Reexamining Misconceptions About β-Blockers in Patients With Diabetes

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Type 2 diabetes and hypertension are two of the most common contributors to cardiovascular disease (CVD) in the United States. Diabetes is estimated to affect 7% of the U.S. population—a total of 21 million individuals. In many patients, diabetes is asymptomatic, and as many as one-third of diabetic individuals are unaware that they have the disorder.[1] Hypertension, defined as blood pressure > 140/90 mmHg, affects one-third of Americans— an estimated 72 million people.[1] Hypertension is a common comorbid condition of diabetes, affecting ~ 20–60% of patients with diabetes, depending on ethnicity, age, and obesity.[2] More than 3 million Americans have both conditions.[3]

Along with cardiovascular complications, hypertension in patients with diabetes contributes to increased risk of end-stage renal disease and diabetic retinopathy.[3,4] In patients with comorbid hypertension and diabetes, intensive pharmacological treatment to reach blood pressure goals may be even more important in reducing cardiovascular risk than blood glucose control.[4] The high CVD risk in patients with diabetes necessitates more aggressive blood pressure targets.[5,6] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recommends that blood pressure in diabetic patients be controlled to levels ≤ 130/80 mmHg.[6] The U.K. Prospective Diabetes Study and the Hypertension Optimal Treatment trial both demonstrated that tight blood pressure control (< 130/85 mmHg) resulted in improved outcomes, including prevention of death and stroke and also prevention of microvascular complications.[7,8] Although tight blood glucose control decreases the frequency of microvascular complications such as retinopathy and nephropathy, it has not been shown to reduce diabetes-related mortality or the incidence of myocardial infarction (MI).[9]

IN BRIEF

Because effectively managing patients with diabetes and hypertension requires multiple medications, the appropriate selection of a treatment regimen with good tolerability and simplified dosing is crucial. Despite the proven benefits of β-blockers in lowering blood pressure and improving cardiovascular morbidity, many physicians are reluctant to prescribe them to patients with diabetes and hypertension. This reluctance is based on the misconception that β-blockers worsen glycemic control, insulin sensitivity, and dyslipidemia and mask hypoglycemia. Unlike traditional β-blockers, vasodilatory β-blockers have favorable tolerability and metabolic profiles while offering effective blood pressure control.

Treatment of Hypertension in People With Diabetes

Patients with diabetes and hypertension have a > 20% 10-year risk of developing coronary heart disease,[10] the single greatest killer of American adults.[1] Both hypertension and diabetes are considered preclinical or Stage A heart failure that, if left untreated, can progress to structural heart failure (Figure 1).[11] The potential for complications associated with hypertension in patients with diabetes emphasizes the need for appropriate and aggressive therapy.

The JNC-7 recommends the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), low-dose thiazide diuretics, calcium channel blockers (CCBs), and β-blockers for first-line treatment of hypertension in patients with compelling indications, including diabetes (Figure 2).[6] These recommendations are based on randomized clinical trials using a variety of antihypertensive agents that have shown that even a modest reduction in systolic blood pressure of 9–11 mmHg and diastolic blood pressure of 2–9 mmHg decreases cardiovascular events by 34–69% and the microvascular complications of retinopathy or nephropathy by 13% within 2–5 years.[7,8,12,13] National guidelines recommend β-blockers as a preferred therapy for the control of hypertension in patients with

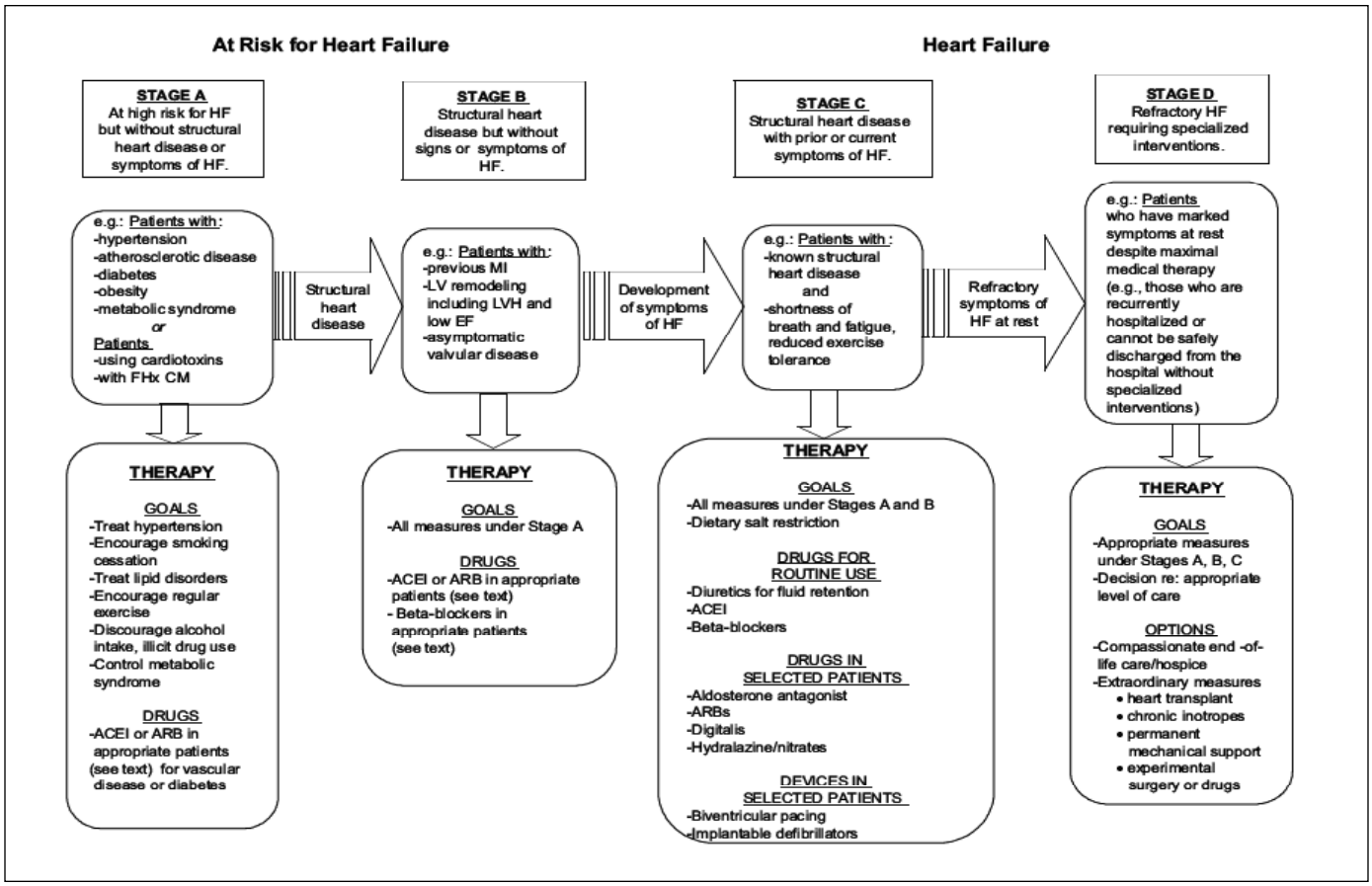

Figure 1. Stages in the development of heart failure and recommended therapy by stage. EF, ejection fraction; HF, heart failure; FHx CM, family history of cardiomyopathy; LV, left ventricle; LVH, left ventricular hypertrophy. Reprinted with permission from Ref. 11. © 2005 American Heart Association.ACEI, ACE inhibitor

diabetes, heart failure, or high coronary heart disease risk or after MI because of the benefits and proven mortality risk reduction in these high-risk groups (Table 1).[6]

Based on current evidence, the American Association of Clinical Endocrinologists (AACE) has also proposed guidelines for the treatment of hypertension in patients with diabetes.[5] Because ACE inhibitors and ARBs are associated with favorable effects on renal function and may improve insulin sensitivity, AACE recommends these agents as first-line therapy in the treatment of hypertension in diabetic patients. AACE recommends the use of diuretics in the lowest effective dosage (in conjunction with potassium replacement or the addition of a potassium-sparing agent) because thiazide diuretics can worsen blood glucose control and increase the likelihood of development of diabetes in individuals with insulin resistance.[5]

In recognition that β-blockers as a class may precipitate or exacerbate type 2 diabetes, these antihypertensive agents are not preferred as first-line agents for the treatment of hypertension in patients with diabetes. However, because β-blockers are effective in the management of ischemic and congestive cardiomyopathies—common cardiovascular complications of diabetes—AACE recommends the preferential use of third-generation β-blockers (e.g., nebivolol and carvedilol) as second- or third-line agents in this high-risk patient population (Table 2).[5]

Benefits of β-Blockers

This class of antihypertensive drugs has anti-ischemic as well as anti-atherogenic and anti-arrhythmic properties.[14,15] These actions are important because both hypertension and diabetes cause cardiac injury that can subsequently activate the renin-angiotensin and sympathetic nervous systems and lead to myocardial remodeling and disease progression. β-Blockers with anti-atherogenic properties can reduce inflammation, shear stress, endothelial dysfunction, and the risk of plaque rupture; the anti-arrhythmic properties result from decreased sympathetic and

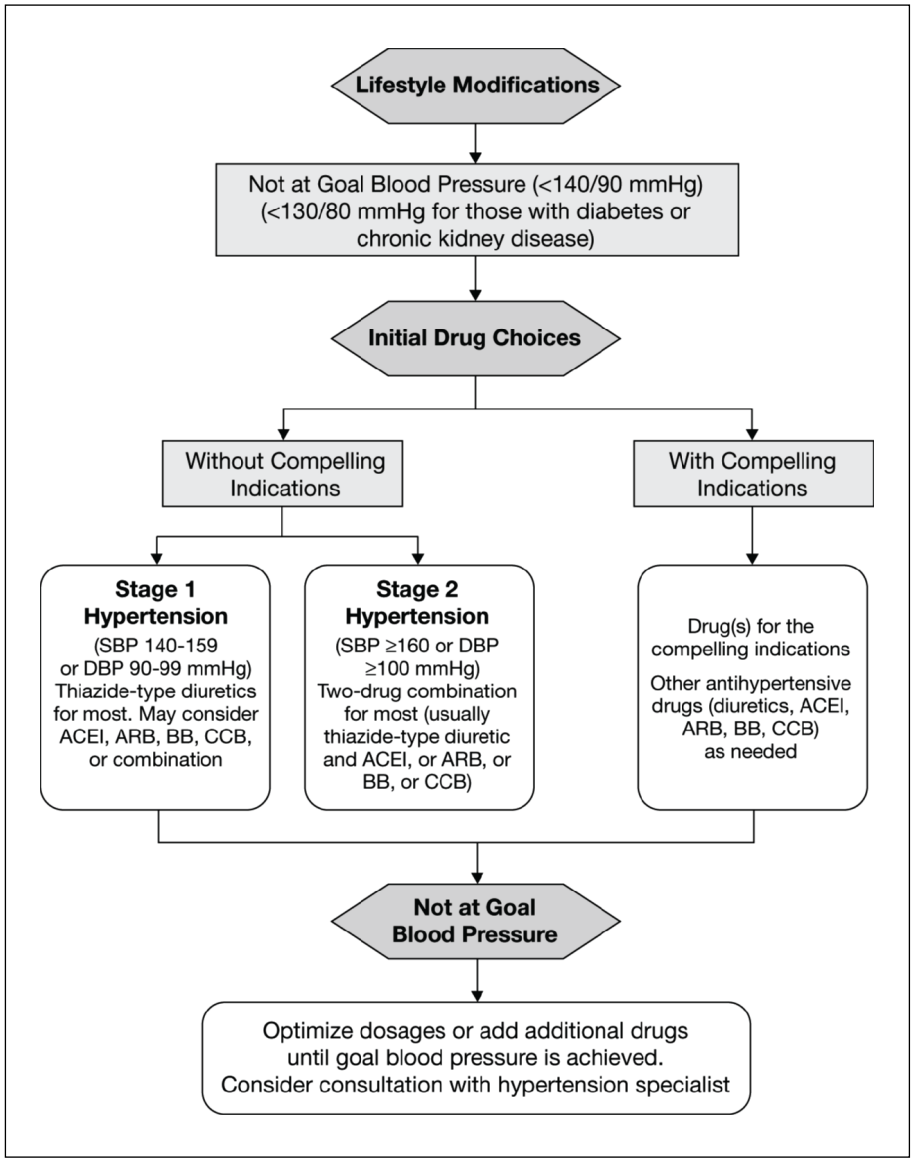

Figure 2. Algorithm for the treatment of hypertension. BB, β-blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure. Reprinted with permission from Ref. 6. © 2003 American Heart Association. ACEI, ACE inhibitor

heart rate activity and increased cardiac vagal tone.[14,15] Considering the detrimental effects of diabetes and hypertension on the myocardium, the beneficial effects of β-blockers beyond blood pressure lowering alone should not be overlooked.

