



National Prescribing Service Limited



**Prescribing
Practice Review**

**No. 23
Managing
hypertension**

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Dear Dr Sample

This issue of the *Prescribing Practice Review (PPR)* discusses new evidence for drug choices in hypertension. NPS is once again highlighting the place of thiazides in managing hypertension. We are aware this is a message which general practice finds challenging to embrace, but ask you to consider your prescribing in the light of cumulative evidence.

Much of the resistance to a message to “try low-dose thiazides as first-line therapy” stems from concerns about their effects on blood glucose, lipids and electrolytes. While it is clear that these well-known metabolic effects are seen at the higher doses used previously, they are much less likely to occur at the low doses recommended today (hydrochlorothiazide ≤ 25 mg or equivalent).

Two new studies

Two large studies were published in the last 12 months which significantly add to what we know about selecting drug therapy for hypertension: ALLHAT¹ and ANBP2.²

In ALLHAT, a slightly higher rate of new-onset diabetes was seen in patients taking a thiazide (12% with chlorthalidone at a dose ≤ 25 mg daily) in comparison with either the ACE inhibitor (8% with lisinopril) or calcium-channel blocker (10% with amlodipine) groups. Yet this observation did not translate into any differences in cardiovascular morbidity or mortality between the three drug groups for either the entire trial population, or for the 12,000 individuals with diabetes, over the 5-years' duration of the study.

The published ANBP2 results do not include information about the onset of diabetes. However, a subanalysis of the ANBP2 data presented at a cardiovascular conference³ has suggested an increase in cases of new diabetes for patients taking a thiazide may similarly have occurred in this study. The full publication of this subanalysis is awaited to see if its findings will allow more definitive conclusions to be drawn about thiazides, diabetes, and long-term cardiovascular outcomes.

Not about cost cutting

A recommendation inviting you to include thiazides in your antihypertensive prescribing is not about cost-cutting. The evidence that has emerged in the last 12 months can give prescribers confidence that thiazides are as suitable a first-line choice to treat people with hypertension, with or without diabetes, as any other antihypertensive alternative.

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An independent, Australian organisation for Quality Use of Medicines

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Consider co-existing conditions

The patient before you may have co-existing conditions which make certain drug classes a more obvious first choice because they have been shown to have favourable effects in more than one condition— the so-called ‘compelling indications’ for choosing an antihypertensive drug. But current evidence continues to support that thiazides in low doses should be considered for anyone with hypertension who does not have a compelling indication for another drug.

Assess cardiovascular risk

Finally, irrespective of the decision-making process of which drug to prescribe, blood pressure should be part of an overall assessment of the patient’s cardiovascular risk factors, with the strongest efforts to reduce blood pressure occurring in those patients at highest risk.

For further information, refer to *NPS News 29*. You may also wish to participate in the NPS clinical audit, *Pharmacotherapeutic management of hypertension*; see inside for enrolment details.

