beta-blocker treatment protocols for our patients at the extremes of failure (class I or class IIIb/IV). The NIH-VA Cooperative study, BEST, is designed to address the latter group and has randomized 2,708 patients with moderate-to-severe heart failure to the nonselective agent bupindolol or placebo. The COPERNICUS trial will randomize 2,000 patients with more advanced (NYHA class IIIb-IV) heart failure to the nonselective agent carvedilol or placebo. The Carvedilol ACE Inhibitors Remodeling Mild Heart Failure Evaluation (CARMEN) trial will randomize patients with symptomless LV dysfunction to the nonselective agent carvedilol or placebo. These studies should also address the possible mediating effects of race and ethnicity on the beta blockers’ outcomes, as they will have more diverse recruitment from the United States.24 Another key question is whether elderly patients with heart failure will enjoy the same beta-blocker protective effects established in previous studies that included a large percentage of young subjects. Clearly, many of these issues will be resolved once the ongoing clinical trials are analyzed.

**Beta Blockers in Clinical Practice**

Beta-adrenergic blocking agents are not rescue therapy for patients with advanced heart failure (e.g., patients on inotropic therapy in coronary care units or with decompensated heart failure). The initial effect of these agents is one of adrenergic withdrawal and sometimes worsening hemodynamics. Furthermore, beta blockers have only been shown to benefit patients with LV systolic failure.

The role of beta blockers in diastolic failure has not been established. At present, carvedilol is the only beta blocker approved by the Food and Drug Administration for heart failure. Not every beta blocker can be used to treat heart failure, as some are poorly tolerated. If the patient is stable, start with a very low dose and titrate up weekly or every other week (doubling as tolerated).41 Concomitant alteration in diuretics or ACE inhibitors should be made according to clinical status of the patient.

Many epidemiologic studies have demonstrated that despite significant evidence of improved survival with the use of ACE inhibitors in heart failure, ACE inhibitors are underused.20 Beta blockers are predicted to have an even greater positive impact on mortality, especially when they are used in combination with ACE inhibitors (Fig. 7).

Efforts must be made to take advantage of the clear benefits of cotreatment with ACE inhibitors and beta blockers in halting and perhaps reversing the pathology of heart failure. Even without the latest clinical trial results, there is currently significant evidence to support aggressive use of beta blockers in our patients with mild-to-moderate LV systolic failure.

**References**


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**Fig. 6** Effect of metoprolol, carvedilol, or placebo on LVEF (mean ± standard deviation). BSL = baseline values, EOS = end-of-study values, LVEF = left ventricular ejection fraction. Reprinted from Ref. No. 33 with permission.

**Fig. 7** Effect on annual rate of mortality of angiotensin-converting enzyme inhibitors alone, with beta blockers added, and with both drugs. Reprinted from Refs. No. 45 and 46 with permission.


