Abstract

Risk factors such as hypertension, type 2 diabetes, obesity, and dyslipidemia are associated with insulin resistance and a predisposition to developing cardiovascular disease (CVD). The progression of CVD follows a continuum associated with numerous related and unrelated risk factors that, if inadequately treated, ultimately can lead to end-stage heart and/or renal failure and eventually death. However, treatment of hypertension in patients with insulin resistance or type 2 diabetes has been shown to reduce morbidity and premature mortality. In order to reduce the risk of cardiovascular events in patients with hypertension and type 2 diabetes, blood pressure should be reduced to a goal of <130/80 mm Hg (or ≤120/75 mm Hg with concurrent proteinuria). Intensive lifestyle modification and aggressive pharmacotherapy utilizing several antidiabetic and/or antihypertensive medications are also typically needed. Since the sympathetic nervous system (SNS) and renin angiotensin aldosterone system (RAAS) play a fundamental role in both insulin resistance and hypertension throughout the CVD continuum, antagonism of the RAAS and SNS can reduce morbidity and mortality in patients with these risk factors. Agents targeting the RAAS need to be considered in patients with hypertension and type 2 diabetes, particularly in the setting of microalbuminuria. Traditional β-blocker therapy has been associated with adverse metabolic and tolerability issues in the patient with type 2 diabetes. However, newer β-blockers that block β₁-, β₂-, and α₁-receptors offer cardiovascular benefits with fewer adverse effects making them a good treatment option for the hypertensive patient with type 2 diabetes.
Introduction
As the US population becomes more sedentary and obese, it is common for patients to present with concomitant cardiovascular risk factors.1 In fact, approximately 20% to 60% of patients with type 2 diabetes also have hypertension.2 Hypertension, type 2 diabetes, obesity, and dyslipidemia, referred to as the “deadly quartet,” predispose patients to early cardiovascular disease (CVD) and are all associated with insulin resistance (Figure 1).1,3 Each of these risk factors cumulatively can contribute to the development of early microvascular complications (amputations, blindness, renal failure) and macrovascular complications (stroke and coronary heart disease [CHD]) when left untreated.1 Specifically, it has been demonstrated that hypertension, hypercholesterolemia, diabetes mellitus, and cigarette smoking generate target-organ damage by promoting oxidative stress, which in turn causes endothelial dysfunction and alterations in vasoactive mediators, inflammatory responses, and vascular remodeling.3

Hypertension
Hypertension, defined as systolic blood pressure of ≥140 mm Hg and diastolic blood pressure of ≥90 mm Hg, is one of the most dominant risk factors for CVD.4 Approximately 72 million Americans have hypertension, yet only 35% of them have their blood pressure under control.4 The need for appropriate management of hypertension is significant as controlling high blood pressure could reduce the incidence of stroke by 35-40%, myocardial infarction (MI) by 20-25%, and congestive heart failure (CHF) by more than 50%.5

Insulin resistance and type 2 diabetes
Insulin resistance is associated with numerous cardiovascular risk factors such as obesity, physical inactivity,
abnormal glucose metabolism, endothelial dysfunction, increased plasminogen activator inhibitor-1 (PAI-1), hypertension, platelet aggregation, increased inflammatory markers such as C-reactive protein, and dyslipidemia including reduced high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and elevated small dense low-density lipoprotein cholesterol (LDL-C). Insulin resistance is also associated with a loss of nocturnal dip in blood pressure experienced by normotensives, a finding that is linked to an increase in left ventricular hypertrophy and microalbuminuria.

which leads to hyperinsulinemia, further stimulating the SNS. Chronic sympathetic nerve activation induced by excessive hyperinsulinemia in hypertensive patients with type 2 diabetes may constitute a mechanism leading to increased cardiovascular complications in these patients. Additionally, animal models have also demonstrated upregulation of the angiotensin II type 1 receptor, a key mediator of the RAAS when insulin resistance is present.

