# First-line medicines in the treatment of hypertension

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## Summary

**The goal of therapy in uncomplicated hypertension is to reduce cardiovascular risk by lowering the patient's blood pressure. If non-drug treatment is ineffective, the choice of drug treatment is determined by its safety and efficacy. When safety and efficacy are equal the lowest cost drug should be prescribed. For most patients the first choice drug is a low-dose thiazide diuretic.**

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## Introduction

Hypertension requiring treatment exists when a patient's blood pressure, measured on at least three separate occasions, exceeds the threshold pressures which predict an increased cardiovascular risk, in the absence of complicating features such as diabetes mellitus and overt cardiovascular disease. These patients commonly have a family history of hypertension, but clinical assessment and selective investigation reveal no primary underlying cause of the hypertension.

While there is no absolute cut-off between normal and elevated blood pressure, current guidelines advise treatment for patients whose systolic pressure is 160 mmHg or greater, or whose diastolic pressure is 95–100 mmHg or greater. If other risk factors for cardiovascular disease are present, such as hyperlipidaemia, smoking, obesity or a family history, treatment should be started at 140/90–95 mmHg.[1] The patient's predicted cardiovascular risk, which can be calculated from available tables[2], should determine the time for intervention. The higher the risk, the sooner treatment should start.

Once a decision has been taken to intervene, and provided that urgent reduction of the blood pressure is not needed, a period of non-drug treatment is recommended. Reducing excess weight, salt and alcohol intake coupled with increased exercise all reduce blood pressure. However, few studies have shown prolonged effectiveness of these interventions and study design has often been poor.[3] In a majority of patients medication will also be needed to reach their target blood pressure.

## Can we rely on trials to guide the choice of antihypertensive drug?

Controlled clinical trials are often criticised for their lack of representativeness. This may undermine the doctor's confidence in applying the results to individual patients, however, we have no better evidence than these trials. The differences which occur between trials are often exploited in drug promotion, so how do we account for these discrepancies?

The differences may reflect the design of the trials. Results from non-randomised studies are more likely to be favourable to the drug of interest than those of randomised trials. Within randomised trials, less weight should be given to the results if allocation to treatment or control arms was not concealed. The populations included in the trials may not be comparable (for example, the ALLHAT and the ANBP2 studies[4]). Patient outcomes may be expressed in different ways (incidence of stroke, of coronary disease, 'all-cause' cardiovascular morbidity or mortality) that render comparison difficult or impossible. Undeclared conflict of interest may impinge, if not on the results of a study, then at least on its interpretation. Finally, all studies work with samples of the total patient population and the simple play of chance influences the result of any one trial. This is why greater reliance should be placed on the results of trials with larger patient numbers or on systematic reviews or meta-analyses of several studies.

## Choice of first-line drugs

Although the results of clinical trials vary, it is important to select a drug that works well and is safe and affordable for the individual patient.

### *Comparative efficacy*

The criteria by which we select one class of drug as first-line treatment are usually dominated by comparative efficacy. In hypertension all the five major drug classes (low-dose thiazides, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists) are efficacious in reducing blood pressure and cardiovascular events.

Recent results from very large studies and (many) meta-analyses show that it is the reduction in blood pressure itself that leads to lower cardiovascular morbidity and mortality. It is the reduction in blood pressure that counts and not the drug class used to reduce it.

While the conclusion of the National Heart Foundation guidelines (2004)[5] that 'Drugs from any of the five major classes are suitable for initiation and maintenance of antihypertensive therapy' is correct, this is true only if efficacy is considered

alone. Other considerations also have a place in the choice of first-line drugs. The World Health Organization program, the 'Guide to good prescribing', emphasises comparative safety, convenience and cost as well as efficacy as important discriminators in making choices.[6]

### *Comparative safety*

Compared with drugs used for other chronic disorders, antihypertensives are among the safest. They cause very little specific organ toxicity and many of them have been in use for many years so their adverse effects are well known. Periodically there are alarms about particular classes – for example, the precipitation of vascular occlusion with short-acting calcium channel blocking drugs or cardiovascular collapse with hypotension when starting an ACE inhibitor. However, most of these problems can be avoided with appropriate prescribing and monitoring of treatment.

