

Therapeutic Controversies in Hypertension

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Although numerous prospective randomized trials since the Veterans Administration studies clearly have attested to the efficacy and safety of antihypertensive therapy, there remain some controversial issues with all classes of antihypertensive drugs. Thiazide diuretics increase the risk for new-onset diabetes and their long-term safety has been questioned. Alpha-blockers do not reduce morbidity and mortality in uncomplicated hypertension but are well known to cause a variety of poorly tolerated side effects. The safety of calcium antagonists has been questioned for many years, although recent large prospective randomized trials such as Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, International Verapamil-Trandolapril Study, Intervention as a Goal in Hypertension, Valsartan Antihypertensive Long-Term Use Evaluation and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) have attested to their safety and efficacy. Angiotensin-converting enzyme inhibitors, in general, are well tolerated but have potentially fatal adverse effects in a few patients. Angiotensin-receptor blockers are exceedingly well tolerated, but may be less-efficacious antihypertensive agents than other drug classes. Most antihypertensive drug classes have an effect on new-onset diabetes that should be taken into account in patients at risk. No head-to-head comparison of combination therapy looking at efficacy and safety has been available. The long-term safety of antihypertensive therapy is documented poorly because most trials only last 4 to 6 years. Despite these drawbacks and concerns, the benefits of antihypertensive therapy clearly outweigh its potential risk.

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Ever since the Veterans Administration studies,^{1,2} numerous prospective randomized trials have established that lowering blood pressure in hypertensive patients will decrease the risk for stroke, myocardial infarction, congestive heart failure, and other cardiovascular morbidity and mortality. Decreasing blood pressure levels has been relatively safe and beneficial. Despite the overall benefits of antihypertensive therapy, there remain some areas of controversy. We point out some of these controversies and discuss them in the context of safety and efficacy of antihypertensive therapy.

Diuretics in the Treatment of Hypertension

Although many prospective trials have attested to the safety and efficacy of diuretics in reducing morbidity and mortality

in hypertensive patients,^{3,4} the safety of diuretics in some hypertensive patients remains open to question.

Twelve years ago, Warram et al⁵ showed that in diabetic hypertensive patients the risk for cardiovascular mortality was 3.8-fold higher in those treated with diuretics than in untreated patients. In contrast, later prospective studies showed that diuretics reduced cardiovascular morbidity and mortality in elderly diabetic hypertensive patients.⁶⁻⁸ The old belief that diuretics paradoxically may increase cardiovascular morbidity and mortality has been defeated by the recent evidence of clear benefit with low-dose diuretics. We learned that low-dose diuretics are effective in lowering blood pressure with minimal side effects. Increasing the dose adds very little to the control of blood pressure, although it increases substantially the rate of adverse effects such as hypokalemia, hyponatremia, hyperuricemia, glucose intolerance, and so forth.⁹ Similarly, the risk for sudden cardiac death was low in diuretic users when the dose was low and a potassium-sparing agent was added.¹⁰ However, thiazide-type diuretics, when used as an antihypertensive agent, have been shown to increase the risk for sudden death in a dose-dependent way when used without a potassium-sparing strategy.¹⁰ The rationale of adding a potassium-sparing agent to a thiazide is

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supported by the recent evidence that the addition of aldosterone antagonists to optimal treatment reduces cardiovascular morbidity and mortality in patients with congestive heart failure.^{11,12} Thus, it seems that the controversy regarding the efficacy and safety of diuretics in hypertension has been resolved by using a low-dose diuretic with the option of adding a potassium-sparing agent.

