Diuretic Treatment of Hypertension

Ehud Grossman, md[1]
Paolo Verdecchia, md, facc, faha, fesc[2]
Ari Shamiss, md[1]

Fabio Angeli, md[3]
Gianpaolo Reboldi, md, phd, msc[4]

Although thiazide and thiazide-like diuretics are indispensable drugs in the treatment of hypertension, their role as first-line or even second-line drugs is a provoking debate.

The European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines recommend that thiazide diuretics should be considered as suitable as β-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers for the initiation and maintenance of antihypertensive treatment (1).

Another European position, endorsed by the British Hypertension Society, is that diuretics and calcium channel blockers should be first-line drugs in hypertensive patients aged ≥55 years or black patients of any age, whereas ACE inhibitors (or angiotensin receptor blockers in the case of intolerance to ACE inhibitors) should be first-line drugs in hypertensive patients younger than 55 years of age (http://nice.org.uk/CG034guidance).

The Seventh Report of the Joint National Committee (JNC VII) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends that thiazide diuretics should be preferred drugs in "most" hypertensive patients, either alone or combined with drugs from other classes (2).

The present review does not intend to negate the important role of diuretics in certain groups of patients (blacks, salt-sensitive patients, concomitant heart failure) or to underestimate their role in

multiple-drug combinations in patients with resistant hypertension. The main argument that will be discussed is the place of diuretics as first-line drugs or add-on drugs in the context of the available antihypertensive armamentarium.

The pro side of the controversy will argue that diuretics should remain the preferred drugs for initial treatment in many hypertensive patients, whereas the cons side will contend that emerging evidence from outcome-based studies is casting doubt on the role of these drugs as first-line and even second-line antihypertensive treatment.

THE PRO SIDE—Lowering blood pressure (BP) has been shown to reduce the risk of cardiovascular (CV) morbidity and mortality. The main benefit of lowering BP is due to the reduction in the risk of stroke and heart failure (HF). In many trials in which a reduction in CV events was documented, antihypertensive therapy was diuretic-based (3–8).

Effect of diuretic treatment on stroke morbidity and mortality

In the era of placebo-controlled trials, several studies attested to the efficacy of diuretics in reducing stroke morbidity and mortality (6,7). In a recent published study from China, indapamide given to patients with a history of stroke or transient ischemic attack reduced the risk of stroke by 31% (3). In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) (9) in patients with

cerebrovascular disease, combination therapy of a diuretic (indapamide) and ACE inhibitor (perindopril) reduced the risk of stroke by 43% compared with placebo. Perindopril alone, despite lowering systolic BP by 5 mmHg, decreased stroke risk only by a nonsignificant 5%.

Several studies attested to the superior efficacy of diuretic therapy over other antihypertensive agents in reducing the risk for stroke (4–6,8,10,11). In the Second Australian National Blood Pressure Study (ANBP2) (10), fatal stroke occurred two times more in patients treated with an ACE inhibitor than in patients treated with a diuretic. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (4,5), chlorthalidone was superior to the α-blocker doxazosin mesylate in the prevention of stroke and was superior to the ACE inhibitor lisinopril in the prevention of stroke in black individuals. In the Medical Research Council (MRC) study in 1985, bendrofluazide was documented to be almost three times as efficacious as the β-blocker propranolol hydrochloride in preventing stroke (8). In the MRC trial in elderly patients (6), hydrochlorothiazide and amiloride reduced the risk of stroke, whereas β-blockers failed to reduce the risk of stroke despite a similar lowering of BP. In the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT), 25 mg hydrochlorothiazide plus amiloride 2.5 were as effective as 30 mg nifedipine for preventing stroke (12).

In a large meta-analysis, including 48,220 patients, Psaty et al. (13) found that high-dose diuretic therapy reduced the risk of stroke by 51%, whereas therapy with β-blockers reduced the risk by only 29% (P = 0.02). Klungel et al. (14) showed that among 1,237 single-drug users with no history of CV disease, the adjusted risk of ischemic stroke was 2 to 2 1/2 times higher among users of β-blockers, calcium antagonists, or ACE inhibitors than among users of a diuretic alone. Interestingly, even in patients with CV disease, diuretics still conferred a lower stroke risk than other drugs, although the difference was considerably smaller. The recent Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial showed

that a combination of the ACE inhibitor benazepril with hydrochlorothiazide was less effective in lowering the risk of the predefined primary end points than the combination of benazepril with amlodipine (15). However, analysis of the benefit for the individual components of the primary end points showed that, for stroke prevention, hydrochlorothiazide and amlodipine were the same. Thus, for stroke prevention, a diuretic is superior to some antihypertensive agents.

