Metabolic Safety of Antihypertensive Drugs: Myth versus Reality

Sameer Stas, MD, Lama Appesh, MS, and James Sowers, MD

Corresponding author
James Sowers, MD
University of Missouri Medical Center, Department of Internal Medicine, Health Sciences Center, MA410, DC043.00, Columbia, MO 652212, USA.
E-mail: sowersj@health.missouri.edu

Current Hypertension Reports 2006, **8:**403–408
Current Science Inc. ISSN 1522-6417

Treatment of hypertension with the major available antihypertensive classes results in a significant improvement in cardiovascular morbidity and mortality. However, there is controversy about whether specific classes of drug therapy have deleterious or beneficial effects on glucose and lipid metabolism. Myths and misconceptions have thus arisen. Although "old" classes of antihypertensives, such as diuretics and β-blockers, seem to have deleterious effects on glucose and lipid metabolism, the "newer" agents appear to have either neutral or beneficial profiles. The long-term significance of these metabolic changes is still debated. It is known that insulin resistance plays a major role in the pathogenesis of hypertension and type 2 diabetes mellitus. There is increasing evidence that blocking the renin-angiotensin-aldosterone system by using angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers favorably affects insulin sensitivity and, accordingly, decreases the incidence of new-onset type 2 diabetes mellitus.

Introduction

Approximately 60 million Americans have hypertension (HTN), and currently normotensive 55-year-old individuals have a 90% lifetime risk for developing high blood pressure (BP) [1,2]. HTN and type 2 diabetes mellitus (T2DM) are both insulin-resistant states [3••,4]. T2DM is frequently associated with concomitant hypertension. T2DM is also 2.5 times more likely to develop in hypertensive people compared to their normotensive counterparts [5]. In a recent cross-sectional study in 420 patients with essential hypertension, approximately 68% had impaired glucose metabolism, and 45% had undiagnosed glucose abnormalities [6]. Similarly, approximately 40% of newly diagnosed T2DM patients are already hypertensive [7]. However, the cardiovascular disease (CVD) complications of T2DM begin well before a clinical diagnosis of diabetes [8,9].

HTN, dysglycemia, and dyslipidemia tend to cluster among the same population. They are components of the cardiometabolic syndrome (CMS), along with other factors such as central obesity, increased inflammation, oxidative stress, and thrombosis. In the case of HTN, several mechanisms of insulin resistance have been observed, as shown in Table 1. These mechanisms include defects in post-receptor insulin action and glucose metabolism, decreased delivery of glucose and insulin to skeletal muscles, and altered skeletal-muscle tissue composition.

The development of HTN in an insulin-resistant state seems to be the result of multiple, interconnected, maladaptive pathways that involve sodium retention, increased sympathetic nervous system (SNS) activity, vascular dysfunction, increased renin-angiotensin-aldosterone system (RAAS) activity, oxidative stress, and inflammation [10••,11].

Controlling BP results in a significant improvement in CVD morbidity and mortality within both diabetic and nondiabetic populations [1,12]. In most patients, monotherapy is not sufficient to achieve current goals of hypertension treatment; this is especially true in diabetics, whose recommended target BP is even lower. More than two thirds of hypertensive individuals need multidrug regimens, consisting of medications from different classes, to manage their hypertension [1,13,14].

When treating a patient with high BP, it is necessary to consider concomitant pathologies, that is, dysglycemia and dyslipidemia. Lowering BP at the expense of worsening other conditions that are known to exacerbate the clinical outcomes might not be the most appropriate approach. Ideally, a medication that improves all aspects of the patient's condition would be best.

The metabolic safety of the various hypertension classes has been at the center of debate for many years. In this respect, different classes of hypertensive medications have been found to possess distinct metabolic profiles. Most of the clinical data concerning new-onset T2DM and antihypertensive drugs come from

Table 1. Factors promoting insulin resistance in essential hypertension

Impaired insulin signaling
Decreased insulin-mediated glucose transport
Decreased glycogen synthesis
Decreased nitric oxide generation
Increased reactive oxygen species
Increased vasoconstruction
Vascular hypertrophy
Increased skeletal muscle fat content
Decreased slow-twitch insulin-sensitive skeletal muscle fibers

observational studies [5,15••] or short-term trials [13], are a product of post hoc analysis [16], or are secondary results of studies projected primarily for different cardiovascular or renal outcomes [14,17–21]. In 2003, a systematic review of the relevant literature found that the incidence of T2DM is likely unchanged or increased by some classes and unchanged or decreased by others. However, the authors concluded that the available data were "far from conclusive" [22].

In this review, we focus on the metabolic safety of the five major antihypertension medication classes that are currently used—namely, thiazide diuretics, β-adrenergic blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II type 1 receptor (AT_1) blockers (ARBs), and calcium channel blockers (CCBs). We discuss the current data on the effects of these drugs on glucose intolerance, insulin resistance, and lipid metabolism and the implications of the recent clinical trials.

Diuretics

Diuretics are considered to be one of the oldest treatment options. According to the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), thiazide diuretics are better or at least similar to other hypertensive classes in their ability to prevent the CVD complications of hypertension [1,14]. ALLHAT is the largest evaluation of antihypertensive medications to date, with more than 33,000 participants. ALLHAT used chlorthalidone as the representative diuretic in comparison to an ACEI and a CCB. There was no difference in fatal CHD, nonfatal myocardial infarction (MI), and all-cause mortality among these drug classes. Similar findings were present in nondiabetic patients, as well as patients with either T2DM or impaired fasting glucose (IFG) [23]. Although the benefit of thiazide diuretics is well recognized, there are concerns regarding the possible metabolic side effects of these agents. Thiazide diuretics may have unwanted effects on glucose metabolism, lipids, electrolytes, and uric acid levels.

Glucose metabolism

There have been reports of glucose intolerance related to thiazide diuretics since the 1950s [24]. Thiazide diuretics are known to increase the activity of the RAAS. Other factors that might contribute to thiazide-induced glucose intolerance are hypokalemia and hypomagnesemia, by affecting insulin release or insulin sensitivity [25]. The evidence from the controlled clinical trials on the diabetogenic effect of thiazide diuretics is mixed. Multiple clinical trials have shown increased incidence of new-onset T2DM. One of these is the re-evaluated SHEP, which compared thiazide-treated hypertensive patients to those given a placebo [26]. Similar trends were also observed when thiazide diuretics were evaluated against the "new" hypertensive agents, such as ACEIs (ANBP 2) [27], ARBs (ALPINE) [20], and CCBs (INSIGHT) [17]. In ALLHAT, following 4 years of treatment with chlorthalidone, amlodipine (CCB), or lisinopril (ACEI), diabetes was found in 11.8%, 9.6%, and 8.1% of participants, respectively [14].

Contrary to these trials, a few other studies have failed to demonstrate the diabetogenic effects of thiazide diuretics [5,28,29]. In one case, Gress et al. [5], in the ARIC Study, evaluated hypertensive individuals taking thiazide diuretics after 3 years and after 6 years and found that they did not have a greater risk for developing T2DM (when compared to subjects taking placebo). Furthermore, it has been suggested that the deleterious effects of thiazide diuretics on glucose intolerance are dose-dependent [30]. Therefore, low-dose diuretics provide nearly the same benefits, but the side effects associated with higher doses are avoided [1].

Some of the data on the prognostic effect of drug-induced T2DM suggest an increased risk for CVD [26]. Verdecchia et al. [15••] reported that in treated hypertensive people, the diagnosis of new-onset diabetes carries cardiovascular risk that is not statistically different from that in previously known T2DM. After adjustment for various confounders, including BP control, the relative risks for CVD events in patients with new diabetes or previous diabetes were 2.92 and 3.75, respectively, as compared with those who did not develop T2DM. In that study, the two independent risk factors for developing new-onset T2DM were increased fasting plasma glucose and diuretic use. Therefore, it seems that diuretics (and β-blockers, as discussed later) have an accelerating effect on the development of diabetes mellitus in predisposed individuals. Consequently, it is advised that patients with IFG or obesity should be monitored for glycemic changes when they are started on these medications [9].

Lipids

Thiazide diuretics increase serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) by 5% to 10%, modestly decrease high-density lipoprotein cholesterol (HDL-C), and increase serum triglycerides by 5% to 15% [31,32]. These changes tend to be dose-dependent and more obvious in the nonresponders [30].

Furthermore, they are short-term; interim lipid changes seen when a patient begins diuretic therapy appear to be ameliorated with time [1,13,32].

β-Blockers

β-adrenergic receptor antagonists have been used to treat HTN for many years. They clearly improve clinical outcomes in patients with coronary artery disease, previous acute MI, and congestive heart failure [1,12]. In the UKPDS, atenolol was as effective as captopril in decreasing microvascular and macrovascular complications in T2DM patients [12]. However, the role of β-blockers in treating uncomplicated essential HTN is less clear [33].

Glucose metabolism

In the ARIC study, β-blocker treatment was associated with a 28% increased risk for developing T2DM [5]. In the same study, neither diuretics, ACEIs, nor CCBs were associated with significant development of T2DM after the 6-year follow-up period. Potential mechanisms by which β-blockers may be related to new-onset T2DM are weight gain, attenuation of pancreatic release of insulin, and promotion of insulin resistance in the peripheral tissues [28]. The majority of clinical studies have shown that "traditional" β-blockers are associated with a higher incidence of T2DM compared to ACEIs [19], ARBs [20], and CCBs [18].

Not all β-blockers are equivalent when it comes to their effects on metabolism and on blood vessel tone. "Traditional" β-blockers, both nonselective β_1 and β_2 antagonists such as propranolol and β_1-selective antagonists such as atenolol and metoprolol, are vasoconstrictive due to the consequent unopposed α_1-adrenergic activity. They all have negative metabolic effects on insulin resistance and lipid metabolism [34]. Conversely, newer vasodilating β-blockers, such as carvedilol, nebivolol, and celiprolol, are associated with better metabolic profiles [35]. In a small, controlled clinical trial, Giugliano et al. [36] reported on 45 diabetic hypertensive patients; carvedilol increased total glucose disposal by 20% compared to atenolol, which showed a 10% decrease. Carvedilol also decreased the plasma glucose response to oral glucose, reduced the triglyceride level by 20% (versus a 12% elevation with atenolol), and increased the HDL-C level by 8% (as opposed to a 12% decrease with atenolol). The GEMINI trial included 1235 hypertensive patients with T2DM, who were taking either an ACEI or an ARB [37]. After 5 months, whereas metoprolol treatment increased hemoglobin A_{1C} by 0.15%, carvediolol had no effect. Furthermore, insulin resistance as determined by Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was decreased in the carvedilol group but increased with metoprolol. There are no data from long-term clinical outcome trials regarding the effects of carvedilol on new-onset T2DM.

Lipids

Although the consequences of β-blockers on TC and LDL-C are slight, these drugs have been found to elevate triglycerides by 10% to 40% while lowering HDL-C by 5% to 20% [31]. In one study [32], atenolol was shown to have a slight tendency to cause temporarily increased triglyceride, TC, and apolipoprotein B levels; however, these changes did not persist for more than 1 year. In the GEMINI trial, metoprolol increased triglycerides by 13%, whereas carvedilol had no significant effect on lipids [37].

Angiotensin-converting Enzyme Inhibitors and Angiotensin-receptor Blockers

Angiotensin II has several deleterious effects in the vessels, heart, kidney, adipose tissue, and skeletal muscles that promote oxidative stress, vasoconstriction, and insulin resistance [3••,4]. There is cumulative evidence from clinical trials suggesting that the inhibition of RAAS by using ACEIs or ARBs decreases the rate of new-onset diabetes in high-risk patients when compared to any other class of antihypertensives [13,14,16,19–21,27,38].

Glucose metabolism

In a recent meta-analysis that included 11 trials, an ACE or ARB prevented new-onset T2DM (odds ratio, 0.78; 95% CI, 0.73–0.83) with the absolute risk reduction of 1.7 (95% CI, 1.3–2.1). The results were valid with either an ACEI or an ARB, regardless of the indication of use—that is, hypertension, coronary artery disease (CAD), or congestive heart failure (CHF) [39]. The positive effect after RAAS inhibition could not be simply interpreted as a worse effect in the comparative group as it was observed not only versus β-blocker or diuretic but also versus placebo or calcium channel antagonist, which is generally considered to be metabolically neutral [39]. The data from the CHARM-added trial indicate that adding an ARB to an ACEI in CHF patients does not seem to offer further protection from T2DM [21].

The mechanisms by which interruption of RAAS might help in preventing new-onset T2DM are complex and may involve increasing pancreatic insulin secretion and insulin sensitivity [40,41]. Our laboratory showed that an ARB improves insulin resistance and decreases oxidative stress in an animal model that overexpresses angiotensin II (Ren-2 rat model with transfection of the mouse renin gene) [42]. In addition, inhibition of RAAS also results in improved muscle blood flow, restoration of insulin-sensitive muscular fiber composition, decreased sympathetic activity, enhanced insulin signaling and glucose uptake, promotion of favorable effects on the adipose tissue, such as adipocyte differentiation and increased adiponectin levels [40,41]. Additionally, certain ARBs, such as telmisartan and irbesartan, were found to have partial peroxisome proliferator-activated receptor-γ (PPAR-γ)

agonism activity, providing a potential mechanism for their antidiabetic effect [43].

There are three large-scale prospective trials underway to confirm the role of ACEIs and ARBs in T2DM prevention in both hypertensive and nonhypertensive individuals: DREAM, NAVIGATOR, and ONTARGET—TRANSCEND [44••]. Meanwhile, based on the available evidence, it is advisable to consider ACEIs or ARBs in all conditions associated with insulin resistance, such as HTN, T2DM, obesity, metabolic syndrome, and CHF [44••].

Lipids

ACEIs do not affect levels of cholesterol fractions in nondiabetic patients, but may decrease triglycerides. In diabetic patients, ACEIs tend to decrease TC and LDL-C levels (5% and 7%, respectively) without affecting HDL-C or triglycerides [31]. In the ALLHAT, after 2-year and 4-year evaluations on cholesterol, values were higher in the chlorthalidone (diuretic)-treated patients compared to those receiving lisinopril (an ACEI) or amlodipine (a CCB) [14].

ARBs appear to have favorable effects on the lipid profile [13]. After 6 months of ARB treatment in 2438 patients, a statistically significant reduction in TC, LDL-C, TC/HDL-C, and apolipoprotein B levels as well as an increase in HDL-C were found [45]. Also, when compared to patients who had been given placebo (n = 60), valsartan patients (n = 63) were found to have statistically significant lowering of TC and LDL-C [46]. Results regarding HDL-C, triglycerides, very low-density lipoprotein (VLDL) triglycerides, VLDL cholesterol, and apolipoprotein B were not significant.

Calcium Channel Blockers

CCBs are safe and effective antihypertensive agents. In the ALLHAT study, the effects of amlodipine were comparable to chlorthalidone on CHD, stroke, and all-cause mortality rate. Interestingly, noncardiovascular mortality rate was significantly lower and renal function better preserved in the amlodipine group [14].

Glucose metabolism

Generally, CCBs are considered to be metabolically neutral [28]. Previous reports suggested that insulin resistance worsens with a short-acting CCB such as nifedipine, is not affected by diltiazem and verapamil, and is probably improved by the newer, long-acting CCBs, such as amlodipine [47]. In the large clinical trials, CCBs have been shown to reduce new-onset T2DM compared to conventional therapy, such as thiazide diuretics and/or β-blockers [14,17,18]. In the ALLHAT trial, the incidence of new-onset T2DM in the amlodipine group (9.6%) was in between lisinopril (8.1%) and chlorthalidone (11.8%) [14]. The VALUE trial compared amlodipine to valsartan and followed-up on more than 15,000 patients for a mean of 4.2 years. The incidence of new-onset T2DM was 3.3% less (13.1% as compared with 16.4%) in the ARB group than in the CCB group [38].

Lipids

CCBs have not been found to influence lipid levels [31].

Conclusions

Generally, lowering BP is more important than the method used to achieve goal levels. Usually, more than one medication is needed to reach therapy goal. Although "old" classes of antihypertensives, such as diuretics and β-blockers, seem to have deleterious effects on glucose and lipid metabolism, the "newer" agents appear to have either neutral or beneficial profiles. It is advisable to be cautious when starting diuretics or old β-blockers in the obese and people with IFG. The combination of RAAS-affecting medications and diuretics seems beneficial and is usually needed to reach the goal of HTN treatment. Agents blocking RAAS appear to have antidiabetic effects as well. Generally, it is appropriate to start with an ACE inhibitor or ARB and add a diuretic as needed to control blood pressure in patients with diabetes and/or proteinuria as well as those with the cardiometabolic syndrome. This strategy will likely abrogate adverse metabolic effects associated with the use of a diuretic alone. The data from ongoing large-scale clinical trials will hopefully help in clearing up some of the confusion about the potential beneficial or harmful metabolic effects of the antihypertensive classes.

Acknowledgments

A grant from the National Institutes of Health (R01 HL73101-01A1 NIH/NHLBI) and a grant from the Veterans Affairs Research Service (VA Merit Review) support Dr. Sowers' research.

Clinical Trials Acronyms

ALLHAT—The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALPINE—Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation; ANBP-2—Second Australian National Blood Pressure Study; ARIC—Atherosclerosis in Communities; CHARM-added—Candesartan in Heart-Failure Assessment of Reduction in Mortality and Morbidity (combining candesartan with ACE inhibition); DREAM—Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications; GEMINI—Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives; INSIGHT—International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment; NAVIGATOR—Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; ONTARGET—Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; TRANSCEND—Telmisartan Randomized Assessment Study in ACE Intolerant

Patients with Cardiovascular Disease; SHEP—Systolic Hypertension in the Elderly Program; UKPDS—United Kingdom Prospective Diabetes Study; VALUE—Valsartan Antihypertensive Long-term Use Evaluation.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Chobanian AV, Bakris GL, Black HR, et al.: **Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.** *Hypertension* 2003, **42:**1206–1252.
2. Hajjar I, Kotchen TA: **Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000.** *JAMA* 2003, **90:**199–206.
3. •• Sowers JR: **Insulin resistance and hypertension.** *Am J Physiol Heart Circ Physiol* 2004, **286:**H1597–H1602.

The relationship between hypertension and insulin resistance is reviewed in this paper. It illustrates the inhibitory effects of angiotensin II on insulin signaling pathways in the vessels and skeletal muscles.

4. McFarlane SI, Banerji M, Sowers JR:. **Insulin resistance and cardiovascular disease.** *J Clin Endocrinol Metab* 2001, **86:**713–718.
5. Gress TW, Nieto FJ, Shahar E, et al.: **Hypertension and antihypertensive therapy as risk factors for type 2 mellitus. Atherosclerosis Risk in Communities Study.** *N Engl J Med* 2000, **342:**905–912.
6. Garcia-Puig J, Ruilope LM, Luque M, et al.: **AVANT Study Group Investigators: Glucose metabolism in patients with essential hypertension.** *Am J Med* 2006, **119:**318–326.
7. **Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications.** *J Hypertens* 1993, **11:**309–317.
8. Haffner SM, Stern MP, Hazuda HP, et al.: **Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes?** *JAMA* 1990, **263:**2893–2898.
9. Bakris GL, Sowers JR: **When does new onset diabetes resulting from antihypertensive therapy increase cardiovascular risk.** *Hypertension* 2004, **43:**941–942.
10. •• Stas SN, El-Atat FA, Sowers JR: **Pathogenesis of hypertension in diabetes.** *Rev Endocr Metab Disord* 2004, **5:**221–225.

In this review article, the mechanisms involved in the development of hypertension and insulin-resistant states, including diabetes, are discussed.

11. Gill H, Mugo M, Whaley-Connell A, et al.: **The key role of insulin resistance in the cardiometabolic syndrome.** *Am J Med Sci* 2005, **330:**290–294.
12. **Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group.** *BMJ* 1998, **317:**703–713.
13. Lindholm LH, Persson M, Alaupovic P, et al.: **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* 2003, **21:**1563–1574.
14. 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* 2002, **288:**2981–2997.
15. •• Verdecchia P, Reboldi G, Angeli F, et al.: **Adverse prognostic significance of new diabetes in treated hypertensive subjects.** *Hypertension* 2004, **43:**963–969.

This long-term follow-up study examined the predictive ability of new-onset diabetics in hypertensives. It shows that the levels of CVD events in these individuals on antihypertensives were comparable with those levels found in previously known diabetics.