Whether a diuretic should be the first drug of choice in most hypertensive patients remains controversial. The Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)⁸ and the Second Australian National Blood Pressure Study (ANBP2)¹³ are the first completed trials comparing first-step treatment with a thiazide-type diuretic versus an angiotensin-converting enzyme (ACE) inhibitor for morbidity and mortality outcomes. Unfortunately, each study came to a different conclusion. Comparison between the studies is difficult because blood pressure control was not the same. In ALLHAT,⁸ systolic blood pressure was reduced 2 mm Hg more in the diuretic group than in the ACE-inhibitor group, which possibly explained the diuretic advantage for stroke reduction. However, the advantages of diuretics for heart failure and combined cardiovascular disease could not be explained merely by the systolic blood pressure difference. In the ANBP2 study,¹³ blood pressure levels at the end of the study were the same in the diuretic and ACE-inhibitors arms. Conceivably, the different results may be explained by the selection of the thiazides (chlorthalidone in the ALLHAT and hydrochlorothiazide in the ANBP2) and the ACE inhibitors (lisinopril in the ALLHAT and enalapril in the ANBP2 study). Of note, in the Multiple Risk factor Intervention Trial (MRFIT) study there was a change in protocol after 5 years because in the clinics where patients received chlorthalidone the outcome was better than in the clinics where patients received hydrochlorothiazide.¹⁴ The investigators argued in retrospect that this switch in the diuretic treatment may have explained the favorable outcome of the MRFIT study. The 2 studies also differed in racial distribution, in blinding, and in sample size, and, most relevant, in the number of morbid events observed. Thus, the question still is unresolved whether chlorthalidone is better than hydrochlorothiazide, (or enalapril is better than lisinopril). Data from other studies, such as the Swedish Trial in Old Patients with Hypertension 2¹⁵ and the Captopril Prevention Project,¹⁶ cannot solve this question because in the conventional arm clinicians were given free choice of starting with a diuretic or β -blocker.

Thiazide diuretics also have been documented to increase the risk for new-onset diabetes in a variety of recent prospective randomized trials (see later). Although this diabetogenic effect may be related partially to hypokalemia, other factors such as low-grade sympathetic stimulation and an increase in the activity of the renin-angiotensin system may play an additional role.

There is little question as to the safety and efficacy of a low-dose diuretic with a potassium-sparing agent in hypertension and in diabetes-hypertension. This does not mean, however, that thiazide diuretics should be the preferred agents in most patients. This controversy is reflected by the

diametrically different approach presented by the recent American and European hypertension guidelines.^{17,18}

β -Blockers in the Treatment of Hypertension

Until the recent publication of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), diuretics and β -blockers both were recommended as the drug of choice for essential hypertension.¹⁹ Although numerous epidemiologic studies attest to the safety and efficacy of diuretics in this regard, the data for β -blockers are sketchy and unconvincing. In fact, the available data suggest that clinical benefits of β -blockers are documented poorly and that β -blockers may be inefficacious in the elderly, who account for a large segment of the hypertensive population.²⁰ Monotherapy with a β -blocker in the elderly does not reduce morbidity and mortality compared with placebo. The British Medical Research Council (MRC)-2 trial, a randomized, placebo-controlled, single-blinded study in patients aged 65 to 74 years, clearly documented that although blood pressure was lowered effectively by the cardioselective β -Blocker atenolol, the morbidity and mortality of the β -Blocker group did not differ from that of the placebo group.⁴ Moreover, patients who received the combination of β -blockers and diuretics fared consistently worse than those receiving diuretics alone.²¹ In a recent meta-analysis, we showed that β -blocker-based therapy does not reduce cardiovascular coronary heart disease and total mortality in elderly hypertensive patients.²⁰ Two prospective randomized trials in patients with cerebrovascular disease showed no cerebroprotective effects of atenolol over placebo.^{22,23} Thus, there are a total of 4 independent studies attesting to the inefficacy of β -blockers in reducing strokes, despite the fact that these drugs, similar to all antihypertensive drugs, do lower blood pressure.

The recent Losartan Intervention For Endpoint reduction in hypertension study showed that losartan distinctly was superior in reducing stroke in elderly hypertensive patients when compared with atenolol. However, these data have to be interpreted in the context of the previous studies in which atenolol was no better than placebo.^{24,25}

Thus, despite their having a beneficial effect on the surrogate end point, that is, blood pressure, β -Blocker therapy failed to affect the real end point favorably, that is, myocardial infarction, strokes, and sudden death in elderly patients.