Yours sincerely,



Dr Stephen Phillips
Chair, National Prescribing Service

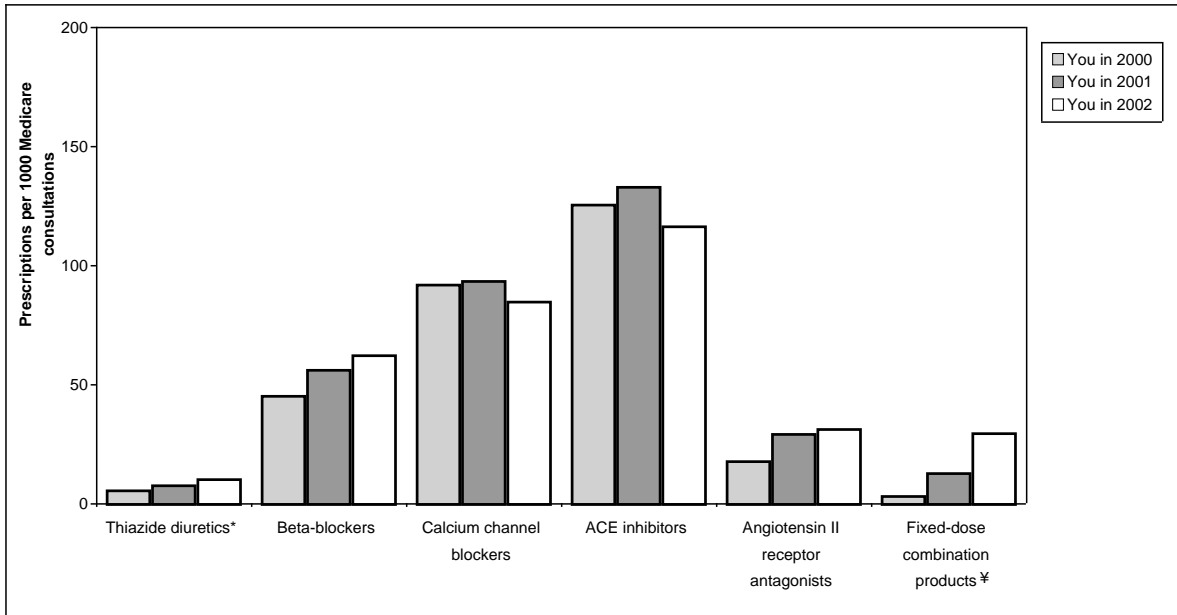
References:

1. ALLHAT Officers and Co-ordinators for the ALLHAT Collaborative Research Group. *JAMA* 2002;288:2981–97.
2. Wing LMH, et al. *N Engl J Med* 2003;348:583–92.
3. Annual meeting of the Cardiac Society of Australia and New Zealand, Adelaide, 2003.

Your confidential prescribing data

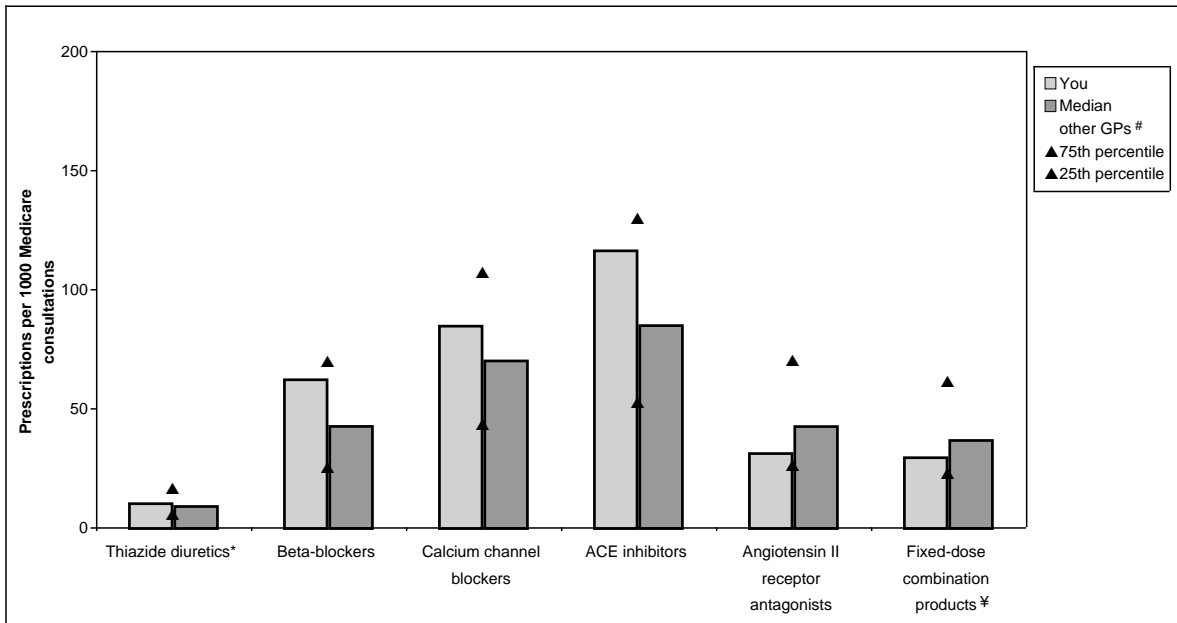
Depending on the cost of the drug the data shown will cover all your patients (if the drug is above the patient co-payment) or only concession card holders (if the drug is below the patient co-payment).