Effect of diuretic treatment on HF

Thiazide diuretic is very effective in preventing the development of HF in hypertensive patients. In a large meta-analysis that included 18 long-term placebo-controlled randomized trials, high-dose diuretic therapy reduced the risk of HF by 83% and low-dose diuretic reduced the risk of HF by 42% (13). In the Hypertension in the Very Elderly Trial (HYVET), indapamide reduced the rate of HF by 64% in very elderly patients with hypertension (16). In INSIGHT, diuretic was more effective than nifedipine in preventing nonfatal HF (12). In the ALLHAT study, chlorthalidone was superior to doxazosin, lisinopril, and amlodipine in preventing HF (4,5). The data were validated after a rigorous evaluation of all hospitalized HF events (17). In a subanalysis of ALLHAT, chlorthalidone was superior to the other agents in preventing HF in participants with the metabolic syndrome and in patients with diabetes (18). One of the arguments against the findings of the ALLHAT study was that the achieved BP in the chlorthalidone arm was lower than the achieved BP in the other treatment arms. However, analyses using achieved BP levels as time-dependent covariates in a Cox proportional hazard regression model showed that after adjustment for BP, the differences in risk of stroke and HF between treatment arms remained statistically significant (18). In the ACCOMPLISH trial, the combination of benazepril with hydrochlorothiazide was as effective as the combination of benazepril with amlodipine in preventing HF (15). Thus, it is clear that diuretic is very effective and may be superior to other agents in preventing new-onset HF in hypertensive patients.

Diuretics in the elderly

Hypertension is much more common in the elderly, and in this age–group, isolated systolic hypertension is particularly common. Several placebo-controlled studies showed the efficacy of diuretics in reducing CV morbidity and mortality in the elderly (6,7,16,19). In the Systolic Hypertension in the Elderly Program (SHEP) (7), chlorthalidone reduced in elderly patients with isolated systolic hypertension the rate of total stroke by 36%, the rate of major CV events by 32%, and the rate of all-cause mortality by 13%. We have shown in a meta-analysis that in the elderly, diuretics are more effective than β-blockers in lowering BP (20). Moreover, only diuretics reduced the risk of coronary heart disease and all-cause mortality (20). The ALLHAT study, which showed superiority of diuretics over other antihypertensive agents in some secondary end points (see above), was not defined as a study of the elderly, but 57.5% of the participants were age ≥65 years; therefore, this study is considered a study in the elderly (4,5). The only exception was the ANBP2 study, in which treatment with an ACE inhibitor in older subjects, particularly men, led to better outcomes than treatment with diuretic agents, despite similar reductions of BP (10). It is noteworthy that the design of the ANBP2 study was less rigorous than other studies, since it was a prospective, randomized, open-label, blinded-endpoint (PROBE) study that is open to bias. In the ANBP2 study, only 83% of the participants received their assigned treatment, only 58% of participants were randomly assigned to an ACE inhibitor, and 62% of those assigned to a diuretic were still receiving assigned treatment at the end of the study (10). In the recent HYVET (16), indapamide reduced the rate of stroke, coronary heart disease, HF, and all-cause mortality. It is noteworthy that in the pilot, HYVET participants received either diuretic or ACE inhibitor or placebo, and only diuretics reduced the risk of stroke, whereas ACE inhibitors did not reduce the risk of stroke, despite a similar reduction in BP (21). Thus, it seems that for elderly patients, a diuretic should remain the drug of choice.

Additional advantages of diuretics

Several studies showed that diuretics prevent the development of osteoporosis and reduce the risk of hip fractures (22–24). In a randomized double-blind 2-year trial, Reid et al. (24) showed that hydrochlorothiazide slowed cortical bone loss in normal postmenopausal women. Schoofs et al. (23) showed in a prospective population-based cohort study that thiazide protects against hip fractures and that this protective effect disappears within 4 months after use is discontinued. Thus, in addition to their use to lower BP, thiazide plays a major role in the prevention of osteoporosis and fractures.

Diuretic therapy can transform non-dippers to dippers and thereby offer an additional therapeutic advantage of reducing the risk of CV complications (25).

Diuretic-induced glucose elevations

Several studies showed that use of thiazide diuretic increases glucose levels (4,12,26), but in these studies, the second drug was a β-blocker that impaired glucose metabolism. The Atherosclerosis Risk in Communities (ARIC) study assessed the incidence of new-onset diabetes (NOD) after 3 and 6 years in 12,550 adults who did not have diabetes. Patients who received thiazide diuretics were not at greater risk for the subsequent development of diabetes than the subjects with hypertension who were not receiving any antihypertensive therapy (27). In this study, only subjects with hypertension who were taking β-blockers had a 28% higher risk of subsequent diabetes. In the ACCOMPLISH study, the effects of the two treatment arms on glucose levels were not reported (15). It is likely that the use of diuretics with an ACE inhibitor did not adversely affect glucose metabolism, as we have previously shown (28). If a high-dose diuretic has a negative effect on glucose metabolism, it may be related to hypokalemia (29–31). Analysis of the SHEP data showed that each 0.5 mEq/L decrease in serum potassium during the 1st year of treatment was associated with a 45% higher adjusted diabetes risk (32). Potassium supplementation or combination of thiazide with ACE inhibitor or potassium-sparing agents might prevent thiazide-induced diabetes (33). The combination of thiazide with aldosterone antagonist may not only prevent NOD but also improve BP control (34). It seems that not all diuretics are equal in regard to the effect on insulin resistance. Leonetti et al. (35) showed that indapamide does not have a deleterious effect on glucose tolerance. The effects of diuretic-induced glucose elevation on long-term CV risk were reported in several studies. Verdecchia et al. (36) reported a nearly threefold higher CV disease risk after 16 years of follow-up in treated patients with hypertension (54% treated with diuretics) who developed NOD; no relationship was seen between diuretic usage and CV events. In post hoc subgroup analyses of

the ALLHAT data, there was no significant association of fasting glucose level change at 2 years with subsequent coronary heart disease, stroke, CV disease, total mortality, or end-stage renal disease. There was no significant association of incident diabetes at 2 years with clinical outcomes, except for coronary heart disease (risk ratio 1.64; $P = 0.006$), but the risk ratio was lower and nonsignificant in the chlorthalidone group (risk ratio 1.46; $P = 0.14$) (37). Analysis of the 14.3 years of follow-up from the SHEP revealed that incident diabetes during the trial among participants randomized to placebo was associated with a >50% increase in CV mortality but not in individuals randomized to the diuretic (38). Thus, diuretic-induced glucose changes may underline lesser prognostic significance.

Other disadvantages of diuretics

Diuretics may induce some metabolic alterations that are harmful. The most common metabolic derangement is hyponatremia, which appears to be particularly common in elderly women (39). This side effect can be prevented by use of a low to medium dose of diuretics and by instructing patients to limit fluid intake. The deleterious effects of thiazide on lipid profile are mainly observed in the short term and almost disappear in long-term studies (40).

Role of diuretics as an add-on therapy

Recently, two large prospective studies cast doubt on the role of thiazides as an add-on therapy (15,26). The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) compared the β-blocker atenolol with the calcium antagonist amlodipine. A thiazide was added to atenolol and an ACE inhibitor was added to amlodipine when BP did not reach the goal. The primary end points were not significantly different between the two regimens, but fewer individuals on the amlodipine-based regimen had fatal and nonfatal stroke, total CV events and procedures, and all-cause mortality. From this study, we can only learn that atenolol is less effective than amlodipine, but we cannot blame the diuretic in the worse outcome. The ACCOMPLISH trial was stopped early when the data were clear that the single pill combination of ACE inhibitor with calcium antagonist was superior to the combination of ACE inhibitor with a diuretic (15). The amlodipine and hydrochlorothiazide components of the single

pill combination could be titrated to 25 and 10 mg, respectively. Although the dose of amlodipine in the trial was similar to that demonstrating favorable outcomes in other outcome trials, the dose range for hydrochlorothiazide (12.5–25 mg) was lower than the dose range (equivalent to 25–50 mg) used in trials demonstrating benefits of thiazide on CV outcome (4,6,19). Information on supplemented antihypertensive agents was not reported, but the recommended supplementary drugs were α- and β-blockers, for which effects on CV outcomes are inferior. Of note, a small but significant BP difference (0.9 mmHg systolic and 1.1 mmHg diastolic; $P < 0.001$ for both) was recorded between the two arms of treatment favoring the ACE inhibitor–calcium antagonist combination. The right conclusion of the ACCOMPLISH study is that hydrochlorothiazide in a dose of ≤25 mg/day may be less effective in preventing CV disease than a full dose of amlodipine.