Pharmacological Interventions

In order to reduce the risk of CHD events, stroke, and nephropathy in hypertensive patients with type 2 diabetes, the American Diabetes Association (ADA) recommends a blood pressure goal of <130/80 mm Hg. This goal is congruent with the American Association of Clinical Endocrinologists (AACE) and the Joint National Committee 7 (JNC 7) recommendations. The National Kidney Foundation also recommends a blood pressure goal of ≤120/75 mm Hg in the presence of severe proteinuria. Severe proteinuria (>3.5 g protein in 24 hrs) occurs with nephrotic syndrome due to type 2 diabetes or other disease, or with serious cases of nephritic syndrome (<3.5 g protein in 24 hrs) caused by acute inflammatory injury to the glomeruli. Data from the National Health and Nutrition Examination Survey (NHANES) 1999-2000 showed that only a third of adults with a diagnosis of type 2 diabetes have a blood pressure at the level of current ADA recommendations of <130/80 mm Hg. However more recent data suggest that number is actually less than 8%.

Lifestyle modifications, such as smoking cessation, weight reduction, increased physical activity, and sodium restriction have been shown to reduce blood pressure as well as the incidence of type 2 diabetes in nondiabetic patients. However, aggressive control of blood pressure in hypertensive patients with type 2 diabetes has consistently been demonstrated to be associated with dramatic reductions in the risk for microvascular events such as end-stage renal disease and decreased visual acuity as well as death due to cardiovascular events. Therefore, pharmacological therapy should be started if lifestyle modification has not resulted in target blood pressure levels within 3 months.

Selection of agents

To achieve blood pressure goals in patients with type 2 diabetes (and/or renal disease), combination pharmacotherapy is usually required. Numerous landmark clinical studies in high-risk patients with hypertension support the need for a stepwise approach using multiple agents to reach blood pressure goals (Figure 2). As demonstrated in a recent meta-analysis of 75 treatment arms from 64 trials involving more than 400,000 patients, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blocker (ARBs), β-blockers, calcium channel blockers, and diuretics are all similar in their ability to significantly prevent MI. However, some of the currently available agents offer advantages of targeting the underlying neurohormonal systems that contribute to hypertension, namely the RAAS and SNS.
Hypertension 102: Treating the Insulin Resistant Heart

Targeting the RAAS

First- or second-line therapy for patients with type 2 diabetes and hypertension should include a regimen that includes an ACE-inhibitor or an ARB interchangeable with a thiazide diuretic in low dosages with adequate potassium replacement if not potassium sparing.12,13 Use of one of these agents affecting the RAAS is particularly important for patients with concurrent microalbuminuria as ACE-inhibitors and ARBs are associated with delaying the progression and worsening of microalbuminuria.12 The ability of α-blockers to suppress the RAAS is comparable to suppression observed with ACE-inhibitors but they are not associated with renal stimulation of renin secretion typically seen with ACE-inhibitors and ARBs.32

Results of the Heart Outcomes Prevention Evaluation (HOPE) study support the use of an ACE-inhibitor in high-risk patients, including those with type 2 diabetes, in order to reduce the risk of cardiovascular death, MI, and stroke.13 ACE-inhibition was also associated with vasoprotective and renoprotective benefits beyond those attributable to decreases in blood pressure.34 Importantly, the use of an ACE-inhibitor for 3 years in the setting of impaired fasting glucose or impaired glucose tolerance was associated with regression to normoglycemia but was not associated with a reduction in the incidence of type 2 diabetes or death.35

Table 1: Potential Cardiac Benefits of β-Blockade in Patients With Hypertension32, 36-38

<table>
<thead>
<tr>
<th>Benefits</th>
<th>ACE-inhibitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces cardiac events and mortality in patients with diabetes and CAD</td>
<td></td>
</tr>
<tr>
<td>Reverses cardiac remodeling</td>
<td></td>
</tr>
<tr>
<td>Reduces risk of cardiac rupture</td>
<td></td>
</tr>
<tr>
<td>Reduces shear stress and endothelial dysfunction</td>
<td></td>
</tr>
<tr>
<td>Provides RAAS suppression</td>
<td></td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; CV = cardiovascular; CAD = coronary artery disease; RAAS = renin-angiotensin-aldosterone system