Your antihypertensive drug use in 2000-2002



Note: Thiazide diuretics*, beta-blockers and lower strength ACE inhibitors are under the patient co-payment. The antihypertensive drugs shown may also be used for the management of other conditions.

Your antihypertensive drug use in 2002

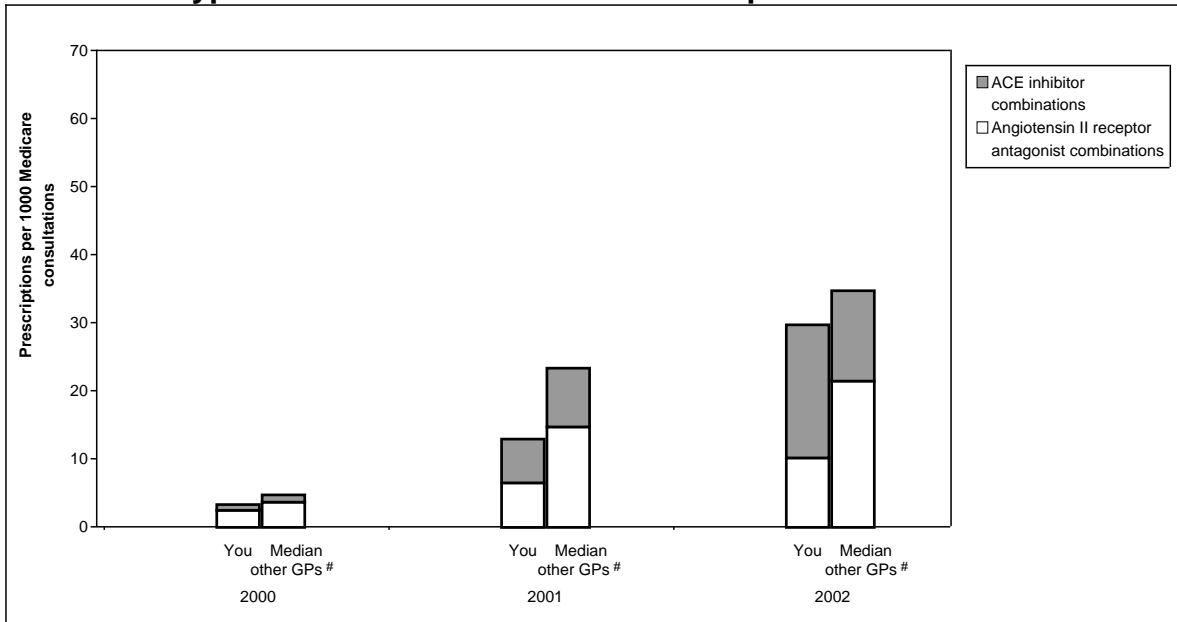


Note: Thiazide diuretics*, beta-blockers and lower strength ACE inhibitors are under the patient co-payment.

Practice Points

- When selecting an antihypertensive agent, consider the potential favourable effects on co-existing conditions.
- Are you reviewing treatment of those patients who are not adequately controlled on monotherapy?