16. **Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators.** *Lancet* 2000, **22:**253–259.
17. Mancia G, Brown M, Castaigne A, et al.: **Outcomes with nifedipine GITS or co-amilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT).** *Hypertension* 2003, **41:**431–436.
18. Bakris GL, Gaxiola E, Messerli FH: **Clinical outcomes in the diabetes cohort of the International Verapamil SR-Trandolapril study.** *Hypertension* 2004, **44:**637–642.
19. Hansson L, Lindholm LH, Niskanen L, et al.: **Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial.** *Lancet* 1999, **353:**611–616.
20. Lindholm LH, Ibsen H, Dahlof B, et al.: **LIFE Study Group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol.** *Lancet* 2002, **359:**1004–1010.
21. McMurray JJ, Ostergren J, Swedberg K, et al.: **Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial.** *Lancet* 2003, **362:**767–771.
22. Padwal R, Laupacis A: **Antihypertensive therapy and incidence of type 2 diabetes: a systematic review.** *Diabetes Care* 2004, **27:**247–255.
23. Whelton PK, Barzilay J, Cushman WC, et al.: **Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).** *Arch Intern Med* 2005, **165:**1401–1409.
24. Goldner MG, Zarowitz H, Akgun S: **Hyperglycemia and glycosuria due to thiazide derivatives administered in diabetes mellitus.** *N Engl J Med* 1960, **262:**403–405.
25. Carter BL, Basile J: **Development of diabetes with thiazide diuretics: the potassium issue.** *J Clin Hypertens (Greenwich)* 2005, **7:**638–640.
26. Mancia G, Grassi G, Zanchetti A: **New-onset diabetes and antihypertensive drugs.** *J Hypertens* 2006, **24:**3–10.
27. Wing LM, Reid CM, Ryan P, et al.: **for the Second Australian National Blood Pressure Study Group: A comparison of outcomes with angiotensin-converting enzyme inhibitors and diuretics for hypertension in the elderly.** *N Engl J Med* 2003, **348:**583–592.
28. Sowers JR, Bakris GL: **Antihypertensive therapy and the risk of type 2 diabetes mellitus.** *N Engl J Med* 2000, **342:**969–970.
29. Neaton JD, Grimm RH Jr, Prineas RJ, et al.: **Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group.** *JAMA* 1993, **270:**713–724.
30. Sica DA: **Diuretic-related side effects: development and treatment.** *J Clin Hypertens (Greenwich)* 2004, **6:**532–540.
31. Mantel-Teeuwisse AK, Kloosterman JM, Maitland-van der Zee AH, et al.: **Drug-induced lipid changes: a review of the unintended effects of some commonly used drugs on serum lipid levels.** *Drug Saf* 2001, **24:**443–456.

32. Lakshman MR, Reda DJ, Materson BJ, et al.: **Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents.** *Arch Intern Med* 1999, **159:**551–558.
33. Sarafidis PA, Bakris GL: **Are beta blockers passé for the treatment of hypertension?** *J Clin Hypertens (Greenwich)* 2006, **8:**239–240.
34. Bell DS: **Beta-adrenergic blocking agents in patients with diabetes—friend and foe.** *Endocr Pract* 1999, **5:**51–53.
35. Jacob S, Henriksen EJ: **Metabolic properties of vasodilating beta blockers: management considerations for hypertensive diabetic patients and patients with the metabolic syndrome.** *J Clin Hypertens (Greenwich)* 2004, **6:**690–696.
36. Giugliano D, Acampora R, Marfella R, et al.: **Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension. A randomized, controlled trial.** *Ann Intern Med* 1997, **126:**955–959.
37. Bakris GL, Fonseca V, Katholi RE, et al.: **Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial.** *JAMA* 2004, **292:**2227–2236.
38. Julius S, Kjeldsen SE, Weber M, et al.: **Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial.** *Lancet* 2004, **363:**2022–2031.
39. Gillespie EL, White CM, Kardas M, et al.: **The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes.** *Diabetes Care* 2005, **28:**2261–2266.
40. Scheen AJ: **Renin-angiotensin system inhibition prevents type 2 diabetes mellitus. Part 2. Overview of physiological and biochemical mechanisms.** *Diabetes Metab* 2004, **30:**498–505.
41. McFarlane SI, Kumar A, Sowers JR: **Mechanisms by which angiotensin-converting enzyme inhibitors prevent diabetes and cardiovascular disease.** *Am J Cardiol* 2003, **91:**30H–37H.
42. Blendea MC, Jacobs D, Stump CS, et al.: **Abrogation of oxidative stress improves insulin sensitivity in the Ren-2 rat model of tissue angiotensin II overexpression.** *Am J Physiol Endocrinol Metab* 2005, **288:**E353–E359.
43. Schupp M, Janke J, Clasen R, et al.: **Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity.** *Circulation* 2004, **109:**2054–2057.
44.•• Abuissa H, Jones PG, Marso SP, et al.: **Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials.** *J Am Coll Cardiol* 2005, **46:**821–826.

After conducting a meta-analysis of the major controlled clinical trials on ACEs and ARBs, these authors concluded that the use of these specific antihypertensive agents in pre-diabetics should be considered in the prevention of T2DM.

45. Kyvelou SM, Vyssoulis GP, Karpanou EA, et al.: **Effects of antihypertensive treatment with angiotensin II receptor blockers on lipid profile: an open multi-drug comparison trial.** *Hellenic J Cardiol* 2006, **47:**21–28.
46. Hanefeld M, Abletshauser C: **Effect of the angiotensin II receptor antagonist valsartan on lipid profile and glucose metabolism in patients with hypertension.** *J Int Med Res* 2001, **29:**270–279.
47. Mukasa K: **Antihypertensive drugs and insulin resistance in obesity.** *Intern Med* 2005, **44:**395–396.