A different insight is obtained from studies in which patients have had to stop their treatment because of adverse effects. In a meta-analysis of 190 monotherapy trials in patients with essential hypertension, discontinuations due to adverse events were commoner with calcium channel blocking drugs (6.7%) than with diuretics or angiotensin receptor blockers (3.1% for each). This suggests that calcium channel blocking drugs have a lower priority as first-line therapy.[7] Although 'discontinuation due to adverse event' may be a relatively crude way of quantifying differences between drugs and may not capture the full details of differences in adverse outcomes, it does provide some objective information about comparative tolerability.

For a patient who experiences an adverse event from a beta blocker or a calcium channel blocker, depending on the nature of the adverse event, there are sufficient differences within these pharmacological classes to warrant trying an alternative within the class in some circumstances. This is not the case for thiazides, ACE inhibitors or angiotensin receptor blockers.

#### *Diabetes*

Patients with hypertension are often overweight and have an increased likelihood of developing diabetes, independent of treatment. The small extra risk of type 2 diabetes with the long-term use of thiazide diuretics was reported in the 1960s when relatively high doses were used. It is re-emerging as a concern based on recent trials suggesting that a greater proportion of patients have developed diabetes on thiazides than on other antihypertensives.

A systematic review of this evidence points out that every estimate of new diabetes in these trials has been derived as a secondary end point, that is, the studies were not designed to focus on incident diabetes as a primary end point, and that a final conclusion cannot be reached at present.[8] The highest quality trials suggest that diabetes incidence is unchanged or increased by thiazides and beta blockers, and unchanged or decreased by ACE inhibitors, calcium channel blockers and angiotensin receptor blockers. However, there are no data on long-term outcomes using the very low doses of diuretic now recommended (daily doses of hydrochlorothiazide, chlorthalidone and indapamide not exceeding 12.5 mg, 12.5 mg and 1.5 mg respectively) although it would be expected that the metabolic effects would be less.

A prudent approach is to measure serum potassium, uric acid and fasting glucose before prescribing and not use diuretics (or beta blockers) if the fasting blood glucose is at, or above, 6.1 mmol/L. Fasting glucose should be monitored periodically in patients on continuing diuretic treatment.

### *Comparative convenience*

Ensuring long-term adherence to medication is one of the major problems in managing hypertension. Anything that will make the task easier will give a competitive edge to drugs in that class. While evidence for better adherence to a regimen with once-daily oral dosing is limited, most patients prefer to take medication once a day. The five main classes of antihypertensive all include drugs, or specific formulations, for once-daily dosing.

### *Comparative cost*

In the absence of major differences in efficacy, safety and convenience, comparative cost may become the final discriminator. In a Pharmaceutical Benefits Scheme (PBS) which is continually under threat, small differences in cost (to the taxpayer) in treating a condition which affects 10–15% of the population can add up to substantial sums, particularly as treatment is usually lifelong.

The comparative cost to the PBS of representative drugs from the five classes of antihypertensive drugs is shown in Table 1. The table includes the dose ranges used in the major studies which showed the efficacy of the drugs in reducing cardiovascular events.

## Conclusion

If we combine the evidence from each of the selection criteria, it is difficult to escape the conclusion that treatment of patients with uncomplicated hypertension should be started with low-dose thiazide-type diuretics. Failure to respond adequately will probably require the addition of another drug, while the emergence of unacceptable adverse effects is a reason for changing to an alternative class of drug.

There will always be the need to tailor treatment to the individual patient, and it will nearly always be inappropriate, for example, to give a patient with gout a diuretic or a patient with asthma a beta blocker. However, for most patients with uncomplicated hypertension low-dose thiazide-type diuretics should be first-line therapy.

*Table 1*

**Costs of monotherapy for essential hypertension**

| Drug | Recommended daily dose | Dispensed price* | 1 month's treatment |
|---|---|---|---|
| Thiazide<br>chlorthalidone† | 12.5–25 mg | $10.92 (100 x 25 mg) | $1.63–$3.28 |
| Beta blocker<br>atenolol†† | 50–100 mg | $9.77 (30 x 50 mg) | $9.77–$19.54 |
| ACE inhibitor<br>lisinopril† | 10–40 mg | $22.12 (30 x 10 mg)<br>$26.63 (30 x 20 mg) | $22.12–$53.26 |
| Calcium channel blocker<br>amlodipine† | 2.5–10 mg | $39.12 (30 x 10 mg) | $9.78–$39.12 |
| Angiotensin receptor antagonist<br>candesartan§ | 8–16 mg | $22.94 (30 x 8 mg)<br>$27.69 (30 x 16 mg) | $22.94–$27.69 |

* dispensed price of maximum quantity listed in the Schedule of Pharmaceutical Benefits (April 2005)

† based on: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981-97.