Perceived Negative Metabolic Effects of β-Blockers

Despite the proven benefits of β-blockers in lowering blood pressure and improving cardiovascular morbidity and mortality in clinical heart failure and post-MI trials, many physicians have been reluctant to prescribe β-blockers to patients with diabetes and hypertension. This reluctance is caused by perceived negative metabolic effects of β-blockers, including worsening of glycemic control, insulin sensitivity, and dyslipidemia and masking of hypoglycemia.[16,17]

Evidence suggests that there are differential effects of β-blockers. The first-generation β-blockers (e.g., propranolol) are nonspecific and thus block both β_1- and β_2-adrenergic receptors. The second generation β-blockers (e.g., atenolol and metoprolol) are β_1-selective. Third-generation β-blockers (e.g., carvedilol and nebivolol) offer additional benefits. Carvedilol is a nonselective β-blocker with vasodilatory activity mediated by α_1-adrenergic receptor blockade. Nebivolol is a β_1-selective blocker that also has vasodilatory properties believed to be a result of stimulation of nitric oxide release.

Many of the negative perceptions surrounding the use of β-blockers in diabetic patients involve traditional (i.e., first- and second-generation) β-blockers. Studies have shown that nonselective propranolol,[18] β_1-selective atenolol,[19] and metoprolol[20] significantly decrease insulin sensitivity in patients with hypertension.

Common Misconceptions About Glycemic Control and Lipids

The Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation study found that antihypertensive treatment with a low-dose diuretic (hydrochlorothiazide) combined with atenolol (if needed to reach blood pressure control) was associated with negative metabolic effects compared with treatment with an ARB (candesartan), combined with a CCB (felodipine) if needed.[21] Both treatment regimens lowered blood pressure, with the majority of patients requiring two-drug therapy. Fasting levels of serum insulin and plasma glucose, as well as LDL/HDL and apolipoprotein B/apolipoprotein A-I ratios increased in the diuretic and atenolol group in contrast to no change in the ARB and CCB group. In addition, at 12 months of treat-

Table 1. Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes

High-Risk Condition With Compelling Indication*	Thiazide-Type Diuretics	β-Blockers	ACE Inhibitors	ARBs	CCBs	Aldosterone Antagonist	Guideline and/or Clinical Trial Basis†
Heart failure	●	●	●	●		●	ACC/AHA Heart Failure guidelines, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES, CHARM
Post-MI		●	●			●	ACA/AHA Post-MI guidelines, BHAT, SAVE, Capricorn, EPHESUS
High coronary disease risk	●	●	●		●		ALLHAT, HOPE, ANBP2, LIFE, CONVINCE, EUROPA, INVEST
Diabetes	●	●	●	●	●		NKF-ADA guidelines, UKPDS, ALLHAT
Chronic kidney disease			●	●			NKF guidelines, Captopril Trial, RENAAL, IDNT, REIN, AASK
Recurrent stroke prevention	●		●				PROGRESS

AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; AIRE, Acute Infarction Ramipril Efficacy; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study; BHAT, Beta-Blocker Heart Attack Trial; CHARM, Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONVINCE, Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints; COPERNICUS, CarvedilOl PropspEctive RaNdomIzed CUmulative Survival; EPHESUS, Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EUROPA, EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease; HOPE, Heart Outcomes Prevention Evaluation; IDNT, Irbesartan Diabetic Nephropathy Trial; INVEST, INternational VErapamil/trandolapril Study; LIFE, Losartan Intervention For Endpoint reduction; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Heart Failure; NKF-ADA, National Kidney Foundation–American Diabetes Association; PROGRESS, Peridopril Protection against Recurrent Stroke Study; RALES, Randomized Aldosterone Evaluation Study; REIN, Ramipril Efficacy in Nephropathy Study; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study; SAVE, Survival and Ventricular Enlargement: Capricorn, Carvedilol Post Infarct Survival Control in LV Dysfunction; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, TRAndolapril Cardiac Evaluation; UKPDS, U.K. Prospective Diabetes Study; ValHEFT, Valsartan Heart Failure Trial.

**Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.*

†Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve blood pressure goal to test outcomes.

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ment, eight patients (4.1%) in the diuretic and atenolol group versus 1 patient (0.5%) in the ARB and CCB group were diagnosed with new-onset diabetes ($P = 0.030$).[21]

Atenolol's unfavorable metabolic effects may have a negative impact on prevention of cardiovascular events.[22] A meta-analysis of trials with atenolol in patients with hypertension revealed that there were no discernible differences between atenolol or placebo in the reduction of all-cause mortality (1.01 [95% CI 0.89–1.15]), cardiovascular mortality (0.99 [0.83–1.18]), or MI (0.99 [0.83–1.19]), despite the fact that 60% of patients were treated with an additional antihypertensive agent.[19] More conclusively, the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm showed that atenolol treatment resulted in significantly worse outcomes, including cardiovascular events and procedures ($P < 0.001$), cardiovascular mortality ($P = 0.001$), and all-cause mortality ($P = 0.0247$), as well as the development of diabetes ($P < 0.0001$) when compared

Table 2. AACE Evidence-Based Recommendations for Management of Hypertension and Concomitant Type 2 Diabetes

Recommendation	Highest Level of Evidence
Goal blood pressure ≤ 130/80 mmHg	2*
Goal blood pressure ≤ 125/75 mmHg when severe proteinuria exists	1*
ACE inhibitor or ARB as first- or second-line agent	1*
Thiazide diuretic as first- or second-line agent (in low dosage with adequate potassium replacement or sparing)	1*
β-Blockers (preferably drugs that block both the α and β receptors) as second- or third-line agent	1*
CCB (preferably nondihydropyridine) as second-, third-, or fourth-line agent	1*

The AACE hypertension guidelines have the following criteria for determining levels of evidence: Level 1 = well-controlled, generalizable, randomized trial; adequately powered; well-controlled multicenter trial; large meta-analysis with quality ratings; all-or-none evidence. Level 2 = randomized controlled trial, limited body of data; well-conducted prospective cohort study; well-conducted meta-analysis of cohort studies.

**AACE recommendation of grade A. The AACE determination of a grade A recommendation is based on the following criteria: homogeneous evidence from multiple well-designed randomized controlled trials with sufficient statistical power; homogeneous evidence from multiple well-designed cohort-controlled trials with sufficient statistical power; ≥ 1 conclusive level-1 publications demonstrating benefit >> risk.*

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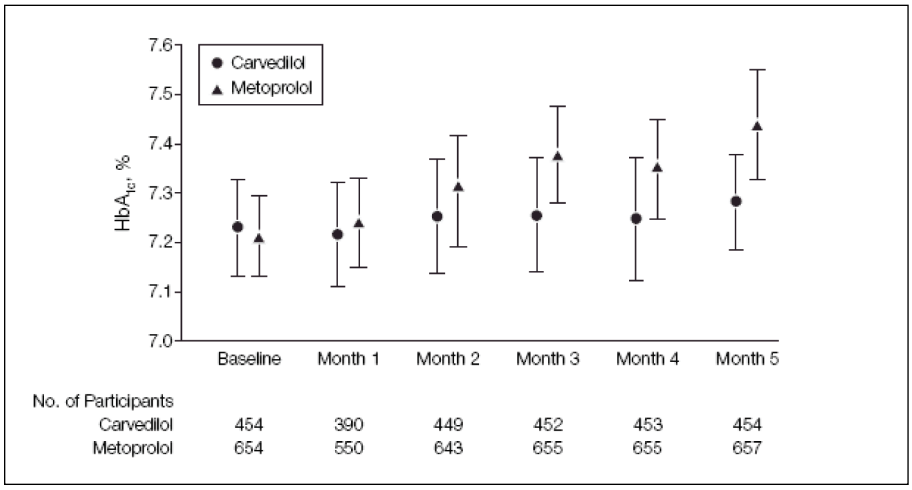

Figure 3. A1C at baseline and each maintenance month by treatment in the GEMINI trial, including the modified intention-to-treat population. The change from baseline to maintenance month 5 (primary outcome) was significant (mean difference [SD], 0.13% [0.05%]; 95% CI –0.22 to –0.04%; P = *0.004). Error bars indicate SD from mean. Reprinted with permission from Ref. 26. © 2004 American Medical Association*

with the CCB amlodipine. A total of 19,257 patients with hypertension were treated an average of 5.5 years.[23]

The vasodilatory β-blockers (e.g., nebivolol and carvedilol) have demonstrated a more favorable metabolic profile with respect to glycemic control and lipids.[24,25] To assess the effect of nebivolol on metabolic parameters, a study randomized 30 patients with hypertension and hyperlipidemia to either atenolol or nebivolol.[25] After 12 weeks of either β-blocker therapy, pravastatin was added for an additional 12 weeks of treatment. Atenolol significantly increased triglyceride levels by 19% ($P = 0.05$) and significantly increased lipoprotein(a) by 30% ($P = 0.028$), whereas nebivolol did not produce significant changes in either parameter. Glucose levels remained the same in the nebivolol-treated patients, while insulin levels were reduced by 10%, and insulin resistance was reduced by 20% ($P = .05$).[25] These parameters were not significantly changed in the atenolol-treated patients. There was also no significant difference in these parameters between the atenolol and nebivolol treatment groups except for insulin-resistance reduction (0 vs. –20%, respectively; $P = 0.05$).[25]

Carvedilol has been uniquely shown to improve the common negative metabolic effects associated with the use of first- and second-generation β-blockers.[24,26] The addition of the α_1-blocking properties of carvedilol, which interfere with vasoconstriction, are theorized to increase blood flow to skeletal muscles, thereby improving metabolic parameters.[27] Beneficial metabolic effects of carvedilol were demonstrated in a comparison study of metoprolol and carvedilol in the treatment of hypertension in nondiabetic patients with impaired insulin sensitivity.[20] Both antihypertensive

agents effectively lowered blood pressure. However, after metoprolol treatment, insulin sensitivity decreased, whereas it increased after carvedilol treatment. There was also a decrease in high-density lipoprotein and an increase in triglyceride levels in patients in the metoprolol-treated group; however, these parameters remained unchanged in patients in the carvedilol-treated group. These findings suggest that β-blocker treatment, when combined with α_1-blocking activity, has advantageous effects on insulin sensitivity and lipids and could therefore be suitable for patients with impaired metabolic function.

Results from the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial elucidated important treatment differences between the β-blockers carvedilol and metoprolol tartrate.[26] Among 1,235 patients with diabetes and hypertension, carvedilol stabilized A1C (Figure 3)[26] and improved insulin resistance (HOMA index) and cholesterol. In contrast, metoprolol tartrate worsened glycemic and cholesterol control. Moreover, more patients treated with metoprolol withdrew because of worsening glycemic control compared with carvedilol-treated patients.

The results of the GEMINI trial support earlier studies demonstrating that metoprolol has a negative glycemic effect.[28–30] A study of patients with essential hypertension revealed that, after 6 months of treatment, once-daily metoprolol succinate did not affect fasting plasma glucose but increased A1C levels by 5% compared to baseline levels ($P = 0.04$).[28] This effect is of importance because an A1C reduction of as little as 0.1% was associated with 12% mortality risk reduction in the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition.[29] Other studies have also found that each 1-percentage point decrease in A1C significantly reduced the risk of mortality, heart failure, and MI in patients with diabetes and hypertension.[30,31]

A further substudy of the GEMINI trial demonstrated that carvedilol and metoprolol tartrate treatment produced statistically significant differences in diabetes symptom scores.[32] In the Diabetes Symptom Checklist, a decrease in score indicates symptom improvement. Compared to baseline and to metoprolol tartrate, carvedilol improved overall symptom score (–0.08 [$P = 0.008$] and –0.08 [$P = 0.02$], respectively), hypoglycemia score (–0.12 [$P = 0.013$] and –0.12 [$P = 0.02$], respectively), and hyperglycemia score (–0.2 [$P = 0.0001$] and –0.16 [$P = 0.005$], respectively). Metoprolol tartrate treatment did not significantly improve these parameters and was associated with a worse psychological fatigue score compared with baseline levels (0.15 [$P = 0.006$]).[32]

Common Misconceptions About Microalbuminuria

Microalbuminuria (defined as urine albumin:creatinine ratio of 30–300 mg/g) is often the first clinical sign of renal dysfunction in patients with diabetes and is a recognized marker of cardiovascular risk and increased cardiovascular morbidity and mortality. A GEMINI substudy demonstrated that carvedilol treatment resulted in more favorable effects on microalbuminuria than metoprolol tartrate treatment.[33] In GEMINI, 25% of patients had microalbuminuria. Carvedilol treatment resulted in a 16% relative reduction in the albumin:creatinine ratio (95% CI 6–25%; $P = 0.003$), and significantly fewer carvedilol-treated patients with normoalbuminuria (< 30 mg/g) progressed to microalbuminuria (6.6 vs. 11.1%; odds ratio [OR] 0.53; 95% CI 0.30–0.93; $P = 0.03$) compared to metoprolol tartrate treatment.[33]

Common Misconceptions About Hypoglycemia

Hypoglycemia is a serious condition that may lead to confusion, irrationality, and in its most severe form, coma, seizure, and even sudden death.[34] Theoretically, β-blockers could increase the risk of severe hypoglycemia by masking the adrenergic warning symptoms of hypoglycemia, including weakness, shakiness, sweating, pallor, and palpitations.[35] Clinical evidence suggests that there may be a relationship of specific antihypertensives to the development of hypoglycemia.[36]

A case-control study that used 1993 Medicaid data evaluated the relative risk of hypoglycemia in a cohort of patients treated for diabetes.[36] The study cohort was divided into patients for whom the physician reported hypoglycemia (using ICD-9 codes) and diabetic control subjects without hypoglycemia. Exposure to specific antihypertensive drugs, including ACE inhibitors, β-blockers, and diuretics, was assessed in the two groups. A principal finding of the study was that, although use of ACE inhibitors as a class was not associated with an increased risk of hypoglycemia, a significantly increased risk was associated with the specific use of enalapril (OR 2.7; 95% CI 1.2–5.7). The lack of class effect of ACE inhibitors on hypoglycemia and the selective association of enalapril with hypoglycemia risk were consistent with earlier reports.[37–40] In contrast, β-blockers were not associated with increased risk of hypoglycemia in either insulin or sulfonylurea users.

A thorough review of the literature concluded that, although adverse effects of β_2-selective blockers on glucose metabolism are recognized, there is no evidence to withhold β_1-selective blocking agents from diabetic patients because these agents are not associated with an increased risk of severe hypoglycemia.[41]

This is especially important in light of the life-threatening consequences of hypoglycemia. Hypoglycemia produces electrocardiographic QTc interval lengthening that may play a pathogenic role in the occurrence of sudden death. Case reports have highlighted the occurrence of sudden overnight death among young patients with type 1 diabetes.[42–46]

It has been suggested that patients with type 1 diabetes with cardiac autonomic neuropathy have a greater risk of sudden death.[47] A study that used an experimental model of hypoglycemia to test this theory in 28 patients with diabetes with and without cardiac autonomic neuropathy refuted the hypothesis.[48] Participants with cardiac autonomic neuropathy tended to exhibit the smallest QTc increases, suggesting that autonomic neuropathy is not an important risk factor for sudden death from hypoglycemia. A subsequent study of eight diabetic patients who had shown QTc lengthening during experimental hypoglycemia found that atenolol, a β_1-blocking agent, significantly reduced hypoglycemic QTc lengthening.[49]

Hypoglycemia is common in type 1 diabetes and is likely to occur more frequently in those who have tighter glycemic control. The potential effect of β-blockers on prevention of sudden death in diabetic patients warrants further investigation.

Common Misconceptions About Weight Gain

β-Blockers, in general, are associated with weight gain, which in turn reduces insulin sensitivity. However, weight gain is not a class effect of β-blockers. An analysis of the GEMINI trial showed that there was a statistically significant difference in weight gain between carvedilol- and metoprolol-treated patients.[49] Compared with baseline, patients taking metoprolol experienced a significant mean weight gain (1.2 ± 0.16 kg; $P < 0.001$), whereas patients taking carvedilol did not (0.17 ± 0.19 kg; $P = 0.36$). Compared with metoprolol-treated patients, carvedilol-treated patients were more likely to experience no weight change (44 vs. 35%; $P = 0.005$) and less likely to experience a weight gain of > 7% (1.1 vs. 4.5%; $P = 0.006$).[49]

Adherence to Guideline-Recommended Medical Care

Current American Diabetes Association (ADA) standards of medical care for patients with diabetes use a mnemonic device (ABC) designed to remind health care providers and patients of the three clinical issues—A1C, blood pressure, and cholesterol— that must be addressed to minimize the vascular complications of diabetes, including MI, stroke, and peripheral vascular disease.[50]

Despite these guidelines, control of these clinical issues is inadequate in the community setting. Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2002 showed that 44% of diabetic patients achieved optimal glycemic control (A1C < 7%).[51] Moreover, only 35% of diabetic patients achieved optimal blood pressure goals (< 130/80 mmHg) in the 2003–2004 NHANES.[52] Blood pressure control, in general, is poor in patients with essential hypertension. Among adults with hypertension, 76% are aware of their disease, 65% are prescribed antihypertensives, and 37% achieve blood pressure goals.[53]

Polypharmacy is the natural consequence of providing guideline-recommended medical care to patients with diabetes.[54] Varying combinations of antiglycemic medications are often necessary to correct abnormally elevated levels of blood glucose in patients with diabetes, including insulin therapy and medications to increase insulin production, to decrease glucose production by the liver, and to decrease carbohydrate absorption. In addition, hypertension management guidelines acknowledge that most patients, especially those with comorbid diabetes, require a combination of antihypertensive agents from different classes to reach blood pressure targets (< 130/80 mmHg).[6] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) found that > 40% of individuals required multiple drug therapy (addition of ACE inhibitors, or CCB, or diuretic) to control blood pressure.[55]

Hyperlipidemia is a common comorbid condition among patients with diabetes and hypertension. A study of 371,221 outpatients at six Veterans Health Administration medical centers found that 30.7% had hypertension and dyslipidemia, and 66.3% had concomitant hypertension, dyslipidemia, and diabetes.[56] If optimal lipid control cannot be achieved with lifestyle modifications, statins or fibrates may be prescribed.[57] The presence of other comorbid conditions (e.g., renal disease or ischemic heart disease) compounds the polypharmacy necessary to reach optimal disease control.

In addition to complex medication regimens, side effects,

inconvenience of dosing, and lack of perception of treatment benefit of an asymptomatic condition (e.g., hypertension) can negatively affect a patient's compliance with a treatment regimen. Physician reluctance to prescribe guideline-supported medications can also play a role in suboptimal disease management.