Use of antihypertensive fixed-dose combination products[¥] in 2000-2002



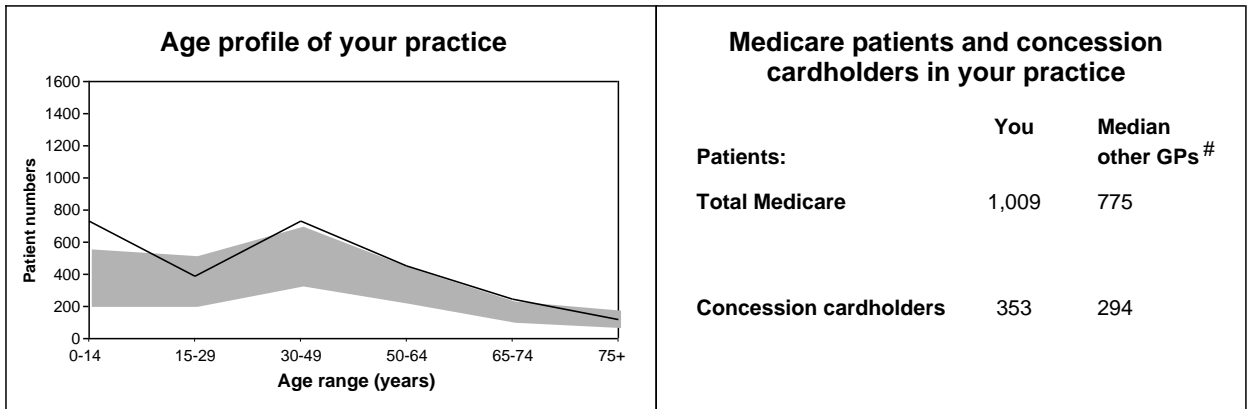
Note: All antihypertensive fixed-dose combination products[¥] are above the patient co-payment.

Practice Points

- Reserve fixed-dose combination products[¥] for patients who are not controlled on monotherapy and who have been stabilised on similar doses of the single agents.
- Fixed-dose combination products[¥] should not be used to initiate therapy.

Practice profile

These data below, based on Medicare claims, are provided to help you review your prescribing data within the profile of your practice and the limitations of the data capture for under co-payment items.



The black line represents the age profile of patients in your practice. 25% to 75% of other GPs# fall within the shaded area.

Concession cardholders include patients who have reached the Safety Net. Data from a three month period (1 April 2002 to 30 June 2002) that best represents your patient mix have been provided.

Notes:

@ Data shown are an aggregate for all your provider locations.

***Thiazide diuretics** include bendrofluazide, hydrochlorothiazide, chlorthalidone, hydrochlorothiazide with amiloride, hydrochlorothiazide with triamterene and indapamide.

¥Fixed-dose combination products

- ACE inhibitor fixed-dose combination products
- hydrochlorothiazide/fosinopril (Monoplus®)
 - hydrochlorothiazide/enalapril (Renitec Plus®)
 - hydrochlorothiazide/quinapril (Accuretic®)
 - indapamide/perindopril (Coversyl Plus®)

- Angiotensin II receptor antagonist combinations
- hydrochlorothiazide/irbesartan (Avapro HCT®, Karvezide®)
 - hydrochlorothiazide/candesartan (Atacand Plus®)
 - hydrochlorothiazide/eprosartan (Teveten Plus®)
 - hydrochlorothiazide/telmisartan (Micardis Plus®)

The comparator group "other GPs" includes all prescribers who are currently located in a similar geographical region ie captial city, other metropolitan area, large rural centre, small rural centre, other rural area, remote centre and other remote area.

▲ 25% to 75% of all doctors in the comparator group fall in the range shown by the triangular symbols.

Managing hypertension

Key messages

- Try low-dose thiazides as first-line therapy; they have the most clinical outcome evidence
- When selecting an antihypertensive drug, consider potential favourable effects on co-existing conditions
- Assess cardiovascular risk and manage hypertension along with other risk factors
- Make the strongest efforts to reduce blood pressure in patients at highest cardiovascular risk
- Fixed-dose combination products should not be used for initiation of therapy

Assess cardiovascular risk to guide management

Assess absolute risk of a cardiovascular event

Base the decision to initiate antihypertensive drug therapy on an assessment of total cardiovascular risk as well as the blood pressure level.

Risk factors that place people at high or very high risk are

- diabetes
- symptomatic cardiovascular disease
- evidence of target organ damage
- Aboriginal, Torres Strait Islander, Maori or Pacific Islander origin.

To assess absolute cardiovascular risk in other people, use a tool such as the New Zealand Guidelines Group's Cardiovascular Risk Calculator (available on the NPS website, www.nps.org.au; click on *Topics* then *Hypertension*).

People at high or very high absolute risk should receive antihypertensive therapy and advice about lifestyle

The absolute benefit of antihypertensive therapy is greatest in those at highest risk. In people at high or very high risk with elevated blood pressure, initiate antihypertensive drug therapy and provide lifestyle advice.

