

Neurohormones and the Progression of Cardiovascular Disease: What's Behind High Risk?

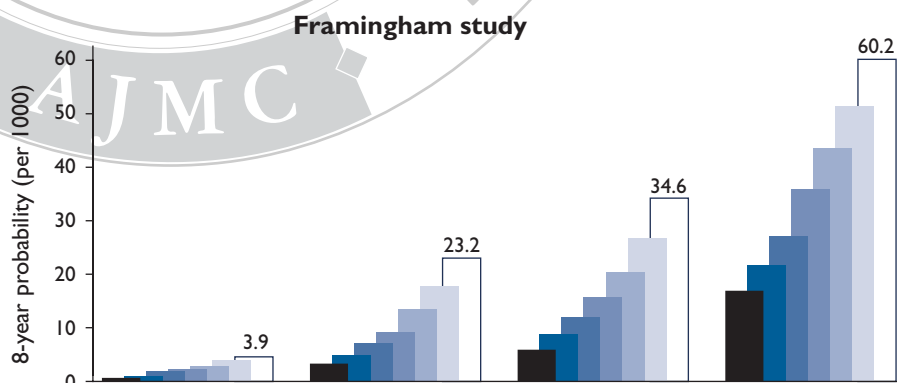
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Cardiovascular (CV) events are the leading cause of morbidity and mortality in the United States and throughout the Western world, accounting for approximately 40% of all deaths in the United States. They are a major cause of long-term disability, lost productivity, and diminished quality of life and therefore are associated with a staggering economic cost to the healthcare industry and to the US economy in general.

Impact of Multiple Risk Factors

It is clear that CV disease seldom presents as a single risk factor. Instead, most patients present with multiple risk factors, which collectively cause progression of disease culminating in an eventual CV event, namely, stroke, myocardial infarction (MI), heart failure (HF), or sudden death. Independent modifiable risk

Figure 1. Additive Nature of Cardiovascular Risk Factors



Total cholesterol (mg/dL)	185-335	185-335	185-335	185-335
Glucose intolerance	-	+	+	+
Systolic BP (mm Hg)	105	195	195	195
Cigarettes	-	-	+	+
LVH on ECG	-	-	-	+

BP indicates blood pressure; LVH, left ventricular hypertrophy; ECG, electrocardiogram.
Source: Reference 1.

factors include insulin resistance, diabetes, hyperlipidemia, ischemic heart disease, renal dysfunction, hypertension, and obesity. These risk factors are additive, and the presence of multiple risk factors in individual patients confers increased risk for CV events.

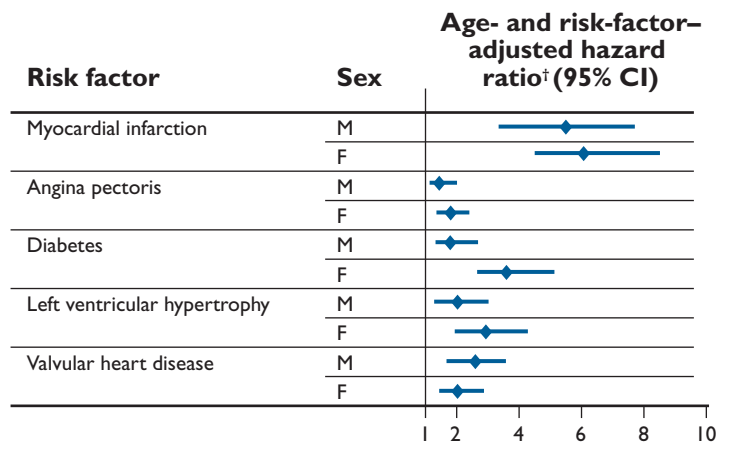
Data from the Framingham study looking at 8-year probability for major CV events clearly illustrate this. For example, the patient who has simply high cholesterol without other risk factors is at relatively low risk. In contrast, patients in a high hypercholesterolemia group with additive risk factors of glucose intolerance, hypertension, cigarette smoking, or diabetes have a > 60% increased risk of a major CV event over an 8-year follow-up period (Figure 1).¹

Treatment programs aimed at attenuating disease progression need to consider the spectrum of risk factors rather than focusing on any single item. Of the modifiable CV risk factors, hypertension is perhaps the most influential and most prevalent. Nonetheless, most patients with hypertension are not optimally managed. Both the level of awareness and adequacy of therapy for hypertension remains poor. Of the more than 50 million patients with hypertension in the United States, > 50% of them have at least 3 metabolic abnormalities. Uncomplicated hypertension is, in fact, uncommon.

High-risk hypertensive patients are at risk for ultimately developing HF. Again, data from the Framingham study have shown that > 90% of patients with HF have antecedent hypertension. Levy and colleagues studied risk factors for congestive HF (CHF) among patients with hypertension. As shown in Figure 2, MI, angina pectoris, diabetes, left ventricular (LV) hypertrophy, and valvular heart disease have been identified as independent risk factors for CHF in hypertensive patients. Based on hazard ratios, it is obvious that most potent among these is MI, followed by diabetes.²

Patients with diabetes represent a group of special concern. A diabetic patient with multiple risk factors has a disproportionate increase in risk of coronary heart disease and death. Diabetic patients without previous MI have as high a risk of MI as nondiabetic patients with a previous MI.³

Figure 2. Risk Factors for CHF Among Subjects With Hypertension*



*Based on 165 CHF events in 1707 men and 192 events in 2118 women with hypertension prior to CHF. Based on dynamic model with reclassification of hypertension and risk factors at each follow-up examination.

[†]Adjusted for angina pectoris, myocardial infarction, diabetes, left ventricular hypertrophy, and valvular heart disease.

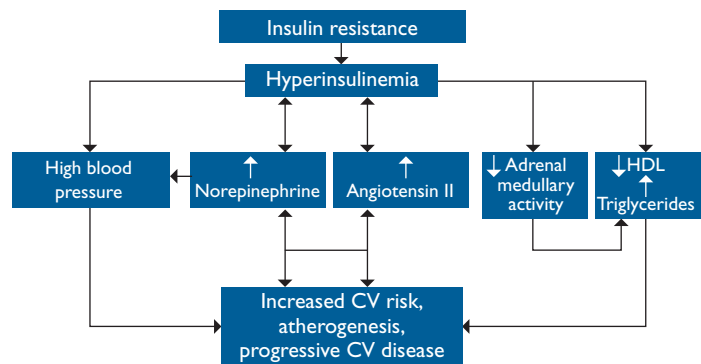
CHF indicates congestive heart failure; CI, confidence interval.

Source: Reference 2.