The results of this study raised the question whether all thiazide-type diuretics are equal. Several successful diuretic studies used chlorthalidone in a dose of up to 25 mg/day (4,5,7,41,42). A meta-analysis of trials done until 2004 reported similar clinical CV outcomes across the class (43). However, these studies used doses of these agents that were higher than the 12.5–25 mg/day dose of hydrochlorothiazide used in the ACCOMPLISH study. Recent data suggest that chlorthalidone is 1.5- to 2-fold more potent in lowering BP than hydrochlorothiazide (44). Thus, to achieve the beneficial effect with diuretics, one should use hydrochlorothiazide in a dose of up to at least 37.5 mg/day. Another thiazide-like diuretic that is less discussed is indapamide. This agent has less adverse effect on metabolic parameters than other diuretics (45,46), is more effective than enalapril in reducing left ventricular mass (47), is equivalent to enalapril in reducing microalbuminuria (48), and is effective in reducing CV morbidity and mortality in clinical trials (3,9,16,49). Thus, the use of indapamide as a leading diuretic agent may be worthwhile.

THE CON SIDE—There is no evidence from systematic overviews and meta-analyses that thiazide diuretics are superior to other classes of antihypertensive drugs in reducing CV risk (50). These results endorse the position of the European guidelines, which leave to the doctor the choice

and flexibility of choosing among available antihypertensive drugs on the basis of several considerations, including efficacy, tolerability, compelling indications, contraindications, race, and cost.

Diuretics as first-line drugs: outcome-based studies

ALLHAT was perceived as the trial that conclusively demonstrated the superiority of diuretics over other classes of antihypertensive drugs. ALLHAT was designed to test the hypothesis that the combined incidence of fatal CHD and nonfatal myocardial infarction will be lower by 16% in hypertensive patients receiving a calcium antagonist (amlodipine), an ACE inhibitor (lisinopril), or an α adrenergic blocker (doxazosin) as first-line therapy than in subjects treated with chlorthalidone as first-line therapy. The study enrolled 42,418 high-risk patients aged ≥55 years, and 35% were black (4). The doxazosin arm was prematurely stopped because of a significantly higher incidence of HF.

It is frequently forgotten that the ALLHAT study failed to demonstrate its primary goal because the incidence of the primary end point did not show any statistical differences between the chlorthalidone group and any other treatment group (6-year event rate: chlortalidone 11.5%, amlodipine 11.3%, lisinopril 11.4%). Compared with chlorthalidone, the relative risks were 0.98 (95% CI 0.90–1.07) for amlodipine and 0.99 (95% CI 0.91–1.08) for lisinopril. Furthermore, all-cause mortality did not differ between the groups (4).

The only significant differences in ALLHAT emerged in the analysis of some secondary end points. The risk of HF, which in itself was not a prespecified secondary end point, but just a component of a secondary end point (named "combined cardiovascular disease" and consisting of CHD + stroke + revascularization procedures + angina + HF [hospitalized or treated] + peripheral arterial disease), was 38% higher with amlodipine and 15% with lisinopril than with chlortalidone (both $P < 0.01$). Furthermore, the risk of stroke, a prespecified secondary end point, was 7% lower with amlodipine than with chlorthalidone ($P = $ NS) and 15% higher with lisinopril than with chlortalidone ($P = 0.02$).

These results were attributed to the lower systolic BP in the patients allocated to chlorthalidone compared with lisinopril (2 mmHg, $P < 0.001$) and amlodipine

(0.8 mmHg, $P = 0.03$) (4). However, >90% of ALLHAT patients were receiving an antihypertensive drug, a diuretic in most cases, at the time of randomization, when they abruptly abandoned the previous agents and were fully switched to trials drugs. Thus, patients allocated to drugs different from chlorthalidone were more likely to regain fluids, with potential rapid disclosure of signs and symptoms of heart failure. Consistent with this view is the early divergence of the Kaplan-Meier curved after randomization. However, subsequent post hoc analyses with validation of HF events and adjustment for pre-entry diuretic use seemed to confirm the original results (17). Thus, ALLHAT did not meet its primary goal, and the evidence of superiority of chlortalidone over comparators was based on the analysis of secondary end points. Consequently, the enthusiastic statement that the "verdict from ALLHAT is that thiazide diuretics are the preferred initial treatment of hypertension" was excessive. Furthermore, results obtained with chlorthalidone cannot be extrapolated to hydrochlorothiazide or other thiazide diuretics. The duration of the antihypertensive effect of chlorthalidone is significantly longer than that of hydrochlorothiazide, as evidenced by 24-h ambulatory BP monitoring (44). The results of ALLHAT are consistent with the INSIGHT study, which failed to detect outcome differences between a diuretic (hydrochlorothiazide plus amiloride) and a calcium antagonist (nifedipine in a long-acting gastrointestinal transport system) in 6,321 hypertensive patients aged 55–80 years. Again, nonfatal HF (a secondary end point) was less frequent in the diuretic group than in the calcium antagonist group ($P = 0.028$) (12).