Initiate lifestyle changes before drug therapy in people at low or medium risk

Lifestyle changes alone may be sufficient to decrease blood pressure and total risk in low-risk patients with mild hypertension. In patients 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.

Lifestyle changes reduce blood pressure and cardiovascular risk

Encourage lifestyle changes in all patients with blood pressure $\geq 120/80$ mmHg

Lifestyle modifications can allow some people to avoid or delay the need for antihypertensive drugs. For patients receiving drug therapy, lifestyle changes may reduce the dose or number of agents required.

Ceasing smoking rapidly and substantially reduces cardiovascular risk. Refer to *Prescribing Practice Review 20* for advice on smoking cessation interventions.

Other lifestyle changes that reduce blood pressure and cardiovascular risk include¹⁻⁶

- increasing physical activity
- weight loss in overweight patients
- adopting a healthy eating plan
- reducing salt intake
- moderating alcohol intake.

Guidelines for lifestyle interventions are available from the National Heart Foundation of Australia (www.heartfoundation.com.au).

Initiating antihypertensive therapy

Initiate on low-dose monotherapy

Use the lowest recommended dose of a single drug to initiate therapy. Starting treatment with a low dose helps minimise adverse effects.

Fixed-dose combination products should not be used for initiation

Fixed-dose combination products make it difficult to titrate doses of the individual drugs or to identify the source of adverse events; they should be reserved for patients stabilised on similar doses of single agents.

A sample of desktop prescribing data indicates that 10% of first prescriptions for antihypertensive therapy are for fixed-dose combination products.⁷ However, both the approved indications and PBS restricted listings for combination products specify that they should not be used for initiation.

If response is inadequate...

If the blood pressure response to a single drug is inadequate, there are several possible approaches.

- Add a low dose of a second drug.
 - Low-dose combinations are usually preferable to higher doses of a single drug. Using low doses of drugs from different classes in combination minimises the risk of dose-related adverse effects while optimising antihypertensive effects.⁸ A low-dose thiazide should generally be included in any combination regimen.
- Increase the dose of the current drug.
 - Suitable when the current drug is well tolerated but the response is inadequate and may be particularly appropriate when issues such as cost or compliance are barriers to prescribing two drugs. However, this approach increases the likelihood of dose-related adverse effects and is not appropriate for thiazides, for which doses should not be increased above hydrochlorothiazide 25 mg or equivalent.
- Substitute a drug from a different class.
 - Only if the first drug produces intolerable adverse effects or adequate doses produce little response.

Try low-dose thiazides as first-line therapy

Strongest evidence supports using thiazides

Of all antihypertensive drugs, thiazides have the strongest body of evidence for reducing morbidity and mortality in hypertension.^{9,10}

ALLHAT*, the largest antihypertensive trial ever conducted, showed that thiazide-based therapy is at least as effective as treatment based on an ACE inhibitor or a calcium-channel blocker in reducing the risk of major cardiovascular events and death.¹¹

A small benefit of ACE inhibitors over thiazides in older men has been suggested based on a post hoc analysis of ANBP2[†]; this result requires confirmation because the study was not designed to detect differences in treatment effect between men and women.¹² ANBP2 reinforces that there is no difference in effect on cardiovascular event rates between thiazides and ACE inhibitors.

A discussion of the implications of ALLHAT and ANBP2 for drug choices in hypertension is available on the NPS website (www.nps.org.au).

Limit thiazide doses to hydrochlorothiazide 12.5–25 mg/day or equivalent to minimise electrolyte and metabolic disturbances

Adverse effects associated with the use of higher thiazide doses during the 1970s and 1980s created the perception that metabolic disturbances are a significant problem with these drugs. At lower thiazide doses, however, metabolic adverse effects are unusual and their clinical significance appears low: while elevated cholesterol and new onset diabetes were slightly more common with thiazides than with either ACE inhibitors or calcium-channel blockers in ALLHAT, these changes did not lead to a higher rate of cardiovascular events or death in the chlorthalidone group.¹¹

In choosing which thiazide diuretic to prescribe, note that most evidence of benefit in hypertension comes from studies involving chlorthalidone or hydrochlorothiazide.^{11,13–16} Outcomes studies with bendrofluazide or indapamide are limited.^{17,18} However, cardiovascular morbidity and mortality benefits seen in clinical trials are assumed to extend to all thiazide and thiazide-like diuretics.