Targeting the SNS

Antagonism of the SNS is an important therapeutic target in the treatment of hypertension and, in CHF patients, SNS blockade reduces morbidity and mortality by interfering with disease progression.36 The metabolic effects of the SNS are mediated by 3 adrenergic receptor subtypes (β1, β2, and α1) each with distinctly different properties.36 Nonselective (or first generation) β-blocking agents, such as propranolol, block both β1- and β2-receptors, whereas selective (second generation) β-blockers such as metoprolol, block only β1-receptors.36 Newer β-blocking agents (third generation) block β1-, β2-, and α1-receptors and provide vasodilating effects. β-blockers offer a variety of cardiovascular benefits to the patient with hypertension and these are displayed in Table 1.32,36-38

Despite cardiovascular benefits observed with SNS suppression, many clinicians are concerned about using traditional β-blockers when treating hypertensive patients with type 2 diabetes. These issues include the potential for increasing triglycerides, LDL-C, and total cholesterol; decreasing HDL-C; negative effects on glucose metabolism and renal blood flow, impotence, peripheral vasoconstriction, and also weight gain.39,40 In addition, β-blockade has the potential to cause hypoglycemia in patients requiring insulin, and may mask the symptoms of palpitations and shaking associated with low blood sugar.39 Selective β-blocking agents that block β1-receptors have also been associated with significant increases in glycosylated hemoglobin (A1C) in patients with high blood pressure without baseline blood glucose abnormalities.41

*SBP achieved in 3rd y of a 5-y study.

AASK = African American Study of Kidney Disease; ABCD = Appropriate Blood Pressure Control in Diabetes; ALLHAT = The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; HOT = Hypertension Optimal Treatment IDNT = Irbesartan Diabetic Nephropathy Trial; RENAAL = Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan; UKPDS = UK Prospective Diabetes Study Group

![Figure 2: Multiple Agents Are Required to Reach Blood Pressure Goals in High-Risk Hypertensive Patients](image-url)
Advantages of newer β-blocking agents

Newer β-blocking agents (third generation), such as carvedilol and labetalol (not available in the United States), block β₁- and β₂-receptors, and also have α₁-blocking capabilities which yield beneficial hemodynamic effects.⁴⁰ Since blockade of the α₁-receptor helps to mediate vasodilation, reduce peripheral load, and decrease peripheral insulin resistance,⁴²,⁴³ agents that block α- and β-receptors are preferable for patients with concurrent hypertension and type 2 diabetes.⁴²,⁴³,⁴⁰ Since these agents have vasodilating properties, the (β-blocker induced) decrease in cardiac output is not negated by a β-blocker induced increase in vasoconstriction and increased afterload.⁴⁰ Due to their vasodilating capabilities, these agents do not worsen ischemia or claudication distance in patients with peripheral vascular disease.⁴⁰

Additionally, this vasodilating effect may help type 2 diabetes patients achieve better glycemic control by improving glucose uptake into the skeletal muscles. This is evidenced by improvements in insulin sensitivity in nondiabetic hypertensive patients evaluated in a randomized, multicenter trial. After 3 months, the subjects taking carvedilol were observed to have improved insulin sensitivity whereas it worsened in those taking metoprolol tartrate (Figure 3).⁴²,⁴³

Vasculoprotective benefits of a newer β-blocker such as carvedilol are likely due to its complex pharmacologic profile.⁴⁴ Compared to traditional β-blocker therapy, the blockade of β₁-, β₂-, and α₁-receptors provides for better endothelium-dependent vasodilation.⁴⁴ The β-blocking activity of abetalol is about half that of carvedilol although carvedilol has fewer vasodilating side effects such as postural hypotension and impotence.⁴⁰ In addition, carvedilol has antioxidative and antiapoptotic properties that may play a role in improving free radical-induced endothelial dysfunction, reducing myocardial injury and infarct size after ischemia-reperfusion, and may alter the formation of atherosclerosis.⁴⁴ And, unlike traditional β-blockers, carvedilol suppresses norepinephrine release from the ischemic heart which is likely to contribute to antischismic, vasodynamic, and vasculoprotective effects of the drug.⁴⁴

