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## Hypertension: What does new evidence mean?

Several new hypertension guidelines will be published later this year, but has any new evidence emerged to substantially change practice?

Elevated blood pressure is strongly related to the risk of cardiovascular death, but there is no obvious threshold at which treatment should be started, nor is there consensus on appropriate blood pressure targets. Recent evidence supports the relationship between blood pressure and cardiovascular risk<sup>1</sup> and the benefit of tight blood pressure control for people at high risk<sup>2</sup>, but not changes to either targets or thresholds.

### Lifestyle changes reduce blood pressure and total risk

Anyone with above-optimal blood pressure ( $\geq 120/80$  mmHg) should be encouraged to make lifestyle changes (see table below).

### Assess cardiovascular risk

The decision to introduce antihypertensive drug treatment should be based on a person's absolute cardiovascular risk<sup>1</sup> and blood pressure. People at high to very high risk<sup>2</sup> are candidates for drug therapy; this includes those with target organ damage (left ventricular hypertrophy, atherosclerotic plaque, hypertensive retinopathy or renal function changes), associated clinical conditions (established heart, vascular, cerebrovascular or renal disease) or diabetes, as well as those of Torres Strait Islander, Aboriginal, Maori or Pacific Islander origin.

To estimate absolute risk and expected treatment benefits in others, use a tool such as the New Zealand Guidelines Group's Cardiovascular Risk Calculator (available on the NPS website, [www.nps.org.au](http://www.nps.org.au); click on *Topics*, then *Hypertension*).

### Benefit is proportional to absolute risk

The absolute benefits of drug treatment in people at low risk with mild hypertension are small; lifestyle changes may be sufficient to manage blood pressure and total risk in this group. In people at medium risk, a 3–6 month trial of lifestyle changes may reduce blood pressure and risk to acceptable levels and allow some to avoid drug therapy. Those at high and very high risk gain most from lowering blood pressure and should receive drug treatment in addition to lifestyle advice.

### Any reduction in blood pressure confers benefit

Evidence for blood pressure targets is limited and recommendations differ between guidelines. Although somewhat arbitrary, targets can present a considerable challenge for both patients and GPs; multiple medications and higher doses, with associated side-effects and costs, may be required.

Some patients are unable to reach target despite drug therapy and lifestyle changes. Remember that even if blood pressure is not at target level, any reduction is of benefit, particularly in those at high cardiovascular risk.

### Lifestyle modifications to reduce cardiovascular risk\*

Weight reduction	Maintain normal body weight (BMI 18.5–24.9 kg/m <sup>2</sup> )
Healthy eating	Consume a diet rich in fruits, vegetables and low-fat dairy products and with a reduced content of saturated and total fat
Dietary sodium restriction	Limit daily sodium intake to 2.3 g/day or less (i.e. $\leq 6$ g of table salt)
Physical activity	Engage in at least 30 minutes of moderate intensity physical activity, such as brisk walking, on 5 or more days per week
Moderation of alcohol consumption	Limit daily consumption to no more than 2 standard drinks in men and no more than 1 in women
Quitting smoking	The most important change a smoker can make

\*Further advice and materials for patients about lifestyle changes to reduce cardiovascular risk can be found on the Heart Foundation website: [www.heartfoundation.com.au](http://www.heartfoundation.com.au)



## Prescribing Pointers

### Thiazides first-line for most patients with hypertension

The publication of ALLHAT\* late last year confirmed the role of thiazides as first-line antihypertensives for most people with elevated blood pressure.<sup>1</sup> An extensive body of evidence now clearly demonstrates that treatment based on low-dose thiazide or thiazide-like diuretics is unsurpassed in reducing the risk of major cardiovascular events and death in people with hypertension.<sup>2</sup>

As well as having the most comprehensive evidence of benefit in hypertension, thiazides are less expensive than other antihypertensive drugs, making them the preferred drugs for initiation in people without co-morbidities that favour the use of other antihypertensive drug classes.

ALLHAT found no difference in coronary event rates between people at high risk treated first-line with chlorthalidone, a thiazide-like diuretic, and those receiving therapy based on either an ACE inhibitor or a calcium-channel blocker.

A benefit of ACE inhibitors in elderly men has been suggested based on a post hoc analysis of ANBP2<sup>†</sup>; this result requires confirmation because the study was not designed to detect differences in treatment effect between men and women.<sup>3</sup> ANBP2 did not provide definitive evidence of a difference in treatment effect between ACE inhibitors and thiazide diuretics and therefore supports the existing evidence for thiazides. (An appraisal of ALLHAT and ANBP2 is available on the NPS website: [www.nps.org.au](http://www.nps.org.au))

#### Limited adverse effects at low doses

The benefits of thiazides are well established yet misperceptions of their safety and tolerability remain. Thiazides are often believed to have significant adverse effects on blood glucose, lipids and electrolytes. Metabolic disturbances are likely to appear at the high doses of thiazides (hydrochlorothiazide 50–100 mg/day or equivalent) that were popular in the 1970s and 1980s. These adverse effects are unusual at the low doses now used in hypertension (equivalent to hydrochlorothiazide 12.5–25 mg/day).