Electrolyte disturbances are possible with all thiazide and thiazide-like diuretics, particularly in older patients; limit doses to a maximum of hydrochlorothiazide 25 mg or equivalent to minimise the risk of hyponatraemia or hypokalaemia. Indapamide is no less likely than other thiazides to cause electrolyte disturbances. ADRAC has most commonly received reports of hyponatraemia with indapamide 2.5 mg^{19,20} as opposed to the low-dose, sustained-release indapamide formulation; further post-marketing surveillance is required to determine whether the sustained-release preparation causes fewer electrolyte disturbances.

*Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
†Second Australian National Blood Pressure study

People with diabetes should receive early and active blood pressure control

Tight blood pressure control reduces risk of complications

Tight blood pressure control produces a greater reduction in both macro- and microvascular disease in diabetes than does intensive blood glucose control.²¹

In people *without* nephropathy, initiate with a thiazide, an ACE inhibitor, or a beta-blocker

Thiazides, ACE inhibitors and beta-blockers all reduce cardiovascular morbidity and mortality in patients with hypertension and diabetes and are suitable first-line agents in people without renal disease.^{11,13,21–23}

Subgroup analyses of comparative outcomes trials have not demonstrated any cardiovascular morbidity or mortality advantage of ACE inhibitors over thiazides in people with diabetes.^{11,22}

Beta-blockers are also appropriate first-line agents in people with both diabetes and hypertension^{21,22} and are particularly indicated in people with a history of recent myocardial infarction. Bear in mind that beta-blockers may predispose some treated diabetics to hypoglycaemia and mask the adrenergic warning signs of hypoglycaemia (tremor and tachycardia).

People with diabetes should receive early and active blood pressure control (continued)

In people with nephropathy...

In people with type 1 diabetes and microalbuminuria or proteinuria, ACE inhibitors slow the progression of nephropathy and should be used first-line.²⁴

In people with type 2 diabetes and microalbuminuria, both ACE inhibitors and angiotensin II receptor antagonists reduce protein excretion^{23,25}, but studies demonstrating an effect on long-term decline in renal function in people with early diabetic renal disease are lacking.

In people with type 2 diabetes and overt nephropathy, angiotensin II receptor antagonists may delay progression of renal disease, although these findings rely in part on changes in the surrogate endpoint of serum creatinine concentration.^{26,27} The effect of ACE inhibitors on renal outcomes in people with type 2 diabetes and nephropathy has not been studied.

Calcium-channel blockers are second-line in diabetes

Calcium-channel blockers should be reserved for second-line use in people with diabetes and hypertension. There is inconsistent evidence of a benefit of using calcium-channel blockers in diabetes. Some comparative trials have suggested that dihydropyridine calcium-channel blockers are associated with a higher risk of major vascular events than ACE inhibitors in diabetes.^{28,29} In the diabetic subgroup of ALLHAT, however, amlodipine and lisinopril were associated with similar coronary event rates to chlorthalidone.¹¹

When selecting an antihypertensive drug, consider potential favourable effects on co-existing conditions

Choose antihypertensive therapy based on compelling indications

Some antihypertensive drug classes should be favoured for initiation in certain patient groups because they have evidence of benefit in particular co-existing conditions. For example, beta-blockers and ACE inhibitors are particularly indicated after acute myocardial infarction and calcium-channel blockers and thiazides are suitable in isolated systolic hypertension.

A complete table of compelling indications is available in *Therapeutic Guidelines: Cardiovascular, Version 4* (available from Therapeutic Guidelines Pty Ltd, from August).

Where there is no compelling indication for another class, initiate with a thiazide, unless contra-indicated.

Reviewer:

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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.



National Prescribing Service Limited

Our goal To improve health outcomes for Australians through prescribing that is: ■ safe ■ effective ■ cost-effective
Our programs To enable prescribers to make the best prescribing decisions for their patients, the NPS provides ■ information ■ education ■ support ■ resources

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