The major causes of mortality in patients with diabetes are coronary heart disease and HF—far outstripping other causes, such as cancer, stroke, and infection.⁴

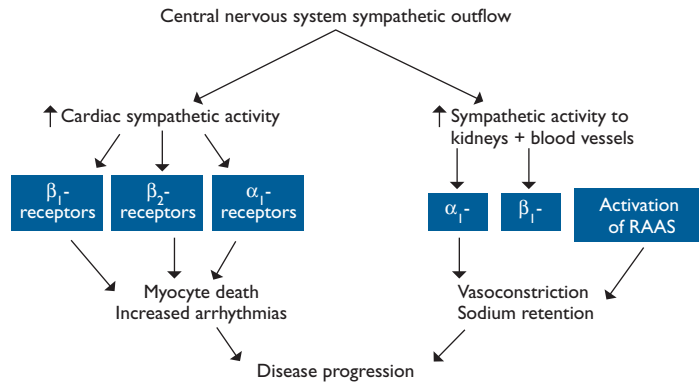
Recommendations from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Figure 3. Insulin Resistance, Angiotensin II, and Norepinephrine in the Metabolic Syndrome



HDL indicates high-density lipoprotein; CV, cardiovascular. Adapted, with permission, from reference 10.

Figure 4. Effects of Sympathetic Activation in Cardiovascular Disease



RAAS indicates renin-angiotensin-aldosterone system.
 Source: Packer M. *Progr Cardiovasc Dis.* 1998;39(suppl 1):39-52.

(JNC VI),⁵ American Diabetes Association,⁶ and the National Kidney Foundation,⁷ based on data from the United Kingdom Prospective Diabetes Study (UKPDS)⁸ and Hypertension Optimal Treatment (HOT)⁹ trials suggest that the ideal target blood pressure in a patient with diabetes and hypertension is 120 to 130/80 mm Hg. A high normal blood pressure or stage 1 hypertension is no longer considered to be acceptable in these patients.

CV risk factors, many of which are often asymptomatic, may lead directly to the onset

and progression of HF and acute MI. It is this progression of heart disease that we attempt to interrupt with early and aggressive therapy in high-risk hypertensive patients.

Pathological Basis for CV Disease: Neurohormonal Imbalance

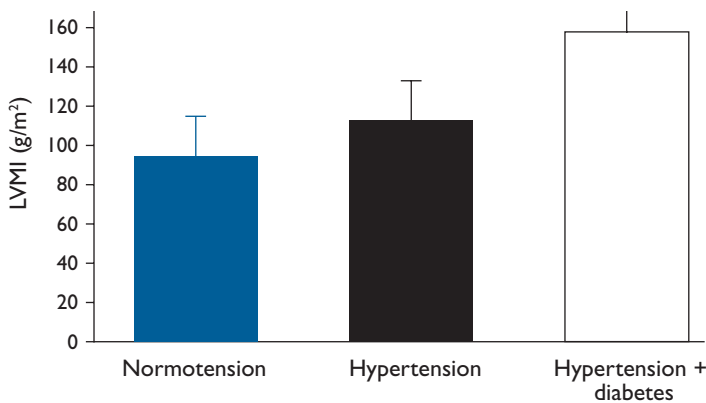
The metabolic syndrome is central to the progression of CV disease. Hypertension plays a key role in activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). A patient with the metabolic syndrome may progress down one of many pathways to MI or cardiomyopathy and, ultimately, the development of CHF unless there is an intervention that can block or antagonize the deleterious effects of SNS or RAAS activation. Drugs that treat the metabolic syndrome, diabetes, hypertension, or atherosclerosis may all interrupt or improve this process.

Figure 3 illustrates the interrelationship between insulin resistance, angiotensin II, and norepinephrine in the metabolic syndrome, starting at the top with insulin resistance.¹⁰ Insulin resistance leads to hyperinsulinemia, which, in turn, is a stimulus for increased norepinephrine and angiotensin II. Together, these factors contribute to increased CV risk. For example, hyperinsulinemia influences aldosterone and angiotensin II levels, which, in turn, can lead to fibrosis and hypertrophy not only of the heart or the myocardium, but also of blood vessels, leading to vascular remodeling and arteriosclerosis.

The Role of the SNS

An increase in central nervous system (CNS) sympathetic outflow results in an increase in sympathetic activity to blood vessels and the kidneys, acting mainly via peripheral alpha₁ receptors to promote vasoconstriction and sodium and water retention in the kidney. In addition, activation of beta₁ receptors in the kidney leads to an increase in renin release. Thus, activation of the SNS leads to activation of the RAAS.

Figure 5. LV Mass: Increasing Along the CV Disease Continuum



LV indicates left ventricular; CV, cardiovascular; LVMI, left ventricular mass index.
 Source: Reference 11.

But perhaps most important, this increase in CNS sympathetic outflow occurring in the setting of CV disease leads to an activation of cardiac sympathetic activity, which may act via β_1 , β_2 , and α_1 receptors—all of which are present in the human heart—to promote disease progression (Figure 4). Among the consequences of increased cardiac sympathetic activity are an increased risk of ventricular arrhythmias and LV hypertrophy or adverse remodeling.

Remodeling is of particular interest because it ultimately defines the progression of CV disease. Remodeling is a process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape, and function. It occurs in most heart diseases, including MI, cardiomyopathy, hypertension, aging, diabetes, and valvular heart disease. Remodeling can be reversed, or at least delayed, and an improvement in this remodeling process may be associated with an improvement in patient outcomes.

There are 2 pathways for adverse remodeling. One is a hypertrophic pathway, the other, a dilated pathway. In response to chronic pressure overload, concentric LV hypertrophy

is associated with normal cavity size, but a stiff ventricle and diastolic dysfunction ultimately progresses to the onset of diastolic HF. Conversely, progressive LV dilation and dysfunction associated with the development of a globular heart with systolic dysfunction with mitral regurgitation can ultimately lead to the onset and progression of symptomatic HF as well.

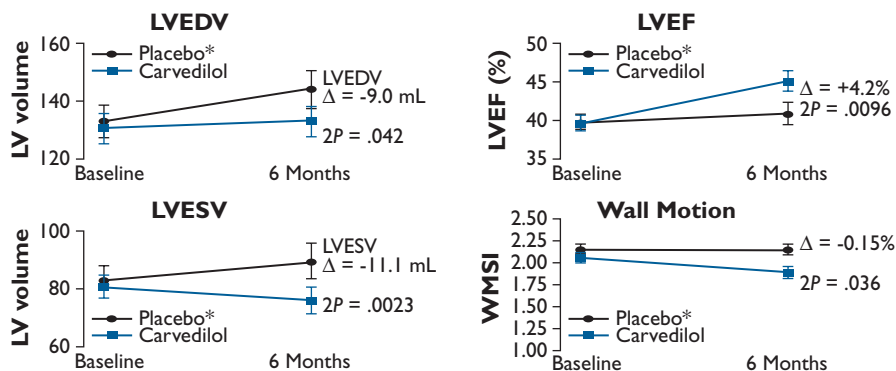
Figure 5 shows LV mass, specifically LV mass index, in normotensive individuals, patients with hypertension alone, and patients with hypertension plus diabetes. Compared with normotensive persons, hypertensive patients have an increased LV mass index.