In the Glycemic Effects in Diabetes Mellitus: Carvedilol Metoprolol Comparison in Hypertensives (GEMINI) study, patients with type 2 diabetes and hypertension were assigned to treatment with carvedilol or metoprolol tartrate plus conventional RAAS blockade.⁴⁵ Target blood pressure of <130/80 mm Hg was achieved in both treatment groups; however, compared to metoprolol, carvedilol was associated with stabilization of A1C, improved insulin resistance, and a slowing in the development of microalbuminuria (Figures 4A and 4B).⁴⁵ Carvedilol's beneficial effects on insulin resistance and A1C were similar whether or not patients were also on insulin-sensitizer (thiazolidinedione (TZD) or metformin) therapy.⁴⁶ In contrast, metoprolol tartrate was associated with worsened insulin sensitivity in nonusers of insulin-sensitizer therapy, a finding that was offset with concomitant administration of a TZD or metformin.⁴⁶
Diabetes, Hypertension, and Heart Failure

Diabetes, insulin resistance, hypertension, obesity, and dyslipidemia are risk factors for the development of heart failure. Approximately one-third of heart failure patients have concurrent type 2 diabetes which is associated with a significant increase in mortality in heart failure patients.42,47 In patients with type 2 diabetes, approximately 66% of deaths that occur post-MI during the first year are due to CHF.48 One large study49 observed that type 2 diabetes patients experienced heart failure at 2.5 times the rate of nondiabetes patients. Patients diagnosed with heart failure had a longer duration of type 2 diabetes at baseline and were more likely to have ischemic heart disease and more advanced renal disease. The relative rate of heart failure declined with increasing age.49

A meta-analysis of placebo controlled trials of β-blocker therapy with bisoprolol, bucindolol, carvedilol, or metoprolol tartrate in more than 13,000 patients with established heart failure, 25% of whom had concurrent type 2 diabetes mellitus, showed that patients (with and without type 2 diabetes) can reduce their mortality risk from therapy with a β-blocker.42 However, the benefit observed in type 2 diabetes patients was somewhat less than in nondiabetes patients. Another study of 5757 heart failure patients (25% with type 2 diabetes) treated with carvedilol, determined that the relative risk for all cause mortality with carvedilol was significantly lower for patients (with or without type 2 diabetes) compared with placebo (Figure 6).50 Carvedilol was also recently compared with metoprolol tartrate in patients who had stable chronic heart failure and left ventricular dysfunction and were treated with ACE-inhibition and diuretics over a period of 58 months.44 The investigators found that carvedilol reduces the risk for MI and cardiovascular death better than metoprolol tartrate.44

The American College of Cardiology (ACC) and AHA guidelines state that all patients with heart failure, regardless of type 2 diabetes status, should be prescribed β-blocker therapy unless contraindicated.44 β-blockers have been shown to reduce the risk of death and the combined risk of death or hospitalization in heart failure patients enrolled in clinical studies.47 Use of a β-blocker at discharge in patients hospitalized due to new onset or worsening heart failure is associated with significant reductions in all-cause mortality and mortality and/or rehospitalization at 60 to 90 days postdischarge.53

Challenges to Treatment

Even though challenges in the pharmacological treatment of high blood pressure exist, effective management of hypertension

Unfortunately, a vicious cycle between insulin resistance and heart failure exists wherein insulin resistance can lead to the progression of heart failure by stimulating the release of excess catecholamines.50 The myocardium is richly innervated by the SNS, and left ventricular dysfunction or heart failure stimulates catecholamine release in order to maintain cardiac output. This in effect increases insulin resistance in skeletal muscle which can progress to type 2 diabetes, and in the heart as well (Figure 5).51 Chronic activation of the SNS also increases myocardial oxygen and high energy phosphate consumption which further decompensates the failing heart.51 Moreover, chronic sympathetic activity in cardiomyopathy may trigger insulin resistance by increasing the circulating levels of nonesterified fatty acids (NEFA) thus altering the balance between glucose and NEFA oxidation in the failing heart.51 NEFA, associated with insulin and obesity, are believed to be cardiotoxic as are inflammatory cytokines (adipokines) secreted from fat.52
can be obtained\textsuperscript{54} and adherence to the prescribed drug regimen is a critical component of blood pressure control. Therefore it is unfortunate that nonadherence to medical management is commonly encountered in chronic diseases such as hypertension for which the perceived benefit of treatment is not readily apparent.\textsuperscript{54} It has been estimated that half of hypertensive patients with poor blood pressure control are actually taking <80\% of their prescribed regimen.\textsuperscript{54} Such noncompliance is clinically meaningful as significantly better blood pressure control has been shown to be associated with adherence rates \( \geq 80\% \) compared to patients with adherence rates of <50\%.\textsuperscript{54}