Similarly, in a large case-control study, the risk for sudden cardiac death distinctly was higher in elderly patients receiving either β -blocker as monotherapy or in combination with a thiazide diuretic than in patients receiving other therapy (calcium antagonists, ACE inhibitors, potassium-sparing diuretics).²⁶ This would indicate that β -blocker therapy needlessly exposes millions of elderly hypertensive patients to adverse effects and cost while not conferring any benefit.

In all studies in the geriatric population in which β -blockers were implied to reduce morbidity and mortality, the β -blockers were used in combination with a diuretic. Thus,

in the Swedish Trial in Old Patients with Hypertension,²⁷ more than two thirds of the patients were receiving combination therapy, and no information was available regarding the effects of β -blocker monotherapy. In the Systolic Hypertension in the Elderly Program study, only 32% of patients were receiving atenolol (or reserpine), only in combination with a diuretic.³ A subanalysis by Kostis et al²⁸ did not identify any additional benefits attributable to atenolol (or reserpine) that were independent of the ones conferred by the diuretic. In the study of Coope and Warrender, which showed a significant reduction in the rate of strokes, 70% of patients in the treatment group were receiving atenolol and 60% were receiving bendrofluazide.²⁹ None of these studies allows us to conclude that either a β -blocker alone or the addition of a β -blocker to the diuretic regimen did indeed significantly and independently impact morbidity and mortality.

Nevertheless, some indirect evidence suggests that β -blockers may have benefits in middle-aged and younger patients. In all 3 trials (MRC, International Prospective Primary Prevention Study in Hypertension, and Heart Attack Primary prevention in Hypertension),³⁰⁻³² the rate of myocardial infarction, stroke, and cardiovascular death was not very different with a β -blocker regimen than with a diuretic. A meta-analysis analyzing the 3 studies showed a trend of a decrease in total cardiovascular mortality in men by 14% and an increase in women by 16% in the β -blocker group when compared with non- β -blocker treatment.³³ Thus, there is still a controversy regarding whether a β -blocker should be considered as one of the first drugs of choice for hypertension.

The use of β -Blockers became even more of a question in diabetic hypertensive patients. The National High Blood Pressure Education Program Working Group³⁴ recommended in 1994 to avoid β -blockers in diabetic hypertensive patients because they can have adverse effects on peripheral blood flow and mask symptoms of hypoglycemia. However, the results from the UK Prospective Diabetes Study³⁵ showed that β -blockers are as effective as ACE inhibitors in reducing cardiovascular events in diabetic hypertensive patients. It seems that β -blockers may be appropriate as a first choice in young and middle-age hypertensive patients, and in those with a fast heart rate, but they should not be considered appropriate as the first-line therapy in the elderly with uncomplicated hypertension.

The class of β -Blockers is heterogeneous, and it is controversial whether all the drugs in the class are the same. The recent Carvedilol Or Metoprolol European Trial showed a superiority of carvedilol over metoprolol in patients with congestive heart failure.³⁶ Also, in the recent Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI study), carvedilol was superior to metoprolol with regard to parameters of hyperglycemia in diabetic hypertensive patients.³⁷ Carvedilol has been shown to be inert metabolically, whereas metoprolol seems to have an adverse effect on insulin resistance.

Calcium Antagonists

Calcium antagonists are used widely as antihypertensive agents. They are liked by physicians and patients because of their efficacy, metabolic neutrality, and clean side-effects profile. Several years ago a plethora of publications showed that hypertensive patients treated with short-acting calcium antagonists are at increased risk for myocardial infarction and have a higher mortality rate compared with patients treated with other antihypertensive drugs.³⁸⁻⁴¹ In addition, calcium antagonists were accused of increasing the risk for cancer among hypertensive patients.^{42,43}

Because these studies were interpreted uncritically and extrapolated to all calcium antagonists as a class, they cast doubt on the safety and efficacy of these drugs. An equally uncritical news media coverage alarmed patients and frustrated physicians. As recently as August 29, 2000, headlines in *The New York Times* stated, "The use of such drugs known as calcium channel blockers is leading to nearly 85,000 unnecessary heart attacks each year worldwide" (New Study Questions Blood Pressure Drug. 2000, August 29. *The New York Times*; p. A1).

