Lessons from ALLHAT

Are low budget diuretics first line therapy in hypertension?

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Summary Diuretics are well-established and nowadays also cheap cardiovascular agents. In contrast to the most recent American hypertension guidelines (JNC 7) which ascribe a singular place to diuretics in the first-line treatment of hypertension following a one-sided interpretation of the ALLHAT results, in the balanced guidelines of the European Society of Hypertension (ESH) published in 2003, they are placed alongside beta-blockers, ACE inhibitors, sartans and calcium antagonists as the drugs of first choice, but not given preference. Previous scientific evidence and clinical experience is to a certain extent in line with this classification of diuretics. On the basis of the indisputable dose-dependent potential for side-effects such as hypokalaemia, diabetogenicity and stimulation of neurohumoral systems, I personally consider diuretics to be inferior to the more recent substance groups, particularly the RAS inhibitors. I would therefore welcome it if diuretics in the future were removed from the monotherapy of hypertension and offered from the outset as low-dosed combination partners for RAS inhibitors, beta-blockers and also calcium antagonists. In this role they could only do good and not cause any damage.

Key words Diuretics – hypertension treatment guidelines – ALLHAT trial – diabetes mellitus – review
Background

**Diuretics as preferred first-line therapy in hypertension?**

Diuretics are effective drugs which have been firmly established for more than 50 years and which should have a regular place on any serious positive list. The treatment of heart failure and many other diseases is inconceivable without them. They are also available relatively cheaply, if this is a permitted argument, although the costs of treatment will be discussed in further detail later. Lastly, they are a peerless combination partner for renin-angiotensin system inhibitors. Does this, however, justify the assumption that they should be the antihypertensives of first choice now and in the future, as the most recent semi-official American treatment guidelines (JNC 7) would suggest [1]?

My response is an unequivocal No: diuretics for me are no longer the antihypertensives of first choice for the "uncomplicated" hypertensive. Not because there is probably no such entity, but in the sense that the better drug is the enemy of the good drug.

I intend to justify this below, firstly from a pharmacological angle in order to provide a better understanding, secondly by means of clinical studies, in particular the ALLHAT study which is currently dominating discussions, and thirdly on the basis of pharmaco-economic considerations which we scientists are now unfortunately required to undertake if we do not want to abandon the field to the regular evening talkshow entertainers. In so doing, I am deliberately confining myself to the specified topic of discussion of the "uncomplicated hypertensive": once cardiac, renal or metabolic comorbidities or complications become involved, antihypertensive monotherapy with diuretics in any case becomes superfluous.

**Pharmacological aspects**

Let us begin with the pharmacological argument. All current diuretics, including the thiazides and their derivatives which are the most commonly used in hypertension and which I intend to employ synonymously with the term diuretics, eliminate sodium and hence water from the body via a renal mechanism. Initially therefore they reduce the circulating blood volume until a new homeostasis is established with lowered blood pressure. In the long-term also they reduce arterial vessel tone – through a mechanism that has never been entirely elucidated – and thus contribute on the afterload side to the lowering of blood pressure, even if far less effectively than the primary vasodilator substances such as calcium antagonists. With their combined renal and vascular approach, diuretics hit the bull's-eye in blood pressure dysregulation so to speak, as well as effectively compensating for our daily vice of an excessive salt intake.

Ideal antihypertensives therefore? No, because they are too weak for this and the burden of their side-effects is too high.

In monotherapy, diuretics exhibit a very flat dose-response curve in terms of blood pressure reduction. In order to meet current requirements for effective blood pressure control, i.e. to reach target values <140/90 mmHg [2], they must be administered in high doses, as used to be the case in the initial phase of diuretic therapy. For hydrochlorothiazide (HCT), the diuretic most often used in Germany, this means a daily dose of 50–100 mg. For chlorthalidone (e.g. Hygroton®) used in the American ALLHAT study, which is more potent and has a longer duration of action than HCT, an equivalent dosage of 25–50 mg/day can be employed. However, in this dosage range, the typical side-effects of this class known to us for many years are increasingly apparent: hypokalaemia, glucose intolerance, hyperuricaemia and sometimes dyslipidaemia [3, 4], not to mention erectile dysfunction. In addition, there is sometimes massive stimulation of neurohumoural systems such as the sympathetic nervous system and in particular the renin-angiotensin system (RAS) [5]. This whole complex of shifts in electrolyte balance, of metabolic and humoural disorders derives from the mechanism of action of the diuretics and is strictly dose-dependent: its occurrence is therefore inevitable at high, antihypertensive doses.

In markedly lower dosage ranges, i.e. 12.5 mg/day (HCT) or 6.25 mg/day (chlorthalidone) for instance, these side-effects are generally not encountered; conversely, given alone, these doses are also not effective from an antihypertensive viewpoint. Borderline results in terms of effect and side-effects have been obtained with daily doses of 25 mg (HCT) or 12.5 mg chlorthalidone.

**Diuretics better in combination therapy**

This represents the fundamental dilemma of diuretics as antihypertensive monotherapy, but also their great strength as a combination partner, particularly with RAS inhibitors (ACE inhibitors, sartans). As they stimulate the RAS even in the low dosage range, they make blood pressure regulation more heavily dependent on this system with the result that RAS