In ALLHAT, chlorthalidone was associated with a significantly higher incidence of hypokalaemia, new onset diabetes and elevated cholesterol levels compared to lisinopril and amlodipine; the clinical significance of these changes is questionable, however, because they did not lead to a higher rate of cardiovascular events in the diuretic treatment arm.<sup>1</sup>

Subjective tolerability of thiazides in ALLHAT was at least comparable to amlodipine and lisinopril; adherence to thiazide therapy was better than on ACE inhibitor therapy at 5 years, with a higher proportion of people on lisinopril ceasing randomised treatment because of symptomatic adverse effects.<sup>1</sup>

#### When prescribing a thiazide

Initiate at a low dose (see back page for low and very low dose equivalents for thiazide and thiazide-like diuretics). Thiazides have a relatively flat dose–response curve, so doses above hydrochlorothiazide 25 mg provide no substantial antihypertensive benefit but increase the risk of metabolic disturbances. A blood pressure response to thiazides is usually evident within 2 to 4 weeks of treatment initiation; allow at least a month between dose increments.

#### Combining thiazides with...

A thiazide may be effectively combined with an ACE inhibitor, an angiotensin II receptor antagonist, a calcium-channel blocker or a beta-blocker. Thiazides can be added as a second-line drug where there is a compelling indication to prescribe a different class initially.

Fixed-dose combination products containing a low-dose thiazide should not be used for initiation because they make it difficult to titrate doses to effect, or identify the source of adverse effects. For people who are not controlled on monotherapy and are stabilised on similar doses of single agents, fixed-dose combinations can reduce costs to the patient and may be useful when multiple tablets present a challenge to compliance.

\*The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

†The Second Australian National Blood Pressure Study



Health professionals, do you need information on therapeutic drugs?

Contact the NPS Therapeutic Advice and Information Service

Phone 1300 138 677

## Intensive blood pressure management for people with diabetes

Diabetes itself is a significant risk factor for cardiovascular events, and the presence of raised blood pressure increases risk further. Tight blood pressure control should be a key goal for anyone with diabetes because it can substantially reduce the excess cardiovascular risk associated with the condition.

The value of low blood pressure targets in diabetes is shown by the UKPDS trial, which found that reduction of mean blood pressure from 154/87 mmHg to 144/82 mmHg significantly reduced the risk of diabetes-related endpoints (cardiovascular events, microvascular complications and deaths related to diabetes) from 67 to 51 events per 1000 patient-years.<sup>1</sup> Similarly, a subanalysis of the HOT study showed that a goal diastolic blood pressure of 80 mmHg halved the rate of major cardiovascular events in people with diabetes (from 24.4 to 11.9 events per 1000 patient-years) compared to a goal diastolic blood pressure of 90 mmHg.<sup>2</sup>

In practice, reaching the goal blood pressure recommended for people with diabetes can be difficult. Most will require at least two antihypertensive drugs and compliance may be compromised when patients are also receiving medications for other conditions. Data from the 2001–2002 NPS clinical audit of general practice drug management of diabetes suggest that many people with diabetes remain above target blood pressure despite receiving antihypertensive drug therapy.<sup>3</sup>

### Drug choices for people with diabetes without renal disease...

Thiazides, ACE inhibitors and beta-blockers all reduce cardiovascular morbidity and mortality in people with both hypertension and diabetes and are suitable first-line drugs for those without renal disease.<sup>1,4-7</sup>

- Subgroup analyses of comparative outcomes trials, including the recent ALLHAT trial, demonstrate no advantage of ACE inhibitors over thiazides in people with diabetes.<sup>5,6</sup>
- Beta-blockers may predispose some treated diabetics to hypoglycaemia and mask the adrenergic warning signs of hypoglycaemia (tremor and tachycardia).
- Calcium-channel blockers should be reserved for second-line use in those with diabetes and hypertension. Evidence for the benefit of calcium-channel blockers in people with both diabetes and hypertension is inconsistent: some comparative trials have suggested that calcium-channel blockers are associated with a higher risk of major vascular events than ACE inhibitors in people with diabetes<sup>8,9</sup>, although in the diabetic subgroup of ALLHAT, lisinopril and amlodipine produced similar coronary event rates to chlorthalidone.<sup>6</sup>

- There is no cardiovascular outcome evidence available for angiotensin II receptor antagonists in the general hypertensive population.

