

## Review

# Diuretics: again the first step in the treatment of most patients with hypertension

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### Abstract

The results and interpretations of the most recent controlled clinical trials on antihypertensive drugs have fuelled the debate about the drug that should be used to begin treatment for hypertension. Every comparison of diuretics with other drugs has shown that the benefits of diuretics are equivalent to, or better than, other options. These findings, together with other practical reasons, such as left ventricular mass reducing effect, easy administration, few side effects and low cost, suggest that diuretics should regain their primacy as the first step in drug management of hypertension.

**Keywords** antihypertensive treatment, diuretics

The stepped care approach for the management of hypertension was introduced in the first United States National Guidelines issued by the National High Blood Pressure Education Program [1]. Diuretics were indicated as the first step, based on their efficacy in the first trials of prevention of cardiovascular disease and because of their better tolerability compared to the other antihypertensive drugs that were available at that time, such as the ganglion blocking agents, guanethidine, hydralazine, and reserpine. These other antihypertensive drugs were recommended as second and third steps for patients who were not controlled by diuretics alone.

In the report by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) in 1984 (JNC-III) [2], the first recommended step was extended to include  $\beta$ -blockers. Four years later, in the JNC-IV report, the recommendations were extended further to include four classes of blood-pressure-lowering drugs [3]. In the subsequent guidelines, the Committee returned to diuretics or  $\beta$ -blockers as the first antihypertensive option, but, because of the "compelling indications", the recommendations were extended to include a wide range of the other classes of blood-pressure-lowering drugs [4].

The introduction of newer classes of antihypertensive drugs was based on their presumed better tolerance and on the expectation that they would improve the prevention of coronary heart disease, which was lower than expected in the first trials, mainly attributed to adverse metabolic effects of diuretics. Physicians around the world became convinced of these advantages and the use of the newer classes of drugs surpassed diuretics and  $\beta$ -blockers for antihypertensive treatment.

The results of recent trials and reanalysis of the previous ones show that we should return to older practices. Two recent reviews of these trials have reached opposite conclusions. Pahor *et al.*, showed that the calcium-channel blockers are inferior to other antihypertensive drugs [5]. The Blood Pressure Lowering Treatment Trialists' Collaboration concluded that any drug with the capacity to lower blood pressure might be regarded as an efficacious antihypertensive drug, regardless of the small differences between classes of drugs that were observed in some studies [6]. Despite the controversial revision of almost the same trials [7–12], there are substantial reasons to believe that diuretics should regain their previous role as the first drugs to be chosen in the management of hypertension. These reasons are based on the critical analy-

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STOP-2 = Swedish Trial in Old Patients with Hypertension-2; TOHMS = Treatment of Mild Hypertension Study.

ACE = angiotensin-converting enzyme; CI = confidence interval; JNC = Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure; RR = relative risk.

sis of both older and new trials on drug treatment of hypertension and on highly practical reasons to choose an antihypertensive drug, such as easiness of administration, infrequent side effects and price.

## What the controlled clinical trials have really shown

### Placebo-controlled studies

Diuretics are the only class of antihypertensive drugs to have been compared to a placebo in a wide range of hypertensive diseases. In the first placebo-controlled trial conducted on severely hypertensive patients, a therapy based on diuretics provided one of the most significant reductions of the incidence of cardiovascular events [13]. A reanalysis of this study [14] showed that only six patients per year required treatment to prevent one major cardiovascular event; this compares favorably with having to treat 15 patients with heart failure with an ACE inhibitor in order to prevent one death per year [15], and needing to treat more than 100 women with a statin per year to prevent one major cardiovascular event [16]. In at least 16 additional trials (conducted in different countries, on both men and women, including patients with mild to moderate hypertension, both under 60 and over 60 years of age, with and without isolated systolic hypertension), diuretics prevented a wide range of cardiovascular events, including cerebrovascular disease, coronary heart disease, and heart failure [17–20]. In the SHEP (Systolic Hypertension in the Elderly Program) trial [21], during a follow-up averaging four and a half years, both fatal and nonfatal heart failure occurred in 4.4% of the participants randomized to placebo, and in 2.3% of those randomized to active therapy (relative risk [RR] 0.51, 95% confidence interval [CI] 0.37–0.71).

The prevention of coronary events in the first trials of diuretics was lower than expected. This was initially attributed to adverse effects of thiazide diuretics on the metabolism of carbohydrates, uric acid and electrolytes. The risk of cardiac arrhythmias, and sudden death, attributed to the use of higher doses of thiazide diuretics (which were not antagonized in their effects on potassium metabolism by potassium-sparing diuretics), however, was the probable reason for the insufficient prevention of coronary events [22].

In trials with elderly (older than 60 years) participants [18–20], with a therapy based on lower doses of thiazide diuretics (in most instances associated with a potassium-sparing agent), the magnitude of prevention of coronary events came closer to that predicted by cohort studies. Taking together these and older studies, and reclassifying the participants by the drug used as the first option, Psaty *et al.*, confirmed the superiority of low doses of thiazide diuretics [23]. Only diuretics at lower doses were effective in preventing both cerebrovascular and coronary events. This is a peculiar situation in terms of drug therapy, that lower doses have a better effect. The ineffectiveness of  $\beta$ -blockers was unexpected, because they are efficacious in the secondary pre-

vention of myocardial infarction. In the first trials, when the effects of diuretics and  $\beta$ -blockers were evaluated together, the unexpectedly lower rates of prevention may be due to the lower efficacy of  $\beta$ -blockers.

Only one agent of other antihypertensive groups, nitrendipine, has been shown to be superior to placebo in a large trial with clinical endpoints [24]. The effect observed in that study, with elderly participants with isolated systolic hypertension, was very similar to that observed in the North American trial with a similar design, which used a thiazide-like diuretic as the first option [18]. In both trials the number requiring treatment to prevent any fatal or nonfatal cardiovascular event was 100 patients per year. An angiotensin-converting-enzyme (ACE) inhibitor was shown to be superior to placebo in patients with evidence of ischemic heart disease or diabetes, but only a proportion of them had hypertension [25].

### Trials comparing the effect of different antihypertensive drugs on clinical endpoints

The results of several trials comparing agents from the different antihypertensive groups were published recently. In the CAPP (Captopril Prevention Project) trial [26], the open design without a centralized randomization of patients involved a systematic allocation of an unknown proportion of participants to captopril 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 endpoint could be achieved with a therapy based on either captopril, diuretics, or  $\beta$ -blockers. Among the *a priori* defined secondary endpoints, the only statistically significant supremacy was of the conventional therapy over captopril in preventing cerebrovascular events, which occurred at a frequency approximately 25% higher in participants randomized to captopril (RR 1.25, CI 1.01–1.55).

The STOP-2 (Swedish Trial in Old Patients with Hypertension-2) study compared new therapies (a calcium-channel blocker or an ACE inhibitor) to older therapies (one of the  $\beta$ -blockers or a diuretic) in very elderly patients aged 70–84 years [11]. The incidence of clinical endpoints did not differ between the two general strategies, but the incidence of adverse effects was more frequent 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 [27].  $\beta$ -blockers are known to be less effective than diuretics, particularly in this age group [19], and the proportion of patients treated with one of these heterogeneous groups was not reported in the publication. Moreover, pindolol, a  $\beta$ -blocker implicated in coronary risk not only due to the absence of a protective effect [28], was one of the  $\beta$ -blockers used by an unknown proportion of patients. This study also showed that ACE inhibitors were superior to calcium-channel blockers in terms of prevention of coronary events and heart failure. In this respect, these results confirm

indirect evidence, from a case-control study [29] and a secondary analysis of clinical trials [7,30], that has implicated short-acting calcium antagonists in an increased risk of myocardial infarction. Similarly, a recent trial with African-American patients with hypertensive renal disease showed that those allocated to ramipril had 48% fewer clinical endpoints (reduction in glomerular filtration rate of more than 50% or 25 ml/min per 1.73 m<sup>2</sup>, end-stage renal disease, or death) than the patients treated with amlodipine [31].

The partial results of the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT), designed to compare drugs from four major classes of antihypertensives, showed the definite superiority of a diuretic over an  $\alpha$ -blocker [32]. Despite the similar effect on total mortality, patients treated with doxazosin 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.

The NORDIL (Nordic Diltiazem) study was another trial that compared a calcium-channel blocker, diltiazem, with an old-strategy treatment, (a diuretic or  $\beta$ -blocker) [12]. The incidence of a composite endpoint was virtually identical in both groups. Patients treated with diltiazem had a lower incidence of stroke (RR 0.80, 95% CI 0.65–0.99) whilst patients on an old treatment strategy showed a trend towards a lower incidence of myocardial infarction (RR 1.16, 95% CI 0.94–1.44). Similarly to the STOP-2 trial, patients in the control group were mainly treated with one  $\beta$ -blocker, which is not the most effective antihypertensive agent. More patients in the diltiazem group (23%) stopped taking their medication, than patients in the control group (7%).

INSIGHT (International Nifedipine-GITS Study: Intervention as a Goal in Hypertension Treatment), a well-designed, double-blind clinical trial, was the last study to be published comparing the effect of antihypertensive drugs on hard endpoints [10]. This study showed the superiority of co-amiloride (a thiazide and a potassium-sparing diuretic) over a gastrointestinal, slow-release preparation of nifedipine, in preventing fatal myocardial infarction (RR 3.22, 95% CI 1.18–8.8), and in reducing nonfatal heart failure (RR 2.2, 95% CI 1.07–4.49). More patients stopped taking nifedipine (22.9%) than diuretics (16.3%) because of unbearable side effects, mainly ankle edema. Among those who tolerated the antihypertensives, some metabolic effects were more common in patients treated with diuretics.

A new report, based on data from the same cohort that identified the risk of short-acting nifedipine [29], demonstrated the superiority of diuretics, over other classes of blood-pressure-lowering drugs, to prevent stroke [33]. Although this was a case-control study, and not a clinical trial, it may have improved the understanding of the effect of antihypertensive drugs in everyday clinical practice.

### Comparison between the effects of antihypertensive drugs on surrogate and other endpoints

Trials designed to study the effects of antihypertensive drugs on intermediate and surrogate endpoints also showed the superiority of diuretics, or at least their equivalence, to other antihypertensive drugs. Many trials have tested the hypothesis that antihypertensive drugs would have differential effects on reducing the ventricular mass of hypertensive patients, since this characteristic is an independent risk factor for coronary events. None of these trials, however, had the sample size, number of drugs tested, duration or homogeneity of criteria for ventricular mass evaluation, of the TOHMS (Treatment of Mild Hypertension Study) trial [34]. In this study, only the group treated with a thiazide diuretic had a greater reduction of ventricular mass compared to the placebo group.

The TOHMS trial, and studies by Materson *et al.* [35], and Philipp *et al.* [36], were the best-designed trials for the evaluation of secondary effects of antihypertensive drugs. None of them showed any substantial difference in the effects of several classes of antihypertensive drugs on blood pressure, blood lipids, adverse effects, quality of life, or compliance. In the study by Materson *et al.*, for instance, more patients stopped taking placebo (6.4%), than diuretics (1.1%), due to an adverse drug effect [35].

### Other reasons that justify the option for diuretics as first-choice antihypertensive drugs

The mechanism of action and the pharmacodynamic effects of drugs were taken as the pharmacological basis of therapeutics in the past and are still important, at least, in terms of drug development. In this regard, diuretics would be considered an important innovation if they were discovered nowadays, since they probably act on the main mechanism of blood pressure increase. The renal capability to handle the overload of sodium, characteristic of the diets of most populations worldwide, seems to establish the blood pressure level of the individual [37]. Aging, and the natural reduction in the number of functioning nephrons, exacerbates this phenomenon, which has been thought to be one of the mechanisms responsible for the increased prevalence of hypertension among the elderly. Independently of the intrinsic or extrinsic mechanisms responsible for the relative impairment in sodium excretion in individuals genetically predisposed to hypertension, or already with hypertension, the thiazide diuretics exert their main effect by increasing the renal excretion of sodium and water, and consequently lowering blood pressure. The potassium-sparing diuretics complement the effect of thiazide diuretics and prevent the potassium losses induced by them.

There are other very practical reasons justifying the preference for diuretics in the management of hypertension. The majority of antihypertensive drugs can be taken once a day, since even drugs with short half-lives are presented in slow-

releasing formulations. In contrast, diuretics do not need such formulations, since their main effect is not dependent on steady blood levels. In trials that identified their effectiveness in the prevention of cardiovascular disease, thiazide diuretics were employed once a day, but they may be active even when taken at 48-hour intervals, at least in terms of blood pressure control.

Even when diuretics are not employed as the first drug of choice, it is quite common to combine them with the drug in use to obtain a better control of blood pressure. On the basis of the above considerations, it seems more rational to start with a diuretic, later adding a second drug if necessary. And, last but not least, diuretics are comparatively inexpensive.

## Conclusion

If the historical sequence was inverted, and diuretics were being introduced on the market nowadays, after calcium-channel blockers, ACE inhibitors and other antihypertensive classes of drugs, they would be very easy to promote.

The following is a summary of the advantages of combined thiazide and potassium-sparing diuretics over other antihypertensive drugs:

1. Active in the main mechanism of blood pressure elevation.
2. Easy administration.
3. Superior to placebo in a wide range of hypertensive diseases (e.g. severe to mild hypertension, isolated systolic hypertension) in different sex and age strata, in studies conducted in several countries.
4. More effective at lower doses.
5. Superior to  $\beta$ -blockers in preventing coronary events.
6. Superior to ACE inhibitors in preventing cerebrovascular disease.
7. Superior to  $\alpha$ -blockers in preventing stroke, cardiovascular events, and heart failure.
8. Superior to dihydropyridine calcium-channel blockers in preventing fatal myocardial infarction, and nonfatal heart failure.
9. Reduces left ventricular mass.
10. Well tolerated in terms of quality of life, with few side effects.
11. Potentiates other antihypertensive drugs.
12. Relatively inexpensive.

Diuretics are the first step in the treatment of most patients with hypertension and the new clinical trials should focus on drugs to be added to them as the second step in the management of hypertension.

## Competing interests

None declared.

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