†† based on: Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003.

§ based on: Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 2003;21:875-86.

The choice of add-on therapy, which may be required later in up to two-thirds of patients, is not as clearly defined. Beta blocking drugs and ACE inhibitors are effective when used with a diuretic. Beta blockers may also be used with dihydropyridine calcium channel blocking drugs (but should not be used in combination with verapamil or diltiazem).

How do these recommendations match those of expert bodies in Australia and overseas? They are consistent with the recommendations of Therapeutic Guidelines: Cardiovascular, 2003 and go further than those of the National Heart Foundation, 2004 which provide no specific recommendation as to first-line choice. The 2003 World Health Organization (WHO)/International Society of Hypertension statement on management of hypertension advises: 'for the majority of patients without a compelling indication for another class of drug, a low dose of a diuretic should be considered as the first choice of therapy on the basis of the comparative trial data, availability, and cost.'[9] Other guideline groups, such as the National Institute for Clinical Excellence in the UK, have adopted a similar position to that of WHO, again based on an independent, comprehensive review of the clinical evidence.[10]

## References


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10. National Institute for Clinical Excellence. Hypertension - management of hypertension in adults in primary care. Clinical Guideline 18. August 2004. http://www.nice.org.uk [cited 2005 Mar 14]

*Dr Hill was a member of the World Health Organization/ International Society of Hypertension group which constructed the 'Statement on management of hypertension'. Professor Smith was Chair of the Writing Group which assembled Therapeutic Guidelines: Cardiovascular, 2003. Neither has an affiliation with any pharmaceutical company.*

### Self-test questions

*The following statements are either true or false (answers on page 51)*

3. Patients with essential hypertension taking calcium channel blockers stop their medication because of adverse effects more frequently than those patients taking diuretics.
4. Thiazide diuretics are no longer first-line treatment for uncomplicated hypertension.

# Top 10 drugs

These tables show the top 10 subsidised drugs in 2003–04. The tables do not include private prescriptions.

*Table 1*

### Top 10 drugs supplied by DDD/1000 pop/day *

| Drug | PBS/RPBS † |
|---|---|
| 1. atorvastatin | 80.697 |
| 2. simvastatin | 51.468 |
| 3. diltiazem hydrochloride | 35.470 |
| 4. ramipril | 31.725 |
| 5. omeprazole | 21.631 |
| 6. irbesartan with hydrochlorothiazide | 20.889 |
| 7. irbesartan | 19.931 |
| 8. salbutamol | 19.919 |
| 9. frusemide | 19.403 |
| 10. sertraline | 17.108 |

*Table 2*

### Top 10 drugs by prescription counts

| Drug | PBS/RPBS † |
|---|---|
| 1. atorvastatin | 7,097,744 |
| 2. simvastatin | 6,008,468 |
| 3. paracetamol | 4,714,533 |
| 4. omeprazole | 4,537,098 |
| 5. irbesartan | 3,371,882 |
| 6. celecoxib | 3,240,047 |
| 7. salbutamol | 3,220,045 |
| 8. atenolol | 3,136,071 |
| 9. rofecoxib | 3,028,529 |
| 10. ramipril | 2,871,065 |

*Table 3*

### Top 10 drugs by cost to Government

| Drug | Cost to Government ($A) | DDD/1000/day PBS/RPBS † | Prescriptions PBS/RPBS † |
|---|---|---|---|
| 1. atorvastatin | 397,430,210 | 80.697 | 7,097,744 |
| 2. simvastatin | 363,667,949 | 51.468 | 6,008,468 |
| 3. omeprazole | 197,471,882 | 21.631 | 4,537,098 |
| 4. salmeterol and fluticasone | 163,196,875 | – ‡ | 2,666,465 |
| 5. olanzapine | 150,962,947 | 2.941 | 717,460 |
| 6. clopidogrel | 128,213,796 | 6.446 | 1,617,367 |
| 7. pravastatin | 125,298,133 | 14.150 | 2,131,080 |
| 8. esomeprazole | 111,540,717 | 9.694 | 2,265,197 |
| 9. alendronic acid | 99,266,727 | 7.942 | 1,921,121 |
| 10. rofecoxib | 95,196,777 | 10.912 | 3,028,529 |

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people, in every thousand Australians, are taking the standard dose of a drug every day.

† PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

‡ Combination drugs do not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC): Drug Utilisation Database 