### ...and for diabetic people with renal disease

In type 1 diabetes accompanied by microalbuminuria or proteinuria, ACE inhibitors delay progression of renal disease and are preferred first-line.<sup>10</sup>

In type 2 diabetes, there is no conclusive evidence for therapies that slow the progression of existing renal disease. Trials employing surrogate endpoints indicate that ACE inhibitors and angiotensin II receptor antagonists reduce protein excretion in people with diabetes and microalbuminuria<sup>7,11</sup>, but evidence for their effects on progression to end-stage renal disease in type 2 diabetes is lacking.

In patients with type 2 diabetes and overt nephropathy, angiotensin II receptor antagonists might slow the progressive loss of renal function, although results rely heavily on the surrogate endpoint of serum creatinine.<sup>12,13</sup> Furthermore, results from studies in people with advanced diabetic renal disease cannot be generalised to people with early nephropathy.

#### Hydrochlorothiazide availability in Australia

A new brand of hydrochlorothiazide (Dithiazide) has recently become available. The product has been available since March 2003, and first appeared in the printed Pharmaceutical Benefits Schedule in May 2003. Dithiazide is available in 25 mg tablets which can be split to provide a low-dose 12.5 mg formulation.

Hydrochlorothiazide was previously available as Dichlotride but was withdrawn by the manufacturer in November 2002. The re-listing of hydrochlorothiazide from an alternative supplier means that there are now two thiazide diuretics in Australia that allow a very low dose, the other being chlorthalidone (Hygroton 25).





# A complementary update: Herbal medicines and hypertension

Hawthorn, garlic, ginger, ginseng, parsley and celery are all purported to lower blood pressure, but evidence for their efficacy is poor.

Other herbal medicines may raise blood pressure and complicate hypertension management. For example, preparations containing liquorice root, commonly used in laxative and expectorant preparations, can increase blood pressure and may induce hypokalaemia, especially in combination with thiazides.<sup>1</sup> Amongst others,

ginseng<sup>2</sup> and black cohosh<sup>3</sup> have also been associated with elevated blood pressure.

If blood pressure control is difficult, remember to consider whether herbal medicines are being taken. The above is not a complete list of complementary medicines that may modify blood pressure; further information is available for health professionals from the Therapeutic Advice and Information Service on 1300 138 677 or for consumers from *Medicines Line* on 1300 888 763.

## What's what

Generic Drug Name	Product Name	Low dose equivalent	Very low dose equivalent
<b>Thiazide diuretics</b>			
Bendrofluazide 5 mg	Aprinox	2.5 mg (1/2 a tab)	Not practical
Hydrochlorothiazide 25 mg	Dithiazide	25 mg (1 tab)	12.5 mg (1/2 a tab)
<b>Thiazide-like diuretics</b>			
Chlorthalidone 25 mg	Hygroton	25 mg (1 tab)	12.5 mg (1/2 a tab)
Indapamide 2.5 mg	Dapa-Tabs, Indahexal, Insig, Napamide, Natrilix	Not practical	Not practical
Indapamide 1.5 mg	Natrilix SR	1.5 mg (1 tab)	Not possible (slow release preparation)

## Prize winners

Thanks to all those who completed the reader's survey for *NPS News* and *Australian Prescriber*. Prizes in the draw went to:

Dr Brian Kerr – Yellow Rock NSW  
Dr Dermot Kiely – Marmion WA  
Dr Bill Wilson – Newport NSW

Ms Yin Shen Ng – St James WA  
Gwendolyn Morris – Balgowlah NSW  
Bruce McGowan – Albany Creek Qld

## Contributing reviewer

Mark R Nelson, NHMRC Research Fellow, Department of Epidemiology and Preventive Medicine, Monash University, Prahran NSW

Any correspondence regarding content should be directed to the NPS. Declarations of interest have been sought from all reviewers.

## Reviewers

Dr James Best, General Practitioner  
A/Prof Nick Buckley, Clinical Pharmacologist, the Canberra Hospital  
Ms Jan Donovan, Consumer  
Dr John Dowden, Australian Prescriber  
Ms Simone Rossi, Australian Medicines Handbook  
Prof John Murtagh, Dept of General Practice, Monash University, Melbourne

Ms Susan Parker, Australian Self-Medication Industry

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*The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence.*

*Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each patient.*



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Level 1 / 31 Buckingham Street, Surry Hills NSW 2010

Phone: 02 9699 4499 | Fax: 02 9699 5155 | email: info@nps.org.au | net: http://www.nps.org.au