Another major study that failed to demonstrate the superiority of diuretics over comparators was the ANBP2 trial. This was a randomized open-label study between diuretics and ACE inhibitors conducted in 6,083 elderly subjects with hypertension. The ACE inhibitor enalapril and the diuretic hydrochlorothiazide were recommended as initial therapy, but the final choice of the specific agent was left to investigators, who were family practitioners. The primary end point of the study, a composite of CV morbidity and all-cause mortality, was marginally less frequent in the ACE inhibitor group than in the diuretic group (hazard ratio [HR] 0.89, 95% CI 0.79–1.00; $P = 0.05$) (10).

Diuretics as second-line drugs: outcome-based studies

ASCOT-BPLA (Blood Pressure–Lowering Arm) was a multicenter randomized controlled trial conducted in 19,257 hypertensive patients aged 40–79 years who had at least three other CV risk factors. Patients were randomized to a first-line treatment with either atenolol or amlodipine. In the case of lack of BP control, bendroflumethiazide was added to atenolol and perindopril to amlodipine. Hence, the trial compared an "old-drug" strategy (β-blocker alone or with a diuretic) with a "new-drug" strategy (calcium antagonist alone or with an ACE inhibitor). The trial was stopped prematurely after 5.5 years because of statistically significant lower incidence of all-cause mortality, CV mortality, and other important secondary end points in the new-drug strategy group. The primary end point, a composite of nonfatal myocardial infarction and fatal CHD, did not differ between the groups (HR 0.90, 95% CI 0.79–1.02, $P = 0.105$) (26).

Although the benefits of amlodipine and perindopril over atenolol and bendroflumethiazide appeared to be largely driven by the 2.7 mmHg greater reduction in systolic BP, this study clearly demonstrated that a new-drug strategy is superior to an old-drug strategy in patients with complicated hypertension or associated risk factors.

ACCOMPLISH was a double-blind randomized study in which 11,506 patients with hypertension complicated by organ damage or associated with diabetes or overt CV disease were randomized to either benazepril plus amlodipine or benazepril plus hydrochlorothiazide as first-step treatment. The trial was prematurely stopped after a mean follow-up of 36 months because the boundary of the pre-specified stopping rule was exceeded. The risk of primary composite end point (death from CV causes or nonfatal CV disease) was 20% lower with benazepril-amlodipine than with benazepril-hydrochlorothiazide (HR 0.80, 95% CI 0.72–0.90, $P < 0.001$). Also, the composite secondary end point (death from CV causes, nonfatal myocardial infarction, and nonfatal stroke) was less frequent in the benazepril-amlodipine group than in the benazepril-hydrochlorothiazide group (HR 0.79, 95% CI 0.67–0.92, $P = 0.002$) (15).

The ACCOMPLISH study is unique in its design by substantiating the superiority of a fixed combination of ACE inhibitor plus amlodipine over a fixed combination of ACE inhibitor plus diuretic.

These data may relegate thiazide diuretics to third-line therapy. However, since the study population was composed of complicated patients with hypertension and prior history of CHD, diabetes, or organ damage, it is unclear to what extent these findings can be extrapolated to less uncomplicated hypertensive subjects.

Diuretics and new-onset diabetes

Diuretics increase the risk of NOD. In a network meta-analysis of 22 clinical trials, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and placebo were associated with a significantly lesser risk of NOD compared with diuretics (51). The risk of NOD did not differ between diuretics and β-blockers (51).

Importantly, NOD was not a prespecified primary end point in any of these trials. Diuretic-induced hypokalemia is believed to be one possible cause of the rise in glucose (52), perhaps through an impaired insulin secretion by pancreatic β-cells. Also diuretic-induced hyperuricemia was associated with impaired glucose tolerance.

The controversy surrounding the issue of NOD in treated hypertensive subjects is not focused on the diabetogenic effect of diuretics and β-blockers, which is taken for granted (1), but on the controversial interpretation of the few data on the prognostic impact of NOD induced by these drugs.

In a cohort study from our group, NOD portended a risk for subsequent CV disease that was not dissimilar from that of previously known diabetes. Notably, plasma glucose at entry and diuretic treatment at the follow-up visit were independent predictors of NOD (36). In a post hoc analysis of the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) study, the hypertensive subjects who developed NOD showed a 43% higher risk of cardiac morbidity when compared with individuals who did not develop diabetes (53). NOD was associated with a marginally higher risk of myocardial infarction ($P = 0.057$) and a significantly higher risk of congestive HF ($P = 0.017$) (53). These findings are consistent with a report from the Ongoing Telmisartan Alone and In Combination With Ramipril Global End Point Trial (ONTARGET), in which NOD was associated with a 74% excess risk of congestive HF requiring hospitalization (54).

Individuals who are skeptical about the adverse prognostic value of NOD

argue that NOD failed to translate into a prognostic disadvantage in most trials. In the ALLHAT study, the higher incidence of NOD in the chlorthalidone group did not translate into a prognostic burden in this group, and a similar situation occurred in other studies (12). However, a frequently forgotten consideration is that different risks of NOD are unlikely to translate into different risks of hard end points in the setting of available mega-trials. We estimated that one CV event specifically associated with NOD may be prevented for every 385–449 subjects treated with new, rather than old (diuretics, β-blockers), antihypertensive drugs for ~4 years (55). Consequently, even large trials such as ALLHAT may be under-powered to detect the adverse prognostic impact of NOD (55).

Consistent with this view, in the ALLHAT study, the incidence of coronary artery disease was 64% higher (95% CI 15–233) in the subjects who developed NOD in the first 2 years of follow-up than in those who did not (56). However, when the chlorthalidone, amlodipine, and lisinopril groups were analyzed separately, the excess risk of coronary artery disease was significant only in the lisinopril group (HR 2.23, 95% CI 1.07–4.62) and not in the other groups, although the *P* value for the interaction term was not significant (*P* = 0.21). The power of the chlorthalidone and amlodipine groups might have been inadequate to detect the adverse impact of NOD on coronary artery disease demonstrated in the total ALLHAT cohort. We argued that the lesser BP reduction in the lisinopril group compared with the other groups might have allowed NOD to unveil its adverse prognostic impact (55).

In line with this interpretation, in a post hoc analysis of the SHEP study, NOD was associated with a higher risk of all-cause mortality (HR 1.35, 95% CI 1.05–1.72) and CV mortality (HR 1.56, 95% CI 1.12–2.18) in the placebo group, not in the active treatment group (38). Because the SHEP population was composed by elderly hypertensive patients at high risk of events in the short term, the favorable prognostic impact of BP reduction in the active treatment group may have outweighed the adverse prognostic impact of NOD.

In conclusion, we should refrain from underestimating the adverse prognostic impact of NOD induced by diuretics and β-blockers, alone or combined, solely because of the failure by most randomized trials to disclose a significant association between NOD and outcome. NOD, whether or not induced by drugs, remains an important adverse prognostic marker that should be prevented. We suggested that in subjects at increased risk of NOD (impaired fasting glucose, obesity, metabolic syndrome), diuretics and β-blockers should *1*) be used cautiously, with the lowest effective dose and plasma glucose periodically checked, and *2*) be avoided in subjects with BP normalized by different classes of antihypertensive drugs.

Diuretics and lipids
Thiazide diuretics increase total cholesterol and HDL cholesterol by 5–7%. In a meta-analysis of 474 studies (57), diuretics increased cholesterol and triglyceride levels, and the rise in total cholesterol was paralleled by a rise in LDL cholesterol. The rise in cholesterol was dose dependent and greater in blacks. A reduction in the HDL cholesterol levels was noted only in patients with diabetes. The potentially adverse prognostic impact of increased total and LDL cholesterol in the very long term may be underestimated by the relatively short duration (generally 3–5 years) of available intervention trials. When dealing with a young hypertensive patient, it is unlikely that an expected persistent elevation of total and LDL cholesterol over decades may be beneficial.

Diuretics and the kidney
The long-term use of diuretics was associated with an increased risk of renal cell carcinoma. In a meta-analysis, Grossman et al. (58) found a 55% higher odds (95% CI 42–71%, *P* < 0.00001) of renal cell carcinoma in patients treated with diuretics compared with diuretic nonusers. The renal tubular cells, which are the main target of diuretics, are also the site of origin of malignancy. The association between diuretic treatment and renal cell carcinoma is a potentially important issue that requires solid confirmation in larger studies.

Discontinuation of diuretics
Discontinuation of diuretics is ~83% more likely than discontinuation of ACE inhibitors (59). By causing increased production of urine, diuretics may increase the urinary frequency. Overactive bladder defined as a syndrome consisting of urgency, with or without incontinence, usually associated with nocturia, is common in older subjects treated with diuretics.

Although often neglected by doctors, these symptoms may be troubling in elderly subjects.

Diuretics may cause several other adverse reactions, potentially leading to discontinuation. Hypokalemia was suggested as a potential trigger of arrhythmias and sudden cardiac death (60), although its impact is now less than in the past because of the widespread use of low-dose thiazides, potassium-sparing diuretics, and combinations with ACE inhibitors or angiotensin receptor blockers. Muscle cramps may cause suspicion of hypokalemia. Hyponatremia is another insidious side effect of diuretics and is particularly frequent in elderly women after prolonged use of the drug. Hyperuricemia is a dose-dependent effect that may lead to acute gouty arthritis.

CONCLUSIONS—Thiazide-type diuretics are at least as effective as β-blockers, calcium antagonists, and ACE inhibitors in reducing CV outcomes. Thiazide diuretics are particularly effective in preventing stroke and HF in hypertensive patients. These drugs are very effective in the elderly and very elderly patients. The combined use of thiazide-like diuretics with aldosterone antagonists may be worthwhile. Thus, diuretics should remain the leading agents in the management of hypertension. However, the statement that these drugs are superior to other drugs in almost all patients with hypertension is not supported by superiority studies. Particularly in the younger hypertensive subjects, the benefit of diuretics as first-line antihypertensive drugs should be weight against the risk of unwanted effects in the long term. This holds particularly true in subjects at high risk of developing diabetes.

References
1. Mancia G, De Backer G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105–1187

2. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289:2560–2572

3. Liu L, Wang Z, Gong L, et al. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. Hypertens Res 2009;32:1032–1040

4. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. 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

5. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs. chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2000;283: 1967–1975

6. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. BMJ 1992;304:405–412

7. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255–3264

8. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. Br Med J (Clin Res Ed) 1985;291:97–104

9. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358: 1033–1041

10. Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting–enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med 2003;348:583–592

11. 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

12. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet 2000;356:366–372

13. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. JAMA 1997;277:739–745

14. Klungel OH, Heckbert SR, Longstreth WT Jr, et al. Antihypertensive drug therapies and the risk of ischemic stroke. Arch Intern Med 2001;161:37–43

15. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359: 2417–2428

16. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008; 358:1887–1898

17. Einhorn PT, Davis BR, Massie BM, et al. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Heart Failure Validation Study: diagnosis and prognosis. Am Heart J 2007; 153:42–53

18. Wright JT Jr, Probstfield JL, Cushman WC, et al. ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses. Arch Intern Med 2009;169:832–842

19. Amery A, Birkenhäger W, Brixko P, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985; 1:1349–1354

20. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 1998;279: 1903–1907

21. Bulpitt CJ, Beckett NS, Cooke J, et al. Results of the pilot study for the Hypertension in the Very Elderly Trial. J Hypertens 2003;21:2409–2417

22. Bolland MJ, Ames RW, Horne AM, Orr-Walker BJ, Gamble GD, Reid IR. The effect of treatment with a thiazide diuretic for 4 years on bone density in normal postmenopausal women. Osteoporos Int 2007;18:479–486

23. Schoofs MW, van der Klift M, Hofman A, et al. Thiazide diuretics and the risk for hip fracture. Ann Intern Med 2003;139: 476–482

24. Reid IR, Ames RW, Orr-Walker BJ, et al. Hydrochlorothiazide reduces loss of cortical bone in normal postmenopausal women: a randomized controlled trial. Am J Med 2000;109:362–370

25. Uzu T, Kimura G. Diuretics shift circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. Circulation 1999;100:1635–1638

26. Dahlöf B, Sever PS, Poulter NR, et al. 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 2005;366:895–906

27. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus: Atherosclerosis Risk in Communities Study. N Engl J Med 2000;342:905–912

28. Shamiss A, Carroll J, Peleg E, Grossman E, Rosenthal T. The effect of enalapril with and without hydrochlorothiazide on insulin sensitivity and other metabolic abnormalities of hypertensive patients with NIDDM. Am J Hypertens 1995;8:276–281

29. Plavinik FL, Rodrigues CI, Zanella MT, Ribeiro AB. Hypokalemia, glucose intolerance, and hyperinsulinemia during diuretic therapy. Hypertension 1992;19 (Suppl.):II26–II29

30. Amery A, Berthaux P, Bulpitt C, et al. Glucose intolerance during diuretic therapy: results of trial by the European Working Party on Hypertension in the Elderly. Lancet 1978;1:681–683

31. Langford HG, Cutter G, Oberman A, Kansal P, Russell G. The effect of thiazide therapy on glucose, insulin and cholesterol metabolism and of glucose on potassium: results of a cross-sectional study in patients from the Hypertension Detection and Follow-up Program. J Hum Hypertens 1990;4:491–500

32. Shafi T, Appel LJ, Miller ER 3rd, Klag MJ, Parekh RS. Changes in serum potassium mediate thiazide-induced diabetes. Hypertension 2008;52:1022–1029

33. Jeunemaitre X, Charru A, Chatellier G, et al. Long-term metabolic effects of spironolactone and thiazides combined with potassium-sparing agents for treatment of essential hypertension. Am J Cardiol 1988;62:1072–1077

34. Sharabi Y, Adler E, Shamis A, Nussinovitch N, Markovitz A, Grossman E. Efficacy of add-on aldosterone receptor blocker in uncontrolled hypertension. Am J Hypertens 2006;19:750–755

35. Leonetti G, Rappelli A, Salvetti A, Scapellato L. Long-term effects of indapamide: final results of a two-year Italian multicenter study in systemic hypertension. Am J Cardiol 1990;65:67H–71H

36. Verdecchia P, Reboldi G, Angeli F, et al. Adverse prognostic significance of new diabetes in treated hypertensive subjects. Hypertension 2004;43:963–969

37. Barzilay JI, Davis BR, Cutler JA, et al. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering

Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2006;166: 2191–2201

38. Kostis JB, Wilson AC, Freudenberger RS, Cosgrove NM, Pressel SL, Davis BR; SHEP Collaborative Research Group. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. Am J Cardiol 2005;95:29–35

39. Sharabi Y, Illan R, Kamari Y, et al. Diuretic induced hyponatraemia in elderly hypertensive women. J Hum Hypertens 2002; 16:631–635

40. Lakshman MR, Reda DJ, Materson BJ, Cushman WC, Freis ED; Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. Arch Intern Med 1999;159:551–558

41. Multiple Risk Factor Intervention Trial Research Group. Mortality after 10 1/2 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. Circulation 1990;82:1616–1628

42. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 1979;242:2562–2571

43. Psaty BM, Lumley T, Furberg CD. Meta-analysis of health outcomes of chlorthalidone-based vs. nonchlorthalidone-based low-dose diuretic therapies. JAMA 2004;292:43–44

44. Ernst ME, Carter BL, Goerdt CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension 2006;47:352–358

45. Ames RP. A comparison of blood lipid and blood pressure responses during the treatment of systemic hypertension with indapamide and with thiazides. Am J Cardiol 1996;77:12b–16b

46. Gerber A, Weidmann P, Bianchetti MG, et al. Serum lipoproteins during treatment with the antihypertensive agent indapamide. Hypertension 1985;7:II164–II169

47. Gosse P, Sheridan DJ, Zannad F, et al. Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: the LIVE study. J Hypertens 2000;18: 1465–1475

48. Marre M, Puig JG, Kokot F, et al. Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with type 2 diabetes: the NESTOR Study. J Hypertens 2004;22: 1613–1622

49. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–840

50. Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003; 362:1527–1535

51. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet 2007; 369:201–207

52. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. Hypertension 2006;48: 219–224

53. Aksnes TA, Kjeldsen SE, Rostrup M, Omvik P, Hua TA, Julius S. Impact of new-onset diabetes mellitus on cardiac outcomes in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial population. Hypertension 2007;50:467–473

54. Held C, Gerstein HC, Yusuf S, et al. Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. Circulation 2007; 115:1371–1375

55. Verdecchia P, Angeli F, Reboldi G. New-onset diabetes, antihypertensive treatment, and outcome. Hypertension 2007; 50:459–460

56. Barzilay JI, Cutler JA, Davis BR. Antihypertensive medications and risk of diabetes mellitus. Curr Opin Nephrol Hypertens 2007;16:256–260

57. Kasiske BL, Ma JZ, Kalil RS, Louis TA. Effects of antihypertensive therapy on serum lipids. Ann Intern Med 1995;122: 133–141

58. Grossman E, Messerli FH, Goldbourt U. Does diuretic therapy increase the risk of renal cell carcinoma? Am J Cardiol 1999; 83:1090–1093

59. Corrao G, Zambon A, Parodi A, et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. J Hypertens 2008;26:819–824

60. Siegel D, Hulley SB, Black DM, et al. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. JAMA 1992;267:1083–1089