In a community study of 128 diabetic patients, in the week before the study, patients reported taking a mean of four diabetes-related medicines and a total mean of six different medications daily for diabetes and concomitant conditions: glycemic control (87%), hypertension (80%), and dyslipidemia (57%).[54] Despite good adherence to diabetes-related medicines, compliance with other medications was suboptimal in the previous week. The most frequent reasons for noncompliance were side effects (58%) and difficulty remembering to take all medications (23%). Of note, only 23% of patients reported the occurrence of side effects to their physicians. Not surprisingly, self-reported adherence rates for medications that caused side effects were significantly lower (5.4 vs. 6.9 out of 7 days; $P < 0.001$). Patients with negative perceptions of the immediate and future benefit of prescribed medications also had lower 7-day adherence rates ($P < 0.001$).

Adverse effects from antihypertensive treatment vary by drug class.[58] A general practice survey of patients who used antihypertensive medications showed that, when side effects for each drug were compared with the pooled average incidences of other antihypertensive agents, ACE inhibitors were associated with the highest incidence of dry cough (28 vs. 8%, respectively; $P < 0.001$); CCBs were associated with the highest incidence of peripheral edema (22 vs. 12%, respectively; $P < 0.001$); and β-blockers were associated with the highest incidence of sexual dysfunction (17 vs. 10%, respectively; $P < 0.01$).[59]

The occurrence of adverse side effects can lead to medication nonadherence and negatively affect treatment outcomes. When multidosed drugs with short durations of action are taken inconsistently, blood pressure control can be compromised. Reintroduction of drugs after inconsistent use can lead to excessive side effects.[60]

Simplifying treatment regimens by using once-daily dosing and combination drugs may improve adherence. A review of studies that measured medication compliance confirmed that the prescribed number of doses per day is inversely related to compliance. Simpler regimens involving less frequent dosing resulted in better compliance across a variety of therapeutic classes.[61] Compliance is better in patients on once-daily medications (79%) than in patients on multiple-dosing regimens (twice daily, 69%; three times daily, 65%; four times daily, 51%). Not surprisingly, forgetfulness is cited as one of the most important reasons for noncompliance (30%).[62,63]

Another issue that may lead to adverse consequences is patient reluctance to tell their physician that they miss medication doses.[64] Physicians may increase dosage or add medications to the treatment regimen of patients whose inadequate therapeutic response is actually a result of nonadherence to the prescribed medications. Physicians must take a proactive approach and stress the benefits of complying with medications for both short- and long-term benefit in lieu of waiting for their patients to approach them with concerns.

The poor rate of hypertension control in both diabetic and nondiabetic patients may also reflect inadequate prescription of evidence-based medications to control comorbid conditions. In a retrospective cohort study of 3,998 diabetic patients with ischemic heart disease, > 80% of patients received two cardioprotective medications (ACE inhibitor, β-blocker, or statin) despite high levels of concomitant disease, including hypertension (90%), hyperlipidemia (> 80%), heart failure (> 34%), or post-MI (~ 50%).[65] Even fewer patients (< 40%) received all three lifesaving therapies. Not surprisingly, < 50% of these patients had control of blood pressure or A1C regardless of whether they adhered to medication.

Role of β-Blockers in the Therapeutic Management of Patients With Comorbid Diabetes

Proper selection of treatment regimen plays a key role in optimizing patient outcomes and quality of life. Patients with diabetes who have had an MI or have hypertension, heart failure, or coronary artery disease face a real and increased risk of morbidity and mortality that should be countered with appropriate management using evidence-based lifesaving treatments. β-Blockers are indicated not only for the treatment of patients with hypertension, heart failure, or who are post-MI, but also for the treatment of hypertension in patients with diabetes. Because of the prevalence of comorbid hypertension in diabetic patients, physicians must be careful to prescribe a β-blocker that does not complicate a patient's existing medication regimen and has the most favorable side-effect profile to prevent patient noncompliance.

The once-daily formulation of extended-release carvedilol phosphate (carvedilol CR) allows for consideration of a new treatment paradigm that can help overcome barriers to adherence. The GEMINI study demonstrated that carvedilol lowers blood pressure while pro-

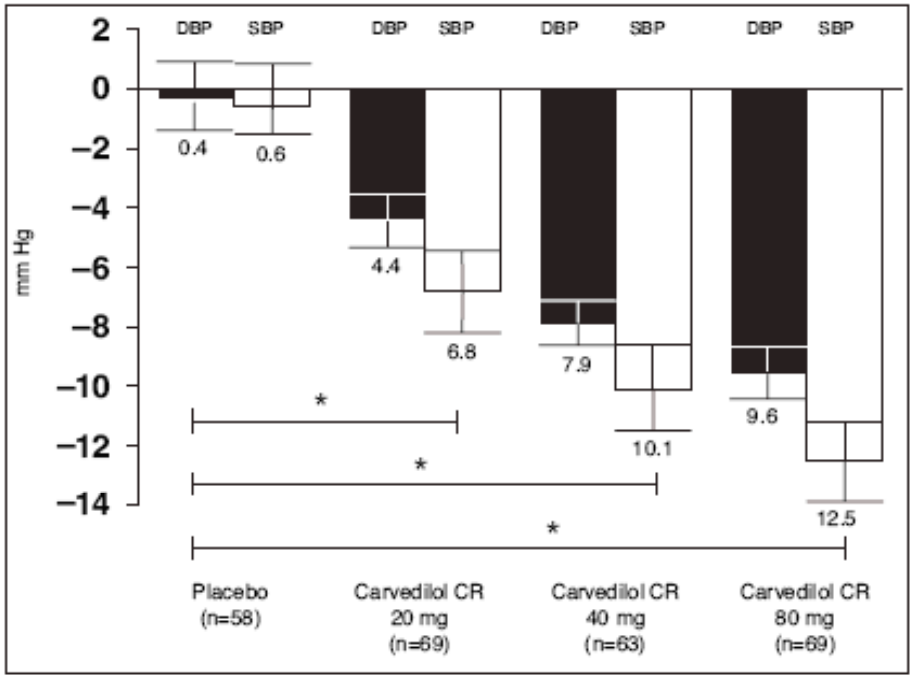

Figure 4. Effects of placebo or carvedilol CR on 24-hour mean systolic blood pressure and diastolic blood pressure obtained by ambulatory monitoring in hypertensive patients after 6 weeks of treatment. Values shown are ± SE. SBP inferences are based on an ad hoc analysis. *P ≤ *0.001 for dose-related trend tests for change from baseline in mean diastolic and systolic blood pressure for all carvedilol CR doses with placebo. DBP, diastolic blood pressure; SBP, systolic blood pressure. Reprinted with permission from Ref. 66.*

viding beneficial metabolic effects compared to metoprolol therapy.[26] Carvedilol CR has shown efficacy in significantly lowering blood pressure in a double-blind, randomized trial involving 338 patients.[66] All three doses of carvedilol CR treatment significantly decreased diastolic and systolic blood pressure by study end compared with placebo (Figure 4).[66] Adverse event findings were similar in the placebo and carvedilol CR groups for headache, fatigue, dizziness, and erectile dysfunction.[66,67] The convenience of once-daily dosing combined with a low adverse event profile is a key strategy to improve medication adherence in patients with hypertension and diabetes.

