

Inside ▶

Antihypertensives in diabetes

Be aware of drug and dose in fixed-dose combinations

Which combination and when?

Role of beta blockers

Case study 48: Achieving tight blood pressure control

Managing hypertension as a cardiovascular risk factor

The primary focus in pharmacological management of hypertension should be on finding a drug regimen that effectively lowers blood pressure and therefore reduces cardiovascular risk.

All antihypertensives reduce blood pressure

— but favourable effects on comorbidity and adverse effects can guide selection

All five major antihypertensive classes (low-dose thiazide diuretics, beta blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II-receptor antagonists, and calcium-channel blockers) reduce blood pressure to a similar extent, and this is their key contribution to preventing cardiovascular events.¹⁻³ Consider favourable effects on patient comorbidity and adverse effects when choosing drug therapy (see page 2).

While new Australian guidelines are expected soon (Heart Foundation guidelines are expected in late 2007), the general principles for treating hypertension are unlikely to change:

- Assess and treat according to overall cardiovascular risk and modify risk factors, initiating drug therapy when lifestