

### Other adverse effects

Aspirin can interfere with blood pressure control in high doses (1 500 mg/day). It can interfere with ACE-I in doses of more than 100 mg/day, and can induce asthma.

### ALTERNATIVES TO ASPIRIN

About 5 - 10% of patients will not tolerate aspirin. The following alternatives are available in those cases:

- Clopidogrel (Plavix). In the Caprie study, 325 mg/day aspirin versus 75 mg/day clopidogrel showed a significant increase in benefit from clopidogrel after 2 years ( $p = 0.04$ ). Neutropenia occurred as a side-effect in 0.1% of patients treated with clopidogrel.
- Dipyridamole. For recurrent stroke prevention, this drug is equally effective.

The problem of the two alternative options for aspirin-intolerant patients is that they are much more expensive.

### CONCLUSION

Aspirin decreases mortality and reinfarction when given in acute MI, unstable angina, and for long-term secondary prevention. Despite the strength of the data, 20 - 50% of patients with clear indications for aspirin are not receiving it. There is still much to be done by general practitioners to increase the use of highly effective drugs like aspirin.

## THE MARVEL OF INEXPENSIVE CARDIOVASCULAR DRUGS: THIAZIDE DIURETICS

**J A KER, MB ChB, MMed (Int), MD**  
Professor: Department of Internal  
Medicine, School of Medicine,  
University of Pretoria

The drugs in this group are called thiazides, benzothiadiazides or sulphamide diuretics. Chlorothiazide is the

prototype of the group. Chlorothalidone is slowly absorbed and therefore has a longer duration of action. These drugs inhibit sodium chloride (NaCl) re-absorption in the distal convoluted tubule. They also indirectly raise potassium excretion and decrease  $Ca^{2+}$  excretion. They are relatively weak diuretic agents but with sustained effects. The mechanism of action of these drugs in the treatment of hypertension is poorly understood. It may take up to 1 month for the maximum effect. They are usually effective within 3 - 4 days.

### ANTIHYPERTENSIVE EFFECT

#### Early effect

The early mechanism for blood pressure reduction is by sodium diuresis and volume depletion (plasma volume and extracellular fluid volume) and by reducing cardiac output. This is however only a temporary effect and all will return to normal in a few weeks. A shrunken volume leads to a reactive rise in renin.

#### Long-term effect

Thiazide diuretics cause a reduction of peripheral resistance, which lowers blood pressure. The mechanism responsible for the lowered peripheral resistance may involve potassium channel activation, but the precise mechanism is still poorly understood.

### ADVERSE EFFECTS

The adverse effects of thiazide diuretics can be kept to a minimum if the dose is kept low (< 25 mg/day).

- **Metabolic effects.** These consist of hyperuricaemia due to uric acid retention, carbohydrate intolerance (via insulin resistance) and dyslipidaemia. The effects are dose related.

- **Hypokalaemia** is due to renal potassium loss and may cause metabolic alkalosis that may lead to secondary hyperaldosteronism.

- **Hypercalcaemia.** A slight rise in serum calcium of little concern is sometimes noted.

• **Impotence (erectile dysfunction)** may on occasion develop but can be kept to the minimum if the dose is kept below the equivalent of 25 mg/day of hydrochlorothiazide.

• **Hyponatraemia.** Only a very small number of patients taking diuretics will develop this side-effect, which on occasion may be severe.

**EFFICACY**

Blood pressure usually falls about 10 mmHg and the antihypertensive effect of diuretics persists indefinitely. Thiazide diuretics provide efficacy in blood pressure reduction similar to that of other classes of antihypertensives. Black patients and the elderly respond better to thiazide diuretics. A diuretic also enhances the effectiveness of all other types of antihypertensive drugs. This potentiation of thiazide diuretics or other antihypertensive drugs depends on:

- contraction of fluid volume with subsequent renin release which potentiates the action of, e.g β-blockers, ACE inhibitors and angiotensin receptor blockers
- prevention of fluid accumulation that frequently follows the use of other antihypertensive drugs.

Diuretics have been used effectively for the treatment of millions of hypertensive patients during the past 40 years. In about half of all hypertensive patients, adequate control of blood pressure with diuretics as monotherapy is possible. The usual dose used could be as low as 12.5 mg/day and even doses as low as 6.25 mg/day may be adequate especially when combined with another antihypertensive drug.

**Duration of action**

The antihypertensive effect lasts beyond the diuretic effect and may persistently reduce blood pressure for 18 - 24 hours. It is important to realise that the full antihypertensive effect of low doses may take up to 4 weeks to develop.

**Combination therapy**

There is a significant effect from small doses, even below 12.5 mg/day, when hydrochlorothiazide (HCTZ) is added to a wide variety of other antihypertensive agents. An HCTZ dose as low as 6.25 mg added to a β-blocker (Bisoprolol) has been on the market for a long time with much efficacy.

**Resistance to diuretics**

- Excessive dietary sodium may cause resistance.
- Renal impairment: with increasing renal failure thiazides will not work.
- The use of non-steroidal anti-inflammatory drugs (NSAIDs) may blunt the effect of most diuretics.

**REDUCTION OF CARDIOVASCULAR EVENTS**

In a meta-analysis published in 1990 by Collins *et al.*,<sup>1</sup> it was demonstrated that diuretics reduced stroke on average by 38% and coronary artery disease by 16%. The reduction of stroke was as effective as expected from epidemiological studies. The reduction of myocardial infarction (MI) was less than expected. Researchers argued that the metabolic side-effects may have prevented the reduction in MI and that this led to the lower doses of diuretics currently used.

In a more recent meta-analysis, significant risk reductions in stroke, coronary heart disease, etc. are demonstrated (Fig. 1).

In the Systolic Hypertension in the Elderly Program (SHEP) study, published in 1991, there were significant decreases in cardiovascular (CV) events and strokes in elderly patients given a diuretic-based regimen.<sup>3</sup> The Swedish Trial in Old Patients with hypertension-2 [STOP-2] in 1999<sup>4</sup> reported no difference in CV events among elderly hypertensives treated with diuretics, ACE-inhibitors or calcium channel antagonists.

In the Antihypertensive and Lipid-lowering Treatment to prevent Heart Attack (ALLHAT) published in 2002 three different medications were compared in the treatment of hypertension with an endpoint of fatal MI or non-fatal MI in > 40 000 patients. In this trial a low-dose thiazide diuretic (chlorthalidone) was similar in outcome reduction to amlodipine (calcium channel antagonist) or lisinopril (ACE inhibitor) (Fig. 2).

**MULTIPLE DRUG THERAPY**

Fewer than 50% of all patients with hypertension will achieve target (goal) blood pressure with monotherapy, and this includes diuretics as monotherapy. The figure may be better for the elderly and black patients using diuretics. Most patients will require more than one drug to achieve target blood pressure. Much of the current data indicate that a diuretic should be part of the combination of drugs necessary to achieve goal blood pressure. In many patients with so-called 'resistant'

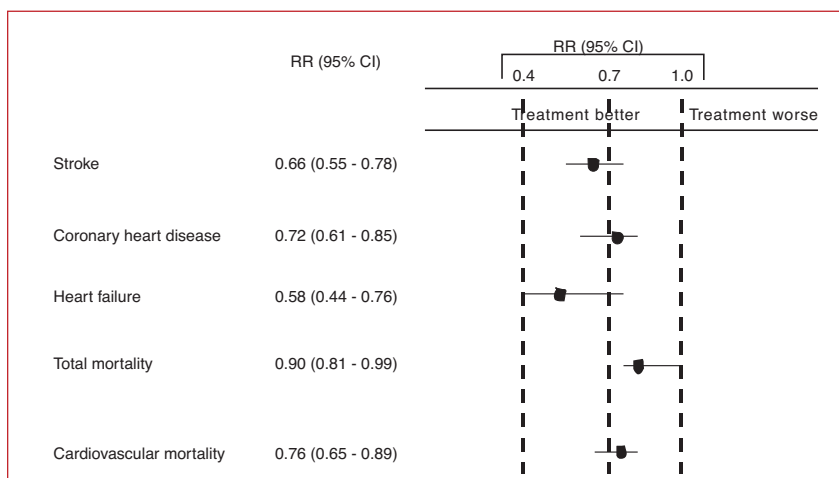


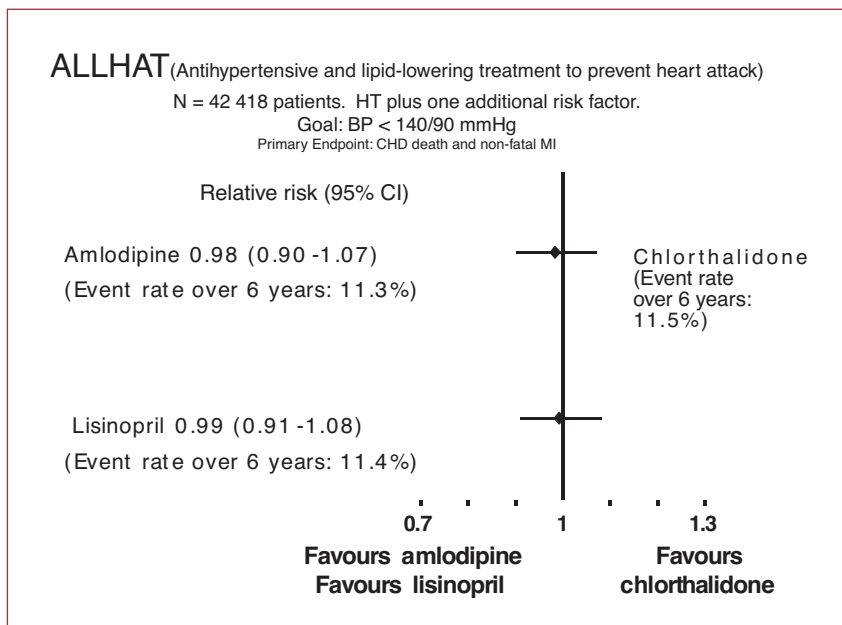
Fig. 1. Risk reductions with low-dose diuretics (RR = relative risk).

hypertension (BP > 160/100 mmHg, using 2 - 3 drugs) a response will be achieved by increasing the dose of diuretic or adding a diuretic if it was not part of the original combination. It is increasingly realised that achieving goal blood pressure is of fundamental importance in hypertension management.

**SUMMARY**

The current state of our knowledge suggests that a low-dose thiazide-type diuretic is inexpensive and effective, and should be used in all combinations of antihypertensive treatment regimens. This is the initial antihypertensive agent of choice, as meta-analysis of randomised controlled trials in hypertension has consistently demonstrated. These large bodies of evidence have clearly shown that diuretics as initial monotherapy, or in combination with other antihypertensive agents, are not only effective in reducing blood pressure, but also in reducing morbidity and mortality in hypertensive patients.

*References available on request.*



*Fig. 2. The ALLHAT study results.*

**SINGLE SUTURE**

**FORENSIC DIALYSIS**

Blood-filled filter cartridges from kidney dialysis machines may be the answer to forensic investigators' interpretation of blood spatter at a crime scene, according to research carried out in New York. The microstructure of the filter cartridges seems to reproduce accurately the effects of shooting at real flesh, which could help detectives model patterns of spilt blood. So far, forensic experts have used 'stand-ins' for human flesh. They normally soak a sponge in blood and shoot at it. But this is not a good model because the body doesn't contain many reservoirs of pooled blood. In fact, contrary to what we see on-screen, unless the bullet hits an artery or open wound, blood spatter is minimal.

(Randerson J. *New Scientist* 2003; 15 March, p.7.)