Fortunately, several recent prospective randomized studies attested to the safety of the calcium antagonists.^{8,15,44-46} These drugs have been documented clearly to reduce cardiovascular morbidity—as efficacious, if not more efficacious, than other antihypertensive drug classes.^{8,15,44,45,47,48} Calcium antagonists are less effective than diuretics and ACE inhibitors in preventing congestive heart failure,^{8,45,48} and less effective than blockers of the renin-angiotensin system in preventing renal failure.^{49,50} However, they are equally as effective as the renin-angiotensin system blockers in reducing cardiovascular morbidity and mortality.^{8,15,51}

In the recent Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) study, more than 15,000 patients were randomized to either valsartan-based or amlodipine-based therapy.⁵² The primary outcome was similar in the 2 arms; however, there was a significantly better reduction in myocardial infarction with amlodipine than with valsartan. Part of this difference could be caused by the fact that amlodipine lowered blood pressure significantly better than did valsartan.

Diabetes mellitus is common among hypertensive patients and is devastating to the cardiovascular system.⁵³ The risk for stroke or any cardiovascular event is doubled when the hypertensive patient has diabetes mellitus.⁵⁴ Lowering blood pressure markedly decreases the rate of cardiovascular events and renal deterioration in these patients.^{46,55-57} A few years ago, 2 studies showed that calcium antagonists are less effective than ACE inhibitors in preventing cardiovascular events in diabetic hypertensive patients.^{58,59} These results cast doubt on the safety and efficacy of calcium antagonists in diabetic hypertensive patients. However, the recent results from the Systolic Hypertension in Europe, Intervention as a Goal in Hypertension, and the ALLHAT studies^{7,8,60} showed that calcium antagonists reduce cardiovascular morbidity and mortality in diabetic hypertensive patients. We recently showed that calcium antagonists are as effective as diuretics and ACE

inhibitors in reducing cardiovascular morbidity and mortality in diabetic hypertensive patients.⁶¹ Thus, calcium antagonists are possibly less effective than other agents in preventing congestive heart failure and renal deterioration, but they are safe and clearly reduce cardiovascular morbidity and mortality in hypertensive patients with or without diabetes mellitus.

ACE Inhibitors

ACE inhibitors became very popular in the treatment of hypertension because, in addition to lowering blood pressure, they prolong life in patients with congestive heart failure,⁶²⁻⁶⁶ they prevent renal deterioration in patients with diabetic nephropathy and with nondiabetic renal failure,^{49,67-72} and they reduce morbidity and mortality in high-risk patients.⁷³⁻⁷⁵ Despite their advantages in subgroups of patients, they were not superior to other agents in prospective randomized trials in hypertensive patients.^{8,15,16,35} Surprisingly, in the Captopril Prevention Project and ALLHAT studies, ACE inhibitors were even less effective than the conventional therapy or diuretic in preventing stroke.^{8,16} In the recent Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial in patients with cerebrovascular disease, combination therapy of a diuretic (indapamide) and ACE inhibitor (perindopril) reduced the risk for stroke by 43% when compared with placebo.⁷⁶ However, perindopril alone, despite lowering systolic blood pressure by 5 mm Hg, decreased stroke risk only by a nonsignificant 5%. It is possible that the benefit observed in high-risk patients was related to blood pressure reduction, and not to the specific effect of ACE inhibition.⁷⁷ This assumption is supported by the observation of Svensson et al⁷⁸ that the mild blood pressure decrease observed in the clinic in the ramipril-treated group of the Heart Outcomes Prevention Evaluation study underestimated the true blood pressure decrease. Despite the controversy regarding whether the beneficial effects of ACE inhibitors are related to blood pressure reduction or to the intrinsic effect of ACE inhibition, it seems safe to recommend ACE inhibitors to many hypertensive patients. It should be noted that most patients benefit from the combination of an ACE inhibitor and a diuretic.

Angiotensin-Receptor Blockers

Angiotensin-receptor blockers (ARBs) have been shown to be safe, well tolerated, and effective for blood pressure control in young and elderly patients.⁷⁹⁻⁸¹ Recently, several studies showed that this class of drugs confers renal benefits in patients with diabetic nephropathy,^{50,82} reduces the rate of stroke in hypertensive patients better than conventional treatment,^{24,25,83} and is effective in patients with congestive heart failure.⁸⁴⁻⁹⁰ However, it is controversial whether ARBs are better at protecting the kidney than ACE inhibitors in patients with type 2 diabetes mellitus, and whether they reduce the risk for stroke better than ACE inhibitors. ARBs and ACE inhibitors were not compared; therefore it remains only a speculation that ARBs should be the drug of choice in these conditions. One should keep in mind that most diabetic pa-

tients are dying of cardiovascular events rather than of renal failure, and because ACE inhibitors have been shown to reduce cardiovascular morbidity and mortality in these patients,⁷³ they may be a better initial choice than ARBs in diabetic patients. This controversy still holds after the recently published studies, and it seems that ARBs may be a substitute or an additional but not a superior therapy to ACE inhibitors.^{84,86,89,91-93} In the recent VALUE study, the ARB valsartan was less efficacious in reducing blood pressure and heart attacks than amlodipine.⁵²

α -Blockers

α -blockers had great promise in the treatment of hypertension because in addition to lowering blood pressure, they improve insulin resistance and lipid profile.^{94,95} However, the recent results of the ALLHAT study showed that α -blockers are less effective than diuretics in preventing cardiovascular events, mainly heart failure.^{96,97} Because of these results, the National Institutes of Health recommended not to use an α -blocker as the first drug of choice in hypertension. It is noteworthy that the systolic blood pressure was higher by 2 mm Hg in the doxazosin-treated patients than in the diuretic-treated patients, and the high rate of heart failure began very shortly after randomization.⁹⁶ The ALLHAT results with the ACE inhibitor were rather similar to the results with α -blockers,⁸ but the ALLHAT investigators reported that ACE inhibitors remained a safe and effective first choice in hypertensive patients. This would indicate that α -blockers are safe antihypertensive agents, but because of the ALLHAT results it should not be used as the first antihypertensive drug.

New-Onset Diabetes with Antihypertensive Therapy

Ever since the pioneering observation of Dollery's team^{98,99} more than 20 years ago, a variety of studies documented that long-term diuretic therapy, particularly when combined with a β -blocker, diminishes glucose tolerance and increases the risk for new-onset diabetes. Conversely, as we learned from recent trials, treatment with antihypertensive drugs such as blockers of the renin-angiotensin system or calcium antagonists seem to decrease this risk (Table 1).^{7,8,16,25,48,83,100-104} Opie et al¹⁰⁵ presented a meta-analysis of 7 studies in almost 60,000 patients showing that compared with old therapies (β -blockers and diuretics), blockers of the renin-angiotensin system decreased the occurrence of new-onset diabetes by 20% ($P < .001$) and calcium antagonists by 16% ($P < .001$), respectively. It must be emphasized that new-onset diabetes was not a prespecified end point in any of the earlier-described prospective randomized trials. Opie et al calculated that the number needed to treat by new rather than by old therapies to avoid 1 case of new-onset diabetes was 60 to 70 for the duration of 4 years.

Table 1 Occurrence of New-Onset Diabetes in Recent Prospective Randomized Trials on Antihypertensive Therapy

Study	Trial Drugs	% Decrease in Risk of New-Onset Diabetes
CAPPP ¹⁶	ACE inhibitor versus conventional	-14
STOP-2 ¹⁰⁰	ACE inhibitor versus conventional	-4 (NS)
ALLHAT ⁸	ACE inhibitor versus diuretic	-40*/+30-40
HOPE ¹⁰¹	ACE inhibitor versus placebo	-34
ANBP 2 ¹⁰²	ACE inhibitor versus diuretic	-33
STOP-2 ¹⁰⁰	Calcium antagonist versus conventional	-2 (NS)
INSIGHT ⁷	Calcium antagonist versus diuretic	-23
ALLHAT ⁸	Calcium antagonist versus diuretic	-25*/+16†
INVEST ¹⁰³	Calcium antagonist versus β -blocker	-16
NORDIL ⁴⁸	Calcium antagonist versus conventional	-13
LIFE ²⁵	ARB versus β -blocker	-25
SCOPE ⁸³	ARB versus conventional	-20
CHARM + ⁸⁸	ARB versus placebo	-22
ALPINE ¹⁰⁴	ARB versus diuretic	-87

Abbreviations: CAPPP, Captopril Prevention Project; STOP, Swedish Trial in Old Patients with Hypertension; HOPE, Heart Outcomes Prevention Evaluation Study; INSIGHT, International Nifedipine GITS study; Intervention as a Goal in Hypertension Treatment; INVEST, International Verapamil-Trandolapril Study; NORDIL, Nordic Diltiazem Study; LIFE, Losartan Intervention For Endpoint reduction in Hypertension Study; SCOPE, Study on Cognition and Prognosis in the Elderly; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; ALPINE, Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation.

*T, 2 y.

†T, 4 y and patients with congestive heart failure.

Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation Study

The recent Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation¹⁰⁴ study was designed to compare the effects of antihypertensive therapy on glucose metabolism in almost 400 patients with uncomplicated hypertension who had never been treated. Patients were randomized to either an angiotensin-receptor blocker (with addition of a calcium antagonist if needed) or to a thiazide diuretic (and a β -blocker if needed). After only 1 year of follow-up evaluation, 18 patients in the diuretic arm reached diagnostic criteria of the metabolic syndrome and 9 had developed frank diabetes. The corresponding numbers in the angiotensin-receptor-blocker arm were 5 and 1, respectively.

VALUE Study

In the VALUE study,⁵² more than 15,000 patients with hypertension and 1 or more additional risk factors were randomized to either amlodipine or valsartan. Investigators found that new-onset diabetes was 23% less common in the patients treated with valsartan than in those treated with amlodipine, despite the fact that blood pressure control was significantly better with amlodipine throughout the duration of the study. These results have to be interpreted in the context of the ALLHAT study in which the risk for new-onset diabetes was significantly lower with amlodipine than with chlorthalidone, but not as low as with lisinopril. Of note, however, patients who were randomized to amlodipine had significantly more hypokalemia than patients who were randomized to valsartan. Hypokalemia can impair glucose tolerance by interfering with insulin release from the pancreas.

Such a sequence of events originally was proposed by Conn¹⁰⁶ to explain the high risk for diabetes in patients with primary aldosteronism. These finding subsequently were confirmed by Fajans et al¹⁰⁷ in patients with islet cell tumors. Helderman et al¹⁰⁸ reported that glucose intolerance associated with thiazide diuretics could be avoided entirely if whole-body potassium balance was maintained. Thus, the higher risk for de novo diabetes in the amlodipine arm possibly could be explained by the greater prevalence of hypokalemia.

ALLHAT Study

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack⁸ study, about 10% of the total study population of patients developed new-onset diabetes during the 4 to 6 years duration of the study. Of note, the risk for becoming diabetic was between 40% and 65% higher in patients on chlorthalidone-based therapy than in patients on lisinopril-based therapy, and between 18% and 30% higher in patients on chlorthalidone than in those on amlodipine. The ALLHAT investigators reassuringly stated that, "Overall, these metabolic differences did not translate into more cardiovascular events or into higher all cause mortality in the chlorthalidone group."⁸ That this statement was taken over almost verbatim by the investigators of the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure¹⁸ report, which perhaps is not surprising given that more than half of them were ALLHAT investigators. However, these reassuring words may strike the practicing physician as slightly myopic given that the follow-up period in the ALLHAT study after the diagnosis of diabetes was 2 to 4 years. Antihypertensive therapy most often is lifelong and a follow-up period lasting a few years is

unlikely to give us any information as to the cardiovascular morbidity and mortality related to thiazide diuretic-associated diabetes.¹⁰⁹