In patients with both hypertension and diabetes, the increase in LV mass index is much greater than that seen in those with hypertension alone.¹¹

Reversing Remodeling

Adverse remodeling of the heart defines disease progression. At the cardiac, cellular, and molecular levels, neurohormonal activation drives this adverse remodeling process. This

Figure 6. CAPRICORN: Effect of Carvedilol on LV Function



*Placebo = angiotensin-converting enzyme inhibitor, aspirin, statin, and thrombolysis. CAPRICORN indicates Carvedilol Post Infarct Survival Control in LV Dysfunction; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; WMSI, wall motion score index. Source: Reference 12.

process can be reversed by neurohormonal interventions, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and beta blockers.

For instance, in an echocardiographic substudy of the Carvedilol Post Infarct Survival Control in LV Dysfunction (CAPRICORN) trial, the effects of carvedilol (a nonselective α_1 , β_1 , and β_2 adrenergic blocking agent) or placebo in addition to standard treatment with an ACE inhibitor and aspirin on LV remodeling post MI were studied. Both groups showed improvement from baseline because each group received a neurohormonal blocking drug. The group receiving carvedilol as well as standard treatment, however, showed greater improvement than the group receiving standard therapy alone (Figure 6).¹²

Conclusion

Activation of the SNS and the RAAS plays a central role throughout the CV disease continuum. Thus neurohormonal antagonists, such as beta blockers and ACE inhibitors, may be the preferred agents for preventing the development or progression of CV disease.

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Role of Neurohormonal Antagonists in Management of Patients With Hypertension, Metabolic Syndrome, and Diabetes

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Approximately 1.1 million individuals will have a new or recurrent myocardial infarction (MI), and more than 500 000 will develop new-onset heart failure (HF) in the United States this year.¹ Diabetes and hypertension are each independent risk factors for cardiovascular (CV) events and HF. Patients with hypertension, diabetes, or both have a substantially higher risk for future CV events and HF. More recently, it has been recognized that the metabolic syndrome is also associated with a significant increased risk of CV events and HF.

Activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) has been demonstrated to play a key role in CV injury, CV events, HF, and CV mortality. The adverse CV risks posed by hypertension, metabolic syndrome, and diabetes can be substantially reduced through the use of angiotensin-converting enzyme (ACE) inhibitors and beta blockers. This article will describe the rationale for and clinical benefits of targeting neurohormonal activation in patients with hypertension and the metabolic syndrome.

CV Risk Factors

Epidemiologic studies have demonstrated that both CV risk and HF risk rise according to the number of risk factors present; these risk factors are often additive or, in some cases, synergistic for the risk of major CV events, including HF and mortality. Hypertension is a significant risk factor for

MI, and more than two thirds of patients with HF have antecedent hypertension. Diabetes is an independent risk factor for CV events, and its presence with other risk factors more than doubles the risk for fatal coronary heart disease (CHD).²

In patients screened for the Multiple Risk Factor Intervention Trial (MRFIT), predictors of CV mortality in 347 978 men aged 35 to 57 years were assessed.³ There were 603 CV deaths among 5163 (11.7%) men with diabetes over 12 years of follow-up compared with 8965 deaths among 342 815 (2.6%) men without diagnosed diabetes. The absolute risk of CV disease-related death was much higher for men with diabetes at every age stratum, ethnic background, and risk factor level. The CV risk for an individual with diabetes with only 1 additional risk factor exceeded that for a patient without diabetes with 3 risk factors.

In the East-West study, patients with diabetes who had suffered a prior MI had a markedly increased risk of mortality over an 8-year follow-up period.⁴ The 8-year incidence of recurrent MI was 45% for patients with diabetes and a prior MI compared with 18.8% for patients with a history of MI but without diabetes. Patients with diabetes who sustain acute coronary syndromes also have a substantially increased risk of developing new-onset HF. Diabetes is now considered to be a CHD risk equivalent because patients with diabetes but without a history of MI have survival rates similar to those individuals without diabetes who have had a prior MI.⁵ Approximately three quarters of patients with diabetes will die of CV disease.¹

Metabolic Syndrome

The metabolic syndrome has been more recently recognized to be associated with a significant increase in risk for CV events and HF as well as new-onset diabetes.^{5,6} The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines define the metabolic syndrome as any 3 of the following: abdominal obesity, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, elevated blood pressure (BP) (>130/85 mm Hg), and elevated fasting glucose occurring in the same patients.

By the ATP III criteria, it is estimated that 22% of US adults 20 years of age or older have the metabolic syndrome (**Figure 1**).⁷ Among men and women > 60 years of age, more than 40% have the metabolic syndrome. In individuals with the metabolic syndrome, CV mortality over time is substantially elevated compared with individuals without the metabolic syndrome. A prospective study by Sattar and associates showed that the metabolic syndrome, as defined

by the ATP III criteria, predicts both CHD events and new-onset diabetes.⁶ The researchers found that men with the metabolic syndrome had 1.7 times the risk of a CHD event and 3.5 times the risk of developing diabetes over 4.9 years of follow-up compared with men without the syndrome. The risk increased as the number of metabolic abnormalities rose. Compared with men with no metabolic abnormalities, those with 4 or 5 had 3.7 times the risk of CHD and 24.5 times the risk of diabetes.

Insulin Resistance, Neurohormones, and CV Risk

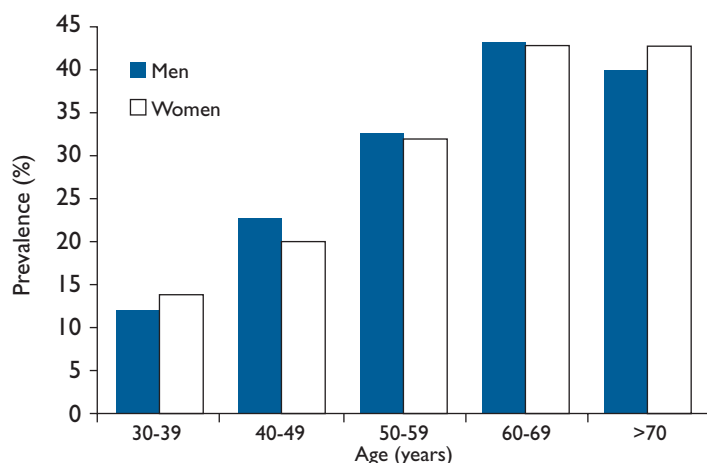
The pathophysiology of both the metabolic syndrome and type 2 diabetes is related to insulin resistance. Insulin resistance states have been strongly associated with an increase in the risk for CV events and HF. Is there a link between insulin resistance, all the conditions that characterize the metabolic syndrome, and CV risk?

