Diuretics: drugs of choice for the initial management of patients with hypertension

Flávio D Fuchs

The optimal first-line treatment of hypertension has been a contentious issue. Despite the probable advantage of diuretics, which was demonstrated in early clinical trials, concern about their metabolic effects meant that therapy was often commenced with drugs of other types. The results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, which compared agents of three groups of new antihypertensive drugs with a diuretic, demonstrated the equivalence between these drugs and chlorthalidone (Tenoretic™, AstraZeneca, London, UK) in the prevention of incident fatal coronary heart disease and nonfatal myocardial infarction. The diuretic was superior to other drugs in preventing some major secondary end-points, such as cerebrovascular disease and heart failure. These findings, together with other very practical reasons, such as easy administration, few side effects and low cost, demonstrate that diuretics are the first option for drug management of hypertension.

Hypertension, a highly prevalent condition worldwide, is one of the risk factors for cardiovascular disease and has been studied by a wide range of investigational models. In terms of treatment, there are many studies of efficacy of drug and nondrug therapies in reducing blood pressure, a surrogate end-point of the goals of treatment nowadays. In comparison to these studies, there are fewer than 30 large clinical trials looking at the effects of treatment on hard outcomes. Until the recent publication of the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) Trial [1], however, the fundamental therapeutic question was still subject to controversial opinions and guidelines, that is, which drug should be used for first-line antihypertensive therapy. A review of these clinical trials, together with the main results of ALLHAT, supports the nomination of diuretics as the first option for the treatment of hypertension.

How everything began: the pioneering trials

Thiazide diuretics were the first group of blood pressure lowering drugs that were tolerable and efficacious in reducing blood pressure. Moreover, a therapy based on diuretics was the first to be tested in a randomized, placebo-controlled trial, with hard end-points, in patients with hypertension [2]. This study was nominated as one of the classic clinical trials [3]. The design and development of this trial are superb. In the selection phase, all participants were hospitalized for 6 days and only male patients whose diastolic blood pressures averaged 90–129 mmHg without treatment from the fourth to sixth day of their hospitalization were considered for admission to the prerandomization period. Following their discharge from the hospital, potential trial participants entered a prerandomization trial period of 2–4 months of duration, during which they received placebo treatment with riboflavin, in order to select those who were the most compliant pill takers (50% were excluded). The active treatment consisted of a thiazide diuretic, reserpine and hydralazine. The terminating events defined by the investigators were death or class A events (mainly hemorrhage of one or both optic fundi), or treatment failure (primarily hospitalization with high blood pressure or adverse effects of the study drugs).

Unit of Hypertension, Division of Cardiology, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil
Tel./Fax: +55 51 3316 8420
ffuchs@hcpa.ufrgs.br

KEYWORDS: antihypertensive treatment, diuretics

© Future Drugs Ltd. All rights reserved. ISSN 1478-7210
A second group of events (class ‘B’) were nonterminating but included serious outcomes, such as cerebrovascular accidents, congestive heart failure (CHF) and myocardial infarction (MI). After 2 years, a strong treatment benefit emerged in patients with a baseline diastolic blood pressure greater than or equal to 115 mmHg. In the reanalysis of this study according to a more current definition of hard outcomes [3], it was demonstrated that the treatment of only six patients with severe hypertension per year prevented a major cardiovascular event (death, cerebrovascular incident, MI, CHF, retinal hemorrhage or doubling of creatinine or urea).

A similar relative efficacy was demonstrated in patients with diastolic blood pressure between 105 and 114 mmHg [4], albeit the absolute benefit was lower (NNT = 35 patients per year). In patients with blood pressure between 90 and 104 mmHg, recognized as mild hypertension at that time, the active treatment was not superior to placebo. The lower risk conferred by these levels of blood pressure and the insufficient statistical power of this study to show small differences between treatment groups, were responsible for such negative results.

Second generation trials

In an attempt to demonstrate the benefit of therapy in patients with mild hypertension, more than 30,000 patients were randomized in subsequent trials to an active treatment or placebo. The first studies were conducted predominantly in younger patients [5] and subsequently in the elderly [6–8]. In most studies, the first drug was a thiazide diuretic and the second drug was a β-blocker, mainly propranolol. In a small number of studies, the first option was a β-blocker and the add-on drug was a diuretic. In only one study, with elderly participants, an association of a thiazide diuretic with amiloride was compared with propranolol and to placebo as the first option [7]. The mean 40% reduction in the incidence of cerebrovascular disease observed in these studies reached the levels predicted by observational studies. The 16% reduction in the incidence of coronary heart disease in the studies with younger participants, however, was lower than the 25% anticipated by studies of risk [5]. This lower than expected efficacy generated heated controversy surrounding possible causes.

Why were diuretics less efficacious in preventing coronary heart disease in older trials?

The prevailing explanation for the lower efficacy of diuretics in earlier studies was derived from the identification of adverse effects of diuretics on the metabolism of carbohydrates and lipids. It was assumed that part of the beneficial effect on blood pressure was negated by the deleterious effect on glucose tolerance and cholesterol levels – a finding of small studies with short duration. The absence of and clinically relevant effects in comparative trials of long duration [9,10], including a large trial with hard end-points [11], was largely ignored. The metabolic hypothesis was the reason for the launch of several clinical trials to demonstrate the superiority of new antihypertensive drugs, which were free of those adverse metabolic effects.

Another explanation for the lower than expected efficacy of diuretics in the prevention of coronary heart disease was their effect on the balance of potassium and uric acid. An elegant case-control study demonstrated that the use of higher doses of diuretics, without a potassium-sparing agent, was associated with sudden death [12]. In a reanalysis of the Systolic Hypertension in the Elderly Program (SHEP) trial [13], participants who had hypokalemia after 1 year of treatment with a low-dose diuretic did not experience the reduction in cardiovascular events achieved among those who did not have hypokalemia. Those with a serum uric acid increase of 0.06 mM or more in the active treatment group in the SHEP trial had a similar risk of coronary events as the placebo group [14].

In trials with participants older than 60 years, with a therapy based on lower doses of thiazide diuretics (in some instances associated with a potassium-sparing agent), the magnitude of prevention of coronary events came closer to that predicted by cohort studies [6–8]. Taking together these and older studies and re-classifying the participants by the drug used as the first option, Psaty and associates confirmed the superiority of low doses of thiazide diuretics [15]. Only diuretics at lower doses were effective in preventing both cerebrovascular and coronary events. That lower doses have a better effect is a peculiar situation in terms of drug therapy. The inefficacy of β-blockers was unexpected because they are efficacious in the secondary prevention of MI. The lower efficacy in the elderly, in particular of atenolol, may be the reason for this finding. In the Medical Research Council (MRC) trial with old participants, only diuretics in lower doses, with a potassium-sparing agent, prevented both coronary and cerebrovascular disease; atenolol was not superior to placebo in any of the predefined end-points [7].

Trials comparing new antihypertensive agents with placebo

Only one agent of other antihypertensive groups, nifedipine, was previously shown to be superior to placebo in a large trial with clinical end-points [16]. The effect size observed in that study, with elderly participants with isolated systolic hypertension, was very similar to that observed in the American trial, which had a similar design and used a thiazide-like diuretic as the first option [6].