Long-Term Follow-Up Evaluation

The recent thorough study of Verdecchia et al¹¹⁰ has thrown some light on this issue. The investigators reported an up to 16-year follow-up evaluation of almost 800 initially untreated hypertensive patients, 6.5% of whom had diabetes at the onset, and 5.8% of whom developed new-onset diabetes throughout the study. The fasting blood sugar level at entry as well as diuretic treatment on follow-up evaluation were independent, powerful predictors of new-onset diabetes ($P < .0001$, and $P < .004$, respectively). Most importantly, compared with patients who never developed diabetes, the risk for cardiovascular disease during the follow-up period was very similar in patients who developed diabetes (odds ratio, 2.92; 95% confidence interval, 1.33-6.41; $P = .007$) and in the group that had pre-existing diabetes (odds ratio, 3.57; 95% confidence interval, 1.65-7.73; $P = .001$). Patients with new-onset diabetes and those with a prior diagnosis of diabetes were almost 3 times as likely to develop subsequent cardiovascular disease than those who remained free of diabetes. These provocative findings not only show again that antihypertensive therapy with a thiazide diuretic and if needed combined with a β -blocker confers a substantial risk for new-onset diabetes, but, more importantly, that patients who have become diabetic will suffer all the adverse sequelae of this disease. Alderman et al,¹¹¹ in an almost 7,000-patient study, showed that cardiovascular disease increased in hypertensive diuretic users who developed hyperglycemia, even when blood pressure was well controlled. The investigators stated, "Cardiovascular disease incidence has a direct dose response relation with diuretic used with frequent users having the highest rate."¹¹¹ Conceivably, the combination of a diuretic and an ACE inhibitor may confer a lesser risk for new-onset diabetes. At least in a small short-term study, ACE inhibitors seemed to prevent the metabolic deleterious effect of the diuretic thiazide.¹¹²

Long-Term Safety of Antihypertensive Therapy

Most prospective randomized trials last 4 to 6 years and therefore provide little, if any, information as to long-term safety of antihypertensive drug classes. Many patients are exposed to blood pressure-lowering drugs for many decades, and drug-induced changes could be cumulative. This potentially is true with the adverse metabolic effects that are seen with diuretics and β -blockers. Clearly, the increased risk for new-onset diabetes with these drugs, single or in combination, will not translate into increased morbidity and mortality in a study lasting only 4 to 6 years.⁸ After decades, however, sustained diabetes may have an important impact on cardiovascular morbidity and mortality. The same reasoning holds true for carcinogenicity of antihypertensive drugs. Recently, we have documented that long-term treatment with thiazide

diuretics is a low-grade risk for renal cell carcinoma.¹¹³ In 10 independent case-control studies and 3 cohort studies, the risk for renal cell carcinoma was increased distinctly with diuretic therapy, and it seemed that the higher the daily diuretic dose, the longer the diuretic exposure and the greater the risk. Also, the risk was higher in women than in men. The tubular cell is the main target of the diuretic's pharmacologic effect. Conceivably, the chronic chemical bombardment of this cell over years and decades may have a low-grade carcinogenic effect. Again, this risk for carcinogenicity is unlikely to be discovered in short-term (4-6 y), prospective, randomized trials because, similar to other carcinogenic substances (tobacco), the exposure needed exceeds 2 decades. Diuretics have the longest track record of any antihypertensive drug class and, therefore, have been scrutinized intensively. Little, if anything, should be concluded as to the long-term safety, particularly with regard to carcinogenicity of other antihypertensive drug classes.

Combination Therapy

Numerous trials have been designed to provide a head-to-head comparison of 2 antihypertensive drugs. In most of these trials, add-on therapy was used in both therapeutic arms. However, little or no information has been provided whether, indeed, add-on therapy over and above lowering blood pressure did reduce morbidity and mortality. In the MRC trial in the elderly, the addition of a β -blocker to the thiazide diuretic distinctly diminished the benefits (cardiovascular morbidity and mortality) and the benefits disappeared with β -blocker monotherapy. Similarly, in the Systolic Hypertension in the Elderly Program trial, the addition of a β -blocker did not provide any further benefits despite the additional decrease in arterial pressure.²⁸ Given that more than two thirds of patients with stage I and stage II hypertension will need combination therapy in one form or the other, we urgently need studies allowing us to assess the benefits of one combination versus another.

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