Reaven et al⁸ proposed an interrelationship between angiotensin II, norepinephrine, and insulin resistance. Insulin resistance leads to hyperinsulinemia, which leads to activation of the sympathetic nervous system and the RAAS. Likewise, activation of these neuroendocrine systems leads to hyperinsulinemia. This contributes not only to the hemodynamic effect of elevated BP but also to an increase in atherogenesis, progressive CV disease, and prothrombotic and proinflammatory CV risk factors. The interrelationships between the components of this deadly triad lead to progression of CV disease and put patients with the metabolic syndrome at high risk for fatal and nonfatal CV events.

Metabolic Syndrome, Diabetes, and Hypertension

For a patient with the metabolic syndrome, the ATP III guidelines⁵ recommend that first an attempt be made to reduce underlying causes via nonpharmacologic measures—weight

Figure 1. Prevalence of the Metabolic Syndrome by ATP III Criteria—NHANES III Population*



*Overall 22% for age 20 and older. ATP III indicates Adult Treatment Panel III; NHANES, National Health and Nutrition Examination Survey. Adapted, with permission, from reference 7.

reduction through dietary measures and exercise and smoking cessation. In most cases, however, it is necessary to use pharmacologic measures to treat the associated lipid and non-lipid risk factors, including hypertension. How is this best achieved? By targeting insulin resistance? By targeting activation of the sympathetic nervous system and RAAS?

According to recent guideline recommendations,⁹ patients with diabetes should be managed as if they have known CHD, which means that their CV risk factors (BP and lipids) should be treated to the same targets as patients with known CHD.

According to the National Kidney Foundation,¹⁰ the BP goal for patients with diabetes and hypertension is systolic BP of <130 mm Hg and diastolic BP of 80 mm Hg. This goal is also endorsed by the recently released *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7).¹¹ BP-lowering medications for patients with compelling indications, such as diabetes, should reduce BP and other risk factors. In the case of diabetes, this includes reducing proteinuria. Such agents include ACE inhibitors, beta blockers, combined alpha and beta blockers, low-dose diuretics, nondihydropyridine calcium channel blockers, and angiotensin receptor blockers. Compelling conditions more often than not will require > 1 antihypertensive agent and likely as many as 3 to 4 agents to achieve the desired BP levels.

The American College of Cardiology (ACC)/American Heart Association (AHA) practice guidelines for patients at high risk for HF¹² now include a staging process that has at its initial stage, or Stage A, patients with hypertension or other conditions strongly associated with development of HF, in recognition of the fact that early identification and management of these patients can delay or halt the progression to more severe stages. The recommendation is to control systolic and diastolic BP in concordance with the guidelines. These guidelines acknowledge that the appropriate antihypertensive regimen frequently consists of several medications used in combination, and recommend medications that are useful for the treat-

ment of both hypertension and HF, such as diuretics, ACE inhibitors, and beta blockers.

The guidelines are less consistent as to whether all BP-lowering agents reduce CV risk to the same extent and whether the goal is merely to lower BP. Although there is compelling clinical trial evidence that various antihypertensive medications with different modes of action have varied effects on CV risk, the guidelines differ in how to interpret these results. Beyond their antihypertensive effects, beta blockers and ACE inhibitors favorably affect the metabolic syndrome constellation of risk factors by preserving kidney function, arresting the atherosclerotic process, and preventing or reversing CV or renovascular end-organ damage.

N Neurohormonal Antagonists and CV Protection

A more direct and clinical trial-supported approach would be to recommend that all patients with diabetes or the metabolic syndrome be treated with CV protective medications that have been demonstrated to lower CV events and HF: aspirin, beta blockers, ACE inhibitors, and statins. Clinical trial evidence demonstrates major benefits from ACE inhibitor and beta-blocker therapy in patients with diabetes.

Antagonism of the RAAS with ACE inhibitors has been shown to provide substantial clinical benefits to diabetic patients with prior CV events, HF, or both. The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated the significant benefits of ACE inhibition in patients with documented coronary, cerebral, or peripheral vascular disease.¹³

This study assessed the effects of treatment with the ACE inhibitor ramipril versus placebo in 9297 patients who had evidence of vascular disease or diabetes plus 1 additional CV risk factor and who did not have left ventricular dysfunction or HF. Treatment with ramipril resulted in reduced rates of death from CV causes, MI, stroke, death from any cause, revascularization procedures, cardiac arrest, HF and complications related to diabetes. Ramipril

treatment also reduced the risk of new-onset HF by 23%.¹³

A substudy of the HOPE trial, the Microalbuminuria, Cardiovascular, and Renal Outcomes Prevention Evaluation (MICRO-HOPE) study, examined whether ramipril could lower the risks of CV disease and renal disease in patients with diabetes.¹⁴ The analysis included 3577 patients with diabetes who had been included in the HOPE study. Ramipril reduced the risk of total mortality by 24%, MI by 22%, stroke by 33%, CV death by 37%, and revascularization by 17% in patients with diabetes. The HOPE and MICRO-HOPE studies provide compelling evidence that ACE inhibition can benefit patients with diabetes, the metabolic syndrome, and prior CV events.

The United Kingdom Prospective Diabetes Study (UKPDS)¹⁵ demonstrated that treatment with either an ACE inhibitor or a beta blocker in patients with type 2 diabetes improved clinical outcomes and reduced risk: MI was reduced by 21%, diabetes-related death by 32%, renal failure by 42%, stroke by 44%, and

new incidence of HF by 56%. The CV benefits with beta blockers were similar in magnitude to that achieved with ACE inhibitors.

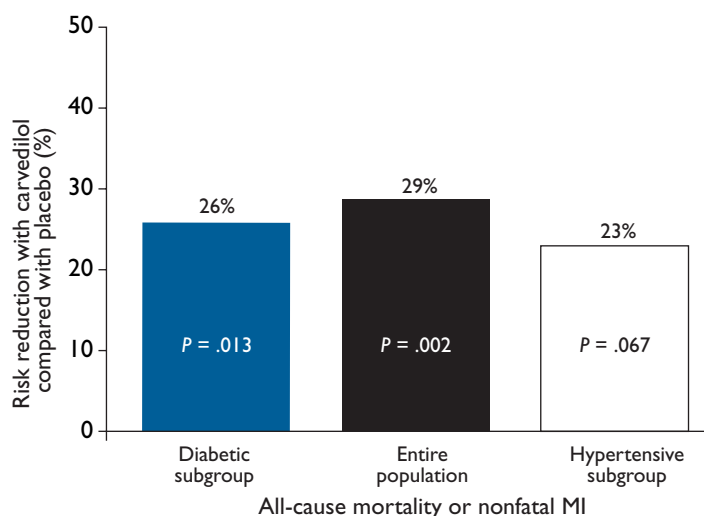
The Bezafibrate Infarction Prevention (BIP) trial,¹⁶ a study of patients with diabetes and coronary artery disease, compared patients treated with beta blockers with those who were not. After 3 years, a 43% reduction in CV events and a 42% reduction in CV mortality was seen in the patients with diabetes treated with beta blockers.

In the Carvedilol Post Infarct Survival Control in LV Dysfunction (CAPRICORN) trial, post-MI patients with left ventricular dysfunction (ejection fraction, $\leq 40\%$) were randomly assigned to treatment with carvedilol or placebo.¹⁷ Patients selected for this trial were already treated with aspirin and ACE inhibition and frequently had undergone revascularization. Treatment with carvedilol, which combines nonselective beta blockade with alpha blockade, substantially reduced all-cause mortality (23% relative risk reduction, $P = .031$), CV mortality (25% relative risk reduction, $P = .049$), and fatal or nonfatal MI (40% relative risk reduction, $P = .010$) compared with placebo in patients with diabetes and those with hypertension as well as the overall population.

Further analysis of results from CAPRICORN indicated that the benefits of carvedilol were not diminished in patients with either diabetes or hypertension. The reduction in risk for all-cause mortality or nonfatal MI for the entire population in this trial was 29% versus 26% for patients with diabetes and 23% for those with hypertension (Figure 2). Thus, even in patients already treated with ACE inhibitors, the addition of carvedilol to the post-MI patient lowered risk even further.

These findings suggest that beta blockade provides multiple CV benefits to patients with the metabolic syndrome and diabetes. Beta blocker therapy can reverse CV remodeling, prevent sudden death and arrhythmias, and decrease myocardial wall stress. These agents are also antiatherogenic, reducing inflammation, shear stress, endothelial dysfunction, and atherosclerotic lesion progression, which reduces the incidence of new-onset HF and CV death in patients with diabetes.¹⁸

Figure 2. CAPRICORN: Similar Effect of Carvedilol in Post-MI Patients With Diabetes, Without Diabetes, and Hypertensive Patients*



*437 (22%) patients with diabetes; 1055 (54%) with hypertension. CAPRICORN indicates Carvedilol Post Infarct Survival Control in LV Dysfunction; MI, myocardial infarction. Source: Reference 17.

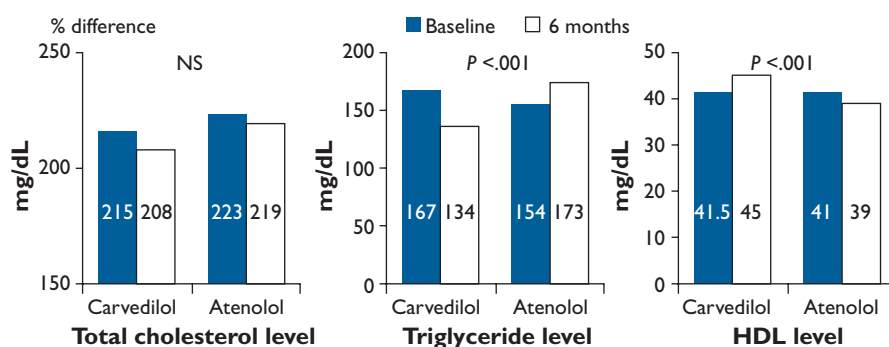
In contrast, benefits seen with the use of insulin or sulfonylureas for tight glycemic control pale in comparison with the magnitude of risk reduction achieved with antihypertensive therapy in the UKPDS. For example, there was a 56% reduction in new-onset HF in the groups receiving an ACE inhibitor or beta blocker, but only a 9% reduction with tight glycemic control. Overall, diabetic mortality was reduced 32% with ACE inhibitors and beta blockers compared with 8% with glycemic control.¹⁵ Although this clearly does not mean

that glycemic control is not important or cannot reduce macrovascular risk, it does highlight that glycemic control alone is not sufficient to substantially lower CV risk in patients with diabetes.

Concerns About Beta-blocker Therapy

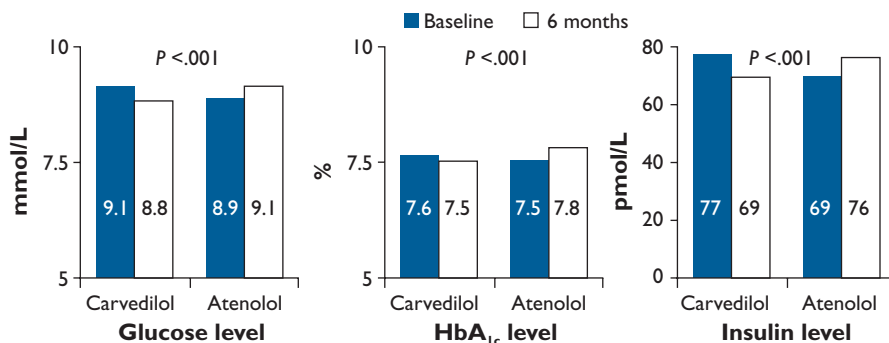
Despite these considerable benefits, physicians have lingering concerns about adding

Figure 3A. Effect of Beta Blockade on Lipid Management in Patients With Diabetes and Hypertension*



*45 patients with diabetes and hypertension treated for 24 weeks. NS indicates nonstatistical; HDL, high-density lipoprotein. Source: Reference 19.

Figure 3B. Effect of Beta Blockade on Glucose and HbA_{1c} in Patients With Diabetes and Hypertension*



*45 patients with diabetes and hypertension treated for 24 weeks. HbA_{1c} indicates hemoglobin A_{1c}. Source: Reference 19.

beta blockade to the treatment of patients with hypertension and diabetes. These concerns have centered on their potential metabolic effects, such as worsening HDL cholesterol, increasing total or low-density lipoprotein cholesterol, or both, negatively affecting glucose metabolism and renal blood flow, and masking hypoglycemia.

The pharmacologic properties of beta blockers have been overgeneralized to be class effects. In reality, the relative selectivity of these agents appears to differentiate them, particularly with respect to their metabolic effects. The potential benefits of balanced adrenergic blockade, including alpha₁ inhibition, are apparent. **Figures 3A** and **3B** illustrate the differences between a beta-selective agent, atenolol, and a balanced adrenergic agent, carvedilol, with respect to lipid levels and glycemic control.¹⁹ This is true also with respect to insulin sensitivity. In patients with hypertension, a 20% to 30% worsening of insulin sensitivity is seen with atenolol, metoprolol, and propranolol, while beta blockers with vasodilating properties—dilevalol, celiprolol, and carvedilol—reduce insulin resistance (**Figure 4**).²⁰

These positive effects of beta blockers on parameters of specific concern in patients with the metabolic syndrome or diabetes, cou-

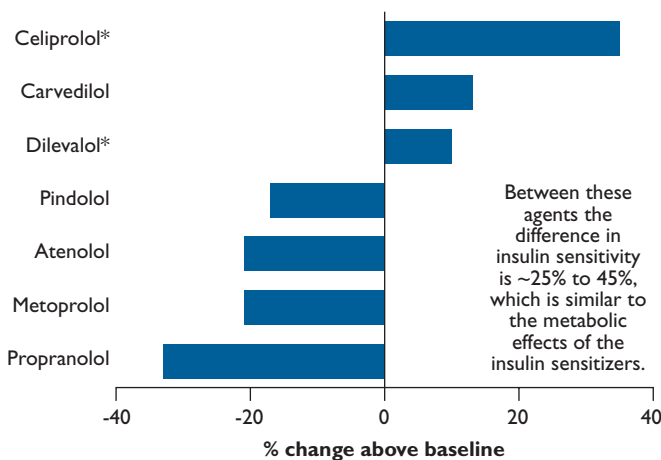
pled with the proven mortality and morbidity benefits of neurohormonal blockade in all patients with diabetes, support the use of carvedilol in conjunction with ACE inhibitor therapy in patients with the metabolic syndrome or diabetes.

Summary

Hypertension, the metabolic syndrome, and diabetes account for a substantial proportion of CV events and HF in the United States. Lowering BP, achieving lipid goals, and obtaining metabolic control is important. However, even patients who have obtained these goals remain at higher risk.

The benefits of RAAS and sympathetic system modulation in reducing CV events in these high-risk patients extend beyond hemodynamic effects alone. A combination of ACE inhibitors and beta blockers provides benefits in patients with the metabolic syndrome, diabetes, hypertension, and atherosclerosis; a consistent reduction in CV morbidity and mortality being the ultimate goal. ACE inhibitors and beta blockers for the treatment of the metabolic syndrome, diabetes, and hypertension represents a major therapeutic advance. Every effort should be made to apply these life-saving therapies in all patients with the metabolic syndrome, diabetes, and hypertension in the absence of contraindications or intolerance.

Figure 4. Effect of Beta Blockade on Insulin Sensitivity in Patients With Hypertension



*Not available in the United States.
Source: Reference 20.

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Case Report

A 64-year-old African American woman who has had type 2 diabetes for the past 6 years presents for a routine follow-up visit. She denies any chest pain or other symptoms and reports that her blood glucose is well controlled. Blood pressure (BP) on this visit is 139/88 mm Hg and heart rate is 82 bpm. Her body mass index is estimated to be 31 kg/m². Her current medical regimen includes glyburide 6 mg/day,

amlodipine 5 mg/day, omeprazole 20 mg/day, and vitamin E.

With this history in mind, the questions one needs to consider for this patient are:

- What is her risk of having a cardiovascular (CV) event in the next 5 years?
- Is her BP well controlled and at goal?
- What other diagnostic tests are needed to help guide her therapy?

The key risk factors for this patient are hypertension and diabetes (the latter is a coronary heart disease risk equivalent). Her risk for

a major CV event is estimated to be > 2% per year, which means that over the next 5 years, her risk would be \geq 10%. Evaluation of her medical regimen reveals that her current therapy will not be sufficient to lower that risk.

The BP goal in patients with diabetes is lower than the goal for those with hypertension alone. For a patient with diabetes, the systolic BP goal is < 130 mm Hg, and the diastolic BP goal is < 80 mm Hg. This patient clearly is not at goal, and, in fact, she may require 3 or more medications to reach her BP goal. In addition, it would be advisable to use medications that lower her overall incidence of CV events and mortality besides just lowering her BP.

Additional tests that would be useful before adjusting her therapeutic regimen include an electrocardiogram (ECG) to identify any evidence of left ventricular (LV) hypertrophy, an assessment of renal function, a determination of glycemic control, a lipid panel, and a measure of urinary albumin. Laboratory reports reveal the following:

- Blood urea nitrogen (BUN): 22 mg/dL
- Creatinine: 1.6 mmol/day
- Glycosylated hemoglobin (HbA_{1c}): 9.4%
- Lipid panel: total cholesterol: 212 mg/dL
 - Low-density lipoprotein (LDL): 128 mg/dL
 - High-density lipoprotein (HDL): 36 mg/dL
 - Triglycerides: 240 mg/dL

The ECG shows LV hypertrophy.

Based on these assessments, what medications should be considered to control her BP?

What are the lipid goals for this patient; does she need a lipid-lowering medication or would diet and exercise alone be adequate?

The medications shown to lower risk for stroke, myocardial infarction (MI), progression of renal disease, or development of heart failure (HF) include low-dose diuretics, angio-

tensin-converting enzyme (ACE) inhibitors, and beta blockers. It is likely, however, that a combination of these agents will be required to achieve adequate risk reduction in this patient.

Calcium channel blockers, specifically the dihydropyridines, have not been shown to lower risk for MI or HF or to provide renoprotection, and, therefore, the amlodipine was discontinued. In its place, hydrochlorothiazide 12.5 mg/day, an ACE inhibitor (enalapril 5 mg/day), and a beta blocker, specifically, carvedilol, 6.25 mg/day, were selected. For additional CV risk reduction, aspirin 81 mg/day, as well as a statin (simvastatin 20 mg/day) were started along with diet and exercise counseling.

The lipid goals for this patient are an LDL cholesterol level of < 100 mg/dL, HDL cholesterol > 40 mg/dL, and triglycerides < 150 mg/dL. The Heart Protection Study showed that patients with diabetes with LDL cholesterol levels in the normal range still derived major benefit from treatment with a statin even in the absence of documented vascular disease. To achieve tighter glycemic control, rosiglitazone 4 mg/day was started with a goal for an HbA_{1c} level of < 7%.

On follow-up 6 weeks later, the patient reports feeling well. She is apparently compliant with her medications, and she has begun a walking program covering a mile a day. Her BP reading is now 128/78 mm Hg. Her BUN is 28 mg/dL; creatinine clearance is still 1.6 mmol/day. Her LDL cholesterol is at goal at 98 mg/dL, HDL cholesterol is > 40 mg/dL, and triglycerides are 120 mg/dL. With the additional therapeutic measures, by 6 weeks, she has achieved both appropriate BP and lipid goals.

Addressing the Gap in the Management of Patients After Acute Myocardial Infarction: How Good Is the Evidence Supporting Current Treatment Guidelines?

Michael B. Fowler, MB, FRCP

Beta-adrenergic blocking drugs were the first agents shown in large clinical trials to improve the outcomes of survivors of acute myocardial infarction (MI). Lower mortality was observed in the group randomized to active therapy, with a beta-adrenergic blocking drug in most, but not all, of the trials.

Evidence Supporting Post-MI Use of Beta-adrenergic Blockers

Table 1 shows the results in individual trial groups according to the properties of the specific beta-adrenergic blocking drug under evaluation. The Beta-Blocker Heart Attack Trial (BHAT),¹ which randomized 3837 patients to propranolol or placebo, and the Norwegian Multicenter Timolol Study,² with 1884 randomized patients convincingly demonstrated that therapy with a nonselective beta-adrenergic blocking agent improved survival.

Conversely, trials with agents with significant intrinsic sympathomimetic activity (ISA) did not generally report positive results, with the exception of a small trial with acebutolol, an agent with a low level of ISA. Similarly, results with agents with specificity for the beta₁ adrenoceptor have not consistently shown an improvement in mortality. Metoprolol, the shorter-acting tartrate salt, did not improve survival in the 2395 patients included in the Lopressor Intervention Trial (LIT).³ However, practolol, also a beta₁-selective agent, did improve survival

in a trial of 3038 survivors of acute MI, although the agent was subsequently withdrawn because of toxicity.⁴

All the original randomized clinical trials that provide support for the long-standing recommendation for routine use of beta-blocking drugs following acute MI were performed in the 1970s and 1980s, which was a very different era in the routine management of patients during and after acute MI and also in our appreciation of the safety and benefit of beta-adrenergic blocking drugs in patients with heart failure (HF). The patients recruited into these trials had not had the benefit of early acute thrombolysis or direct mechanical intervention to the infarct-related coronary occlusion by angioplasty. Aspirin use was not widespread or was actually contraindicated in the trial population to prevent a confounding impact on survival. Angiotensin-converting enzyme (ACE) inhibitors had not yet been developed, and other therapies, such as heparin, were not routinely used. On the other hand, some other probably harmful therapies, such as lidocaine infusions, which are no longer routinely used, were commonly used at that time.

Although not every individual trial showed a survival benefit, the capability, demonstrated for the first time, to improve long-time survival following acute MI resulted in a widespread and general recommendation to use a beta-adrenergic blocking drug routinely in all patients without a contraindication. Because at that time beta-adrenergic blocking drugs were

Table 1. Findings from Major Long-term Beta-blocking Agent Trials Post-MI: Pre-1999*

	Propranolol BHAT^{1,2} (1978-1981)	Timolol Norwegian³ Multicenter Study (1978-1981)	Metoprolol tartrate Lopressor Inter- vention Trial⁴ (1979-1982)	Atenolol No major trials	Metoprolol-XL No major trials
Type of agent	Nonselective	Nonselective	Selective	Selective	Selective
Daily target dosage	180-240 mg	20 mg	200 mg	NA	NA
Number of patients	3837	1884	2395	NA	NA
Effect on mortality	-26% at	-39% at	+4% at	NA	NA
mean duration of trial	25 months <i>P</i> < .005	17 months <i>P</i> < .0005	12 months <i>P</i> = NS		
Effect on reinfarction	-16% at	-28% at	Not studied	NA	NA
mean duration of trial	25 months <i>P</i> < NS	17 months <i>P</i> < .0006			

*Trials longer than 3 months in duration with >1000 patients.

MI indicates myocardial infarction; NA, not applicable; NS, nonsignificant.

¹Beta-Blocker Heart Attack Trial Research Group. *JAMA*. 1982;247:1707-1714.

²Beta-Blocker Heart Attack Trial Research Group. *JAMA*. 1983;250:2814-2819.

³Norwegian Multicenter Study Group. *N Engl J Med*. 1981;304:801-807.

⁴Lopressor Intervention Trial Research Group. *Eur Heart J*. 1987;8:1056-1064.

considered to be contraindicated in HF and perhaps because it was thought that low-risk patients did not require additional long-term therapy, adoption of beta-adrenergic blocking drugs fell short of expectations.

Guidelines on post-MI management⁵ also advocated widespread use of beta-adrenergic blocking agents based on their beneficial effects on the risk of reinfarction. This effect was demonstrated in the Norwegian trial, in which the nonselective beta-adrenergic blocker timolol reduced the risk of infarction by 28% (*P* < .0006). Similarly, in the BHAT study, the nonselective beta-adrenergic blocker propranolol reduced the risk of reinfarction by 16% (*P* = NS).

Although all the trials of beta-adrenergic blocking drugs from this era excluded patients with advanced HF, evidence from subgroup analyses provided a tantalizing prediction, which was confirmed more than a decade later, that beta-adrenergic blockade would be especially beneficial in patients with HF. In the BHAT study, a subgroup of patients with mild HF following the index MI

had a higher subsequent mortality rate and the greatest benefit from randomization to propranolol. Similarly, in the Norwegian study, a subgroup of patients with cardiomegaly on chest radiograph was especially likely to benefit from timolol. Although atenolol and metoprolol (tartrate or succinate salt) are currently the beta-adrenergic blockers most commonly prescribed following acute MI, neither of these agents has been demonstrated in a large-scale randomized trial to improve either survival or the risk of reinfarction.

How Effective Are Other Post-MI Therapies?

Not all agents that have been evaluated for post-MI therapy are effective. Drugs, such as diuretics, nitrates, and calcium channel blockers, that do not directly counter the abnormal neurohormonal environment in this patient population have not been shown to be effective.^{6,7} Despite lowering blood

pressure and reducing myocardial ischemia, calcium channel blocking drugs do not improve survival and are actually detrimental in patients with HF.

Only neurohormonal antagonists have been shown to attenuate or reverse the progressive left ventricular (LV) remodeling that occurs after MI, especially in patients whose LV ejection fraction is reduced to $\leq 40\%$. For example, in the Survival and Ventricular Enlargement (SAVE) trial, ACE inhibitors improved survival and attenuated the LV remodeling process in patients with LV dysfunction after acute MI.⁸

CAPRICORN Trial of Beta Blockers Post-MI

The Carvedilol Post Infarct Survival Control in LV Dysfunction (CAPRICORN) study⁹ is the only trial to date to evaluate the role of beta-adrenergic blocking drugs in patients with significant post-MI LV dysfunction as an entry criterion. Patients also had to have been treated with ACE inhibitors for at least 48 hours prior to randomization (unless there were contraindications). The trial compared carvedilol with placebo in patients who had had an acute MI within the previous 21 days and who had an LV ejection fraction of $\leq 40\%$. HF was present in approximately half of the patients studied.

CAPRICORN is also the only study of beta-adrenergic blocking drugs undertaken in patients who had the benefit of contemporary management of acute MI. Therapies routinely applied to the study population that are known to improve survival included thrombolytic therapy or direct angioplasty when indicated, ACE inhibition (use of which was an actual inclusion criteria), aspirin, and statins. **Table 2** shows the percentage of patients in the CAPRICORN study who received these agents.

The CAPRICORN trial enrolled 1959 patients, 975 randomized to carvedilol and 984 to placebo, who were followed for an average of 1.3 years. The dose of the study medication was uptitrated from 6.25 mg twice daily to a

Table 2. Therapies Routinely Used in CAPRICORN Population

	Carvedilol group (n = 975)	Placebo group (n = 984)
<i>Treatment for index myocardial infarction</i>		
Nitrates	715 (73%)	717 (73%)
IV beta blockers	112 (11%)	100 (10%)
IV heparin	617 (63%)	635 (65%)
SC heparin	460 (47%)	481 (49%)
IV diuretics	338 (35%)	320 (33%)
Thrombolysis/ primary angioplasty	442 (45%)	465 (47%)
<i>Medications at time of randomization</i>		
ACE inhibitor	953 (98%)	955 (97%)
Aspirin	838 (86%)	847 (86%)

CAPRICORN indicates Carvedilol Post Infarct Survival Control in LV Dysfunction; IV, intravenous; SC, subcutaneous; ACE, angiotensin-converting enzyme.

Source: Adapted, with permission, from reference 9.

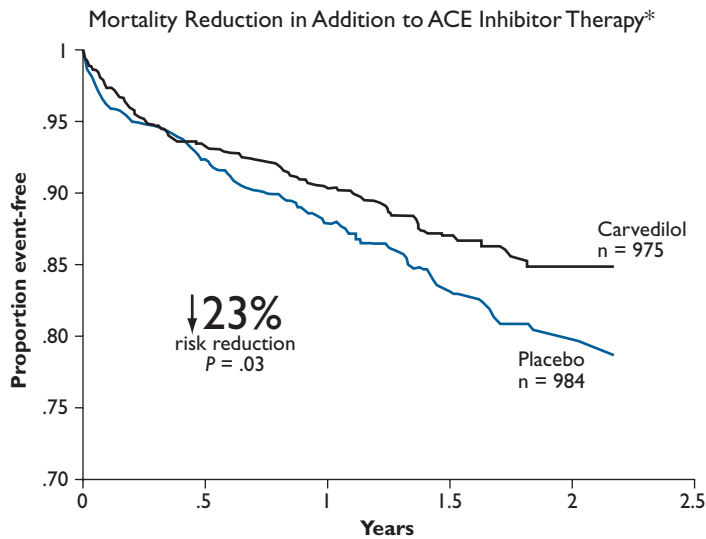
maximum of 25 mg twice daily.

The trial was initially designed and powered to detect a favorable impact of carvedilol on survival. Subsequently, on the advice of an independent end points committee, the primary end point was altered to an analysis of death from any cause or hospitalization for a cardiovascular cause. When the results were analyzed, it was found that carvedilol had improved survival by 23% (**Figure**), whereas there was no statistically significant difference between the carvedilol and placebo groups in the combined end point of death or cardiovascular hospitalization.

The impact of carvedilol on reinfarction was substantial and was the greatest reduction in reinfarction reported in any large trial of beta blockers following acute MI. Carvedilol also had a favorable influence on the risk of supraventricular or ventricular arrhythmias.¹⁰

Carvedilol was well tolerated, and the results are especially remarkable because

Figure. CAPRICORN: All-cause Mortality



*97% of patients were receiving ACE inhibitors.
CAPRICORN indicates Carvedilol Post Infarct Survival Control in LV Dysfunction;
ACE, angiotensin-converting enzyme.
Source: Reference 9.

“drop-in” patients—given open-label beta-adrenergic blocking drugs—would have tended to reduce the observed favorable influence of carvedilol. Patients who received optimal therapy for acute MI, including revascularization by angioplasty or thrombolysis, were no less likely to benefit than the other patients. Approximately half the patients in the trial did not have HF, but they obtained a similar benefit to the group with HF.

Class Effect or Drug-specific Effect?

Meta-analyses suggest that all beta-adrenergic blocking drugs that do not have ISA improve survival following MI. Most meta-analyses and the latest study that included the current data with carvedilol suggest that important and clinically relevant differences may exist between the benefit obtained from beta₁ selective agents and nonselective drugs, such as carvedilol. Meta-analyses of the 26 580 patients in placebo-controlled trials following acute MI and the 15 905 patients evaluated in HF trials do show an average ≥

13% reduction in mortality with the nonselective agents in both clinical scenarios.¹¹

The suggestion that nonselective beta-adrenergic blocker agents may produce a greater clinical benefit after acute MI is well supported on a mechanistic basis, although most of the studies, including the Carvedilol or Metoprolol European Trial (COMET),¹² that confirmed the superiority of a nonselective agent (carvedilol) over a selective agent (short-acting metoprolol), were conducted in patients with HF.

Following acute MI, many of the pathophysiological features that influence disease progression and outcomes are the same as those in HF. Norepinephrine exerts an important influence on the risk of reinfarction, the risk of supraventricular and ventricular arrhythmias, and the adverse remodeling process that develops, particularly in survivors of MI.

Conclusion

Beta-adrenergic blocking drugs have been convincingly demonstrated in large clinical trials to improve the natural history following acute MI. Improved survival and reduced risk of reinfarction have been shown in large-scale randomized trials. Much of the evidence supporting the routine use of beta-adrenergic blocking drugs for the long-term therapy of patients without contraindications comes from trials of nonselective agents. In the modern era of acute MI management, when many successful therapies are combined to improve post-MI outcomes, only carvedilol has been shown not only to improve survival and reduce reinfarction but also to attenuate the remodeling process.

Moreover, carvedilol has been shown to benefit a patient population selected on the basis of high risk and treated because of this high risk with concomitant ACE inhibitors. The CAPRICORN study found that far from being surpassed by more modern agents and approaches to the management of acute MI, beta-adrenergic blocking drugs, specifically carvedilol, are highly effective and important therapy for post-MI patients.

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