The Heart Outcomes Prevention Evaluation (HOPE) study compared ramipril (Altace™, Wyeth, NJ, USA) with placebo in patients at higher risk of presenting a cardiovascular event but was not originally included among the clinical trials with hypertensive patients [17]. Since almost 50% of the participants had hypertension, their results may also apply to these patients. The 22% reduction in the incidence of the primary end-point was originally attributed to other effects of the ACE inhibitor because the reduction of office blood pressure in patients treated with ramipril was slight. A small substudy, however, with ambulatory blood pressure monitoring, demonstrated a large fall in blood pressure, especially at night, in patients treated actively, suggesting that the effect of ramipril could be ascribed mainly to the reduction in blood pressure [18].
The Perindopril Protection Against Recurrent Stroke study (PROGRESS) allocated patients with a previous episode of cerebrovascular disease to an active treatment (perindopril alone or combined with indapamide, a diuretic) or placebo [19]. There was a 40% reduction in the recurrence of strokes in patients treated with the combination but not with perindopril alone. This beneficial effect was independent of the baseline blood pressure, as it was observed in hypertensive and normotensive participants. These findings, together with the results of HOPE trial, may lead to change in the paradigm in terms of hypertension diagnosis and blood pressure goals to be reached with treatment. In patients at higher risk of a cardiovascular event, such as patients with Type 2 diabetes or with a previous cardiovascular event, it is probably worthwhile to reduce blood pressure, independently of a formal diagnosis of hypertension. The absence of effect of perindopril alone for this purpose, and the beneficial effect of indapamide, suggests that a diuretic may have the preference in this context also.

Trials comparing drugs from different antihypertensive groups

The foundation for such trials was the idea that old therapies (i.e., diuretics and β-blockers) were not sufficiently efficacious in preventing coronary heart disease. Besides the scientific reasoning, the pharmaceutical companies have pushed research on new antihypertensive drugs, sometimes more towards conducting placebo-controlled trials than to comparing a new drug with an old drug. National drug agencies, such as the FDA, also requested that comparative, drug-controlled trials be undertaken, which conversely seems ethically and clinically appropriate. Even before the results of these new trials were released, physicians around the world were already convinced about the potential advantages of new drugs, and the newer classes of antihypertensive drugs surpassed diuretics and β-blockers in preference for antihypertensive treatment.

In the Captopril Prevention Project (CAPPP) trial [20], the open design without a centralized randomization of patients involved a systematic allocation of an unknown proportion of participants to captopril (Capoten®, Bristol-Myers Squibb) or to the control group, a fact that raises questions about the inclusion of this study in the category of randomized trials. Nevertheless, this trial showed that similar effects on a combined cardiovascular end-point could be achieved with a therapy based on either captopril, diuretics or β-blockers. Among the predefined secondary end-points, the only statistically significant supremacy was of conventional therapy over captopril in terms of the prevention of cerebrovascular events, which occurred at a frequency approximately 25% higher in participants randomized to captopril.

The Swedish Trial in Old Patients with Hypertension (STOP)-2 trial compared new therapies (a calcium channel blocker or an ACE inhibitor) with older therapies (one of the old β-blockers or a diuretic [21]) in patients aged 70–84 years. The incidence of clinical end-points did not differ between the two general strategies and the incidence of adverse effects was higher in patients treated with a calcium-channel blocker or an ACE inhibitor. Since this trial was not designed to compare individual drugs, some important differences may have been concealed [22]. β-blockers are known to be less effective than diuretics, particularly in this age group [7], and the proportion of patients treated with one of these heterogeneous groups was not reported in the publication. Moreover, pinpindolol, a β-blocker implicated in coronary risk [23] and not only due to the absence of a protective effect, was one of the β-blockers employed by an unknown proportion of patients. Another finding of this study was the observation that ACE inhibitors were superior to calcium-channel blockers in terms of prevention of coronary events and heart failure. In this respect, their results confirm indirect evidence, from a case-control study [24] and in secondary analysis of clinical trials [25,26] that has implicated short-acting calcium antagonists in an increased risk of MI. Similarly, a trial with African-American patients with hypertensive renal disease showed that those allocated to ramipril had 48% fewer clinical end-points (reduction in glomerular filtration rate of more than 50% or 25 ml/min per 1.73 m², end stage renal disease or death) than the patients treated with amldipine [27].

The Nordic Diltiazem trial (NORDIL) was another trial that compared the calcium-channel blocker diltiazem with an old-strategy treatment (a diuretic or β-blocker) [28]. The incidence of a composite end-point was virtually identical in both groups. Patients treated with diltiazem had a lower incidence of stroke whilst patients on an old treatment strategy showed a trend towards a lower incidence of MI. Similarly to the STOP-2 trial, patients in the control group were mainly treated with one β-blocker, which is not the most effective antihypertensive agent. More patients stopped taking diltiazem than patients in the control group stopped one of their drugs.

International Nifedipine-GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT), a well-designed double-blind clinical trial, compared the effect of co-amiloizide (a thiazide and a potassium-sparing diuretic) with a gastrointestinal slow-release preparation of nifedipine (Adalat®, Bayer) [29]. There was a non-significant 12% higher incidence of the composite end-point in patients treated with nifedipine, as a result of a higher and statistically significant incidence of fatal MI and nonfatal heart failure. More patients stopped taking nifedipine than diuretics because of intolerable adverse effects, mainly ankle edema. Among those who tolerated the antihypertensives, some metabolic effects were more common in patients treated with diuretics.

Curiously, two reviews of almost the same trials have reached opposite conclusions. Pahor and colleagues demonstrated that the calcium channel blockers may be inferior to other antihypertensive drugs [30]. The Trailists Collaboration concluded that any drug with the capacity to lower blood pressure might be regarded as an efficacious antihypertensive drug, regardless of small differences between classes of drugs observed in some studies [31]. The quality of some studies included in the meta-analysis and the inclusion of a few different trials may explain the variability of estimates presented in these reviews. Despite
the large number of patients included in these overviews, there were few studies looking at comparisons. The direct comparison of new options with diuretics was scarce and was mainly represented by the INSIGHT trial. The CAPPP, STOP-2 and NORDIL trials had the probe design and the comparison of new and old strategies, one of them represented by diuretics. The probe design, a new denomination for an open (not blinded) clinical trial, generated serious problems in the CAPPP trial due to the noncentral allocation of patients, a problem that was resolved in the other two trials. The old strategy group, however, mixed up drugs with different efficacy, especially in the elderly. β-blockers were the preferred drugs in the conservative strategy and may have concealed a higher efficacy of diuretics.

The LIFE trial compared the effects of losartan (Cozaar®, Merck) with atenolol (Tenormin®, AstraZeneca, London UK) in patients aged 55–80 years with hypertension and left ventricular hypertrophy ascertained by ECG [32]. The primary composite end-point – death, MI or stroke – occurred in 23.8 per 1000 patient-years treated with losartan and in 27.9 per 1000 patient-years treated with atenolol (p = 0.021). This difference was ascribed to the reduction of strokes in participants allocated to losartan and was more intense in patients with diabetes [33]. The large majority of patients in both trial arms used diuretics to reach the blood pressure goal. This study was heavily criticized, mainly for choosing atenolol as the control drug. Besides the overall restriction to β-blockers as the primary option for treating elderly patients with hypertension [34], atenolol may be particularly ineffective, which was suggested in older trials that compared atenolol and metoprolol (Toprol®, AstraZeneca, London, UK) with diuretics [35,36].

The results of the second Australian National Blood Pressure (ANBP-2) study were published recently [37]. In an open-label trial (probe design), 6083 subjects with hypertension who were between 65 and 84 years of age and predominantly white, the majority free of cardiovascular disease or diabetes were randomized, in 1594 family practices, to the recommendation to start treating hypertension with enalapril (Vasotec®, Merck, NJ, USA) or with a thiazide diuretic. The combined primary outcome – any cardiovascular event or death from any cause – occurred in 56.1 per 1000 patient-years in the ACE-inhibitor group and in 59.8 per 1000 patient-years in the diuretic group; the hazard ratio for a cardiovascular event or death from ACE-inhibitor treatment was 0.89 (95% CI: 0.79–1.00; p = 0.05). The advantage of enalapril over diuretics was restricted to male subjects. The results of this study contradicted part of the results of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack trial (ALLHAT) (see below) and originated an immediate questioning of their reasons [38]. These reasons may be among the differences between the studies in terms of statistical power, blind allocation of treatment, treatments actually used, age and race of participants, presence of co-morbidities and differences between the diuretics and ACE inhibitors employed in these trials.

### Table 1. Difference in frequency of end-point occurrence between lisinopril- and chlortalidone-treated patients.

<table>
<thead>
<tr>
<th>End-point</th>
<th>Difference in frequency§ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>15</td>
</tr>
<tr>
<td>CVD</td>
<td>10</td>
</tr>
<tr>
<td>Overall heart failure</td>
<td>19</td>
</tr>
<tr>
<td>Hospitalized/fatal heart failure</td>
<td>10</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>10</td>
</tr>
</tbody>
</table>

§Difference expressed as end-point frequency for lisinopril - frequency for chlortalidone. CVD: Cardiovascular disease.

### ALLHAT trial

ALLHAT was designed to compare the efficacy of drugs from four major classes of antihypertensive drugs in the prevention of cardiovascular events [1]. The primary outcome was the combination of fatal coronary heart disease (CHD) or nonfatal MI. The study was planned with enough statistical power to test the effects of treatment on four major prespecified secondary outcomes – all-cause mortality, fatal and nonfatal stroke, combined CHD events and combined cardiovascular (CVD) events – in different gender, race and age strata, and in patients with and without diabetes. More than 40,000 participants were randomized to chlorthalidone (12.5–25 mg/day), amldopidine (2.5–10 mg/day), lisinopril (10–40 mg/day) or doxazosin (2–8 mg/day), in a double-blind fashion, with a mean follow-up of 4.9 years. To maximize statistical power, 1.7 times as many participants were assigned to the diuretic group as to each of the other 3 groups. Open-label step 2 drugs were atenolol, reserpine or clonidine and step 3 was hydralazine, since the participants could not cross over to drugs from the other groups.

The doxazosin arm was terminated prematurely because patients treated with this α-blocker had a higher incidence of stroke (RR: 1.19; 95% CI: 1.01–1.40), cardiovascular events (RR: 1.25; 95% CI: 1.17–1.33) and heart failure (RR: 2.04; 95% CI: 1.79–2.32) than patients treated with chlorthalidone [39].

The incidence of the primary outcome was not different in patients assigned to chlorthalidone, amldopidine or lisinopril. The incidence of overall and hospitalized/fatal heart failure were 38 and 35% higher, respectively, in patients treated with amldopidine in comparison to those allocated to chlorthalidone. Several secondary end-points were statistically significantly more frequent among patients treated with lisinopril than in patients treated with chlorthalidone (TABLE 1). The incidence of end-stage renal disease was not different among the three groups. The treatment effects for all outcomes were consistent across subgroups by sex and diabetic status in both comparisons with the diuretic. Some differences emerged in other subgroup analyses; it is worth...
noting that there was an interaction of drug treatment by race: stroke and combined CVD were more frequent in black participants than nonblack participants assigned to lisinopril in comparison to chlorthalidone.

Five-year systolic blood pressures were significantly higher in the amlodipine (0.8 mmHg) and lisinopril (2 mmHg) groups compared with chlorthalidone; 5-year diastolic blood pressure was significantly lower with amlodipine (0.8 mmHg). Given the large sample, small differences in some biochemical measurements were statistically significant after 4 years of follow-up, such as cholesterol (197.2, 195.6 and 195.0 mg/dl for chlorthalidone, amlodipine and lisinopril, respectively), potassium (4.1, 4.4 and 4.5 mEq/l, respectively) and fasting glucose (126.3, 123.7 and 121.5 mg/dl for chlorthalidone, amlodipine and lisinopril, respectively). New diagnoses of diabetes occurred in 11.6, 9.8 and 8.1% of the participants allocated to chlorthalidone, amlodipine and lisinopril, respectively. The only difference in the incidence of serious adverse outcomes was a higher frequency of angioedema in patients treated with lisinopril (0.4 versus 0.1% in the other groups, one case in the lisinopril group being fatal).

Some results of the ALLHAT trial will be debated but their main findings are robust and definitive. The similar incidence of the primary end-point occurrence among participants allocated to the four treatments and the higher incidence of some secondary, but clinically relevant, outcomes in participants assigned to doxazosin, amlodipine and lisinopril, together with the consistency of these results among most age, sex, race and diabetes strata, suggest that diuretics are superior to other antihypertensive drugs in preventing cardiovascular events.

The advantage of chlorthalidone on some outcomes may be secondary to better blood pressure control, especially systolic blood pressure. In this regard, these findings are in accordance with the view that the blood pressure lowering effect is the main mechanism responsible for the prevention of cardiovascular events in patients with hypertension [40] and, maybe, in patients without hypertension at higher risk of presenting a cardiovascular event. The postulated antagonism of new drugs on potential cardiovascular toxic effects of angiotensin or calcium and the advantages of these drugs in terms of metabolic effects, did not overcome the real and efficient blood pressure lowering effect of diuretics. The poorest control of blood pressure in patients treated with doxazosin, amlodipine and lisinopril in the ALLHAT may be exactly secondary to the prohibition, by protocol, to use diuretic as the second drug.

Expert opinion

Diuretics are at least as efficacious as other antihypertensive drugs in preventing combined cardiovascular outcomes in a wide range of hypertension severity, age, gender, race and presence of other comorbidities, such as diabetes mellitus. Probably due to their more efficacious blood pressure lowering effect, they are superior to other drugs in preventing some outcomes, such as cerebrovascular disease and heart failure. In the case of heart failure, their unique preload reducing effect among the antihypertensive drugs may be another reason to explain their superiority. The consistent findings of some of the previous clinical trials [41] and now of the ALLHAT trial, together with their easiness of administration, infrequent side effects and low price, recommend diuretics as the first option in the management of hypertension. New clinical trials should focus on drugs to be added to them as the second step in the management of hypertension, which may also be a diuretic (i.e., a potassium-sparing agent).

Five-year view

The next few years will see a modification in the paradigm for hypertension diagnosis and management. The concept of high-risk individuals, such as patients with diabetes, or with a previous cardiovascular event, and the elderly, will probably demand the use of blood pressure-lowering drugs independently of a formal diagnosis of hypertension. The second drug to be added to diuretics to reach such goals in the primary or secondary prevention should be established in newer clinical trials. Ideally, these trials should focus on hard outcomes, but the constraint of costs may justify the use of surrogate endpoints, such as blood pressure and quality-of-life.

Key issues

- The benefit of blood pressure-lowering treatments in preventing cardiovascular disease is fully established.
- Thiazide diuretics are the first-line agents to treat hypertension in a wide range of age, gender and race strata, and in patients with and without diabetes.
- The blood pressure-lowering effect of drugs to be added to diuretics as the second option in the management of hypertension may be an acceptable surrogate (mediator) endpoint, as it correctly anticipates the effects of most drugs on hard outcomes.
- There is compelling evidence for the use of blood pressure-lowering drugs in patients at higher cardiovascular risk, such as patients with Type 2 diabetes and patients recovered from a myocardial infarction or stroke, independently of their basal blood pressure levels.
Fuchs

References

Papers of special note have been highlighted as:
  • of interest
  •• of considerable interest
1 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 Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA 288, 2981–2997 (2002).

2 Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA 202, 1028–1034 (1967).


4 Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 213, 1143–1152 (1970).


Use of diuretics in hypertension


Affiliation

• Flávio D Fuchs, MD, PhD, Serviço de Cardiologia, Hospital de Clínicas de Porto Alegre, Ramiro Barcelos, 2350, 90.035-003, Porto Alegre, RS, Brazil Tel./Fax: +55 51 3316 8420 ffuchs@hcpa.ufrgs.br