Tolerability is a primary influence on compliance with any treatment regimen, including antihypertensive therapy. The frequency of adverse events associated with a particular drug has been inversely correlated with adherence rates.\textsuperscript{54} Importantly in the treatment of hypertension which commonly requires the use of several pharmacological agents to achieve goal blood pressure levels, dosing frequency is also associated with compliance such that a reduction in dose frequency can lead to improved adherence.\textsuperscript{54}

**Conclusions**

The increasing incidence of cardiovascular risk factors in the population, including obesity, insulin resistance, type 2 diabetes, dyslipidemia, and hypertension, is one of our most challenging and important public health issues today. Sympathetic hyperactivity appears to be a critical component of the synergistic effect between these risk factors for increasing the risk of cardiovascular complications in patients with concurrent type 2 diabetes and hypertension. Therefore, management of hypertension in patients with type 2 diabetes should include agents with complementary mechanisms of action, such as RAAS blockade with an ACE-inhibitor or ARB and SNS blockade with a \( \beta \)-blocker. \( \beta \)-blocker therapy provides clinical benefits in patients with multiple comorbidities, such as type 2 diabetes and hypertension; however, different members within the \( \beta \)-blocker class exert different effects. Newer vasodilating \( \beta \)-blocking drugs offer blockade of the \( \beta_1 \)-, \( \beta_2 \)-, and \( \alpha_1 \)-receptors and provide differential therapeutic benefit and improvement in multiple cardiovascular risk factors as compared with traditional \( \beta \)-blockers.

The importance of secondary prevention has also been addressed in guidelines created by the AHA and the ACC for patients with coronary and other atherosclerotic vascular diseases (Table 2).\textsuperscript{55} These strategies include lifestyle modifications (smoking cessation, physical activity, and weight management) as well as with pharmacological therapy.\textsuperscript{55} Specific pharmacological therapy recommended by the ACC/AHA includes anticoagulation with aspirin, blockade of the RAAS with ACE inhibitors or ARBs, manipulation of the SNS with \( \beta \)-blockers, and influenza vaccination.\textsuperscript{55}

**Table 2:**

<table>
<thead>
<tr>
<th>Vascular-protective / Cardioprotective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin or clopidogrel</td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
</tr>
<tr>
<td>( \beta )-blocker</td>
</tr>
<tr>
<td>Statin</td>
</tr>
<tr>
<td>Hemodynamic</td>
</tr>
<tr>
<td>Blood pressure control</td>
</tr>
<tr>
<td>Metabolic</td>
</tr>
<tr>
<td>Blood sugar control</td>
</tr>
<tr>
<td>Lipid control</td>
</tr>
<tr>
<td>Weight control</td>
</tr>
</tbody>
</table>

Overall, every effort should be made to reduce the significant economic and public health burden associated with CVD in patients with hypertension and insulin resistance. Patients with untreated cardiovascular risk factors may progress along the CVD continuum and eventually experience tissue injury, pathological remodeling, target organ damage, end-organ failure, and premature death. Therefore, risk factor modification is essential for proper management and control of these disorders. The attainment of blood pressure goals of \( \leq 130/80 \) mm Hg, or \( \leq 120/75 \) mm Hg in the presence of severe proteinuria, typically requires intensive behavioral modification in addition to combination pharmacotherapy for the patient with hypertension and insulin resistance.