Summary

Diabetes is increasing in the United States as the population ages, becomes less active, and grows more obese, and the prevalence is expected to double in the next 25 years.[68] Diabetes and hypertension frequently coexist, affecting > 3 million adults in the United States.[2] Hypertension in patients with diabetes must be treated aggressively to reduce the risk of macrovascular and microvascular morbidity and mortality.

Because of their intrinsic high CVD risk, patients with diabetes have a more stringent blood pressure target (< 130/80 mmHg) than nondiabetic patients. National guidelines recommend β-blockers among preferred therapies for control of blood pressure in patients with diabetes.[5,6] When more than one drug is necessary to reach blood pressure goals, combinations of antihypertensives of different classes (e.g., a β-blocker and an ACE inhibitor or diuretic) provide complementary actions.

Because of the need for multiple medications to effectively manage patients with diabetes and hypertension, the appropriate selection of a treatment regimen with good tolerability and simplified dosing is crucial to maximize positive outcomes in this high-risk population. Unlike traditional β-blockers, vasodilatory β-blockers have favorable tolerability and metabolic profiles, while offering effective blood pressure control.

REFERENCES

[1]Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y: Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 115:e69–e171, 2007

[2]Arauz-Pacheco C, Parrott MA, Raskin P: Treatment of hypertension in adults with diabetes. *Diabetes Care* 26 (Suppl. 1):S80–S82, 2003

[3]Makrilakis K, Bakris G: Diabetic hypertensive patients: improving their prognosis. *J Cardiovasc Pharmacol* 31 (Suppl. 2):S34–S40, 1998

[4]National High Blood Pressure Education Program Working Group Report on Hypertension in Diabetes. *Hypertension* 23:145–158; discussion 159–160, 1994

[5]AACE Hypertension Task Force: American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Hypertension. *Endocr Pract* 12:193–222, 2006

[6]Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 42:1206–1252, 2003

[7]U.K. Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 317:703–713, 1998

[8]Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 351:1755–1762, 1998

[9]U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with

sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998

[10]Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001

[11]Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B: ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation. Endorsed by the Heart Rhythm Society. *Circulation* 112:e154–e235, 2005

[12]Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J: Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension: Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 276:1886–1892, 1996

[13]Tuomilehto J, Rastenyte D, Birkenhager WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R: Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med* 340:677–684, 1999

[14]Fonarow GC: Role of in-hospital initiation of carvedilol to improve treatment rates and clinical outcomes. *Am J Cardiol* 93:77B–81B, 2004

[15]Tse WY, Kendall M: Is there a role for beta-blockers in hypertensive diabetic patients? *Diabet Med* 11:137–144, 1994

[16]Bell DS: Optimizing treatment of diabetes and cardiovascular disease with combined alpha,beta-blockade. *Curr Med Res Opin* 21:1191–1200, 2005

[17]Ekbom T, Dahlof B, Hansson L, Lindholm LH, Schersten B, Wester PO: Antihypertensive efficacy and side effects of three beta-blockers and a diuretic in elderly hypertensives: a report from the STOP-Hypertension study. *J Hypertens* 10:1525–1530, 1992

[18] Lithell HO: Effect of antihypertensive drugs on insulin, glucose, and lipid metabolism. *Diabetes Care* 14:203–209, 1991

[19]Carlberg B, Samuelsson O, Lindholm LH: Atenolol in hypertension: is it a wise choice? *Lancet* 364:1684–1689, 2004

[20]Jacob S, Rett K, Wicklmayr M, Agrawal B, Augustin HJ, Dietze GJ: Differential effect of chronic treatment with two beta-blocking agents on insulin sensitivity: the carvedilol-metoprolol study. *J Hypertens* 14:489–494, 1996

[21]Lindholm LH, Persson M, Alaupovic P, Carlberg B, Svensson A, Samuelsson O: Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). *J Hypertens* 21:1563–1574, 2003

[22]Sarafidis PA, Bakris GL: Do the metabolic effects of beta blockers make them leading or supporting antihypertensive agents in the treatment of hypertension? *J Clin Hypertens* (*Greenwich*) 8:351–356; quiz 357–358, 2006

[23]Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 366:895–906, 2005

[24]Messerli FH, Grossman E: Beta-blockers in hypertension: is carvedilol different? *Am J Cardiol* 93:7B–12B, 2004

[25]Rizos E, Bairaktari E, Kostoula A, Hasiotis G, Achimastos A, Ganotakis E, Elisaf M, Mikhailidis DP: The combination of nebivolol plus pravastatin is associated with a more beneficial metabolic profile compared to that of atenolol plus pravastatin in hypertensive patients with dyslipidemia: a pilot study. *J Cardiovasc Pharmacol Ther* 8:127–134, 2003

[26]Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright JT Jr, Oakes R, Lukas MA, Anderson KM, Bell DS: Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 292:2227–2236, 2004

[27]Reaven GM, Lithell H, Landsberg L: Hypertension and associated metabolic abnormalities:the role of insulin resistance and the sympathoadrenal system. *N Engl J Med* 334:374–381, 1996

[28]Haenni A, Lithell H: Treatment with a beta-blocker with beta 2-agonism improves glucose and lipid metabolism in essential hypertension. *Metabolism* 43:455–461, 1994

[29]Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N: Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ* 322:15–18, 2001

[30]Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000

[31]Colagiuri S, Cull CA, Holman RR: Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes? UKPDS 61. *Diabetes Care* 25:1410–1417, 2002

[32]McGill JB, Bakris GL, Fonseca V, Raskin P, Messerli FH, Phillips RA, Katholi RE, Wright JT Jr, Iyengar M, Anderson KM, Lukas MA, Dalal MR, Bell DS: Beta-blocker use and diabetes symptom score: results from the GEMINI study. *Diabetes Obes Metab* 9:408–417, 2007

[33]Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli F, Phillips RA, Raskin P, Wright JT Jr, Waterhouse B, Lukas MA, Anderson KM, Bell DS: Differential effects of beta-blockers on albuminuria in patients with type 2 diabetes. *Hypertension* 46:1309–1315, 2005

[34]DCCT Research Group: Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. *Diabetes Care* 18:1415–1427, 1995

[35]Barnett AH, Leslie D, Watkins PJ: Can insulin-treated diabetics be given beta-adrenergic blocking drugs? *BMJ* 280:976–978, 1980

[36]Thamer M, Ray NF, Taylor T: Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clin Ther* 21:1387–1400, 1999

[37]Shorr RI, Ray WA, Daugherty JR, Griffin MR: Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA* 278:40–43, 1997

[38]Herings RM, de Boer A, Stricker BH, Leufkens HG, Porsius A: Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 345:1195–1198, 1995

[39]McMurray J, Fraser DM: Captopril, enalapril, and blood glucose [Letter]. *Lancet* 1:1035, 1986

[40]Arauz-Pacheco C, Ramirez LC, Rios JM, Raskin P: Hypoglycemia induced by angiotensin-converting enzyme inhibitors in patients with non-insulin-dependent diabetes

receiving sulfonylurea therapy. *Am J Med* 89:811–813, 1990

[41]Sawicki PT, Siebenhofer A: Betablocker treatment in diabetes mellitus. *J Intern Med* 250:11–17, 2001

[42]Borch-Johnsen K, Helweg-Larsen K: Sudden death and human insulin: is there a link? *Diabet Med* 10:255–259, 1993

[43]Sartor G, Dahlquist G: Short-term mortality in childhood onset insulin-dependent diabetes mellitus: a high frequency of unexpected deaths in bed. *Diabet Med* 12:607-611, 1995

[44]Tattersall RB, Gill GV: Unexplained deaths of type 1 diabetic patients. *Diabet Med* 8:49–58, 1991

[45]Thordarson H, Sovik O: Dead in bed syndrome in young diabetic patients in Norway. *Diabet Med* 12:782–787, 1995

[46]Ziegler D: Diabetic cardiovascular autonomic neuropathy: prognosis, diagnosis and treatment. *Diabetes Metab Rev* 10:339–383, 1994

[47]Lee SP, Yeoh L, Harris ND, Davies CM, Robinson RT, Leathard A, Newman C, Macdonald IA, Heller SR: Influence of autonomic neuropathy on QTc interval lengthening during hypoglycemia in type 1 diabetes. *Diabetes* 53:1535–1542, 2004

[48]Lee SP, Harris ND, Robinson RT, Davies C, Ireland R, Macdonald IA, Heller SR: Effect of atenolol on QTc interval lengthening during hypoglycaemia in type 1 diabetes. *Diabetologia* 48:1269–1272, 2005

[49]Messerli FH, Bell DS, Fonseca V, Katholi RE, McGill JB, Phillips RA, Raskin P, Wright JT Jr, Bangalore S, Holdbrook FK, Lukas MA, Anderson KM, Bakris GL: Body weight changes with beta-blocker use: results from GEMINI. *Am J Med* 120:610–615, 2007

[50]American Diabetes Association: Standards of medical care in diabetes—2008. *Diabetes Care* 31 (Suppl. 1):S12–S54, 2008

[51]Saydah S, Cowie C, Eberhardt MS, De Rekeneire N, Narayan KM: Race and ethnic differences in glycemic control among adults with diagnosed diabetes in the United States. *Ethn Dis* 17:529–535, 2007

[52]Wong ND, Lopez VA, L'Italien G, Chen R, Kline SE, Franklin SS: Inadequate control of hypertension in US adults with cardiovascular disease comorbidities in 2003–2004. *Arch Intern Med* 167:2431–2436, 2007

[53]Ong KL, Cheung BM, Man YB, Lau CP, Lam KS: Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension* 49:69–75, 2007

[54]Grant RW, Devita NG, Singer DE, Meigs JB: Polypharmacy and medication adherence in patients with type 2 diabetes. *Diabetes Care* 26:1408–1412, 2003

[55]ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288:2981–2997, 2002

[56]Johnson ML, Pietz K, Battleman DS, Beyth RJ: Prevalence of comorbid hypertension and dyslipidemia and associated cardiovascular disease. *Am J Manag Care* 10:926–932, 2004

[57]Steiner G: A new perspective in the treatment of dyslipidemia: can fenofibrate offer unique benefits in the treatment of type 2 diabetes mellitus? *Treat Endocrinol* 4:311–317, 2005

[58]Munger MA, Van Tassell BW, LaFleur J: Medication nonadherence: an unrecognized cardiovascular risk factor [article online]. *MedGenMed* 9:58, 2007. Available from http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18092064. Accessed 11 December 2008

[59]Borrild NJ: Patients' experiences of antihypertensive drugs in routine use: results of a Danish general practice survey. *Blood Press Suppl* 1:23–25, 1997

[60]Leenen FH: Intermittent blood pressure control: potential consequences for outcome. *Can J Cardiol* 15:13C–18C, 1999

[61]Claxton AJ, Cramer J, Pierce C: A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 23:1296–1310, 2001

[62]Lasater M: The effect of a nurse-managed CHF clinic on patient readmission and length of stay. *Home Healthc Nurse* 14:351–356, 1996

[63]Ni H, Nauman D, Burgess D, Wise K, Crispell K, Hershberger RE: Factors influencing knowledge of and adherence to self-care among patients with heart failure. *Arch Intern Med* 159:1613–1619, 1999

[64]Kogut SJ, Andrade SE, Willey C, Larrat EP: Nonadherence as a predictor of antidiabetic drug therapy intensification (augmentation). *Pharmacoepidemiol Drug Saf* 13:591–598, 2004

[65]Ho PM, Magid DJ, Masoudi FA, McClure DL, Rumsfeld JS: Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease [article online]. *BMC Cardiovasc Disord* 6:48, 2006. Available from http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17173679. Accessed 11 December 2008

[66]Weber MA, Sica DA, Tarka EA, Iyengar M, Fleck R, Bakris GL: Controlled-release carvedilol in the treatment of essential hypertension. *Am J Cardiol* 98:32L–38L, 2006

[67]Weber MA, Bakris GL, Tarka EA, Iyengar M, Fleck R, Sica DA: Efficacy of a once-daily formulation of carvedilol for the treatment of hypertension. *J Clin Hypertens (Greenwich)* 8:840–849, 2006

[68]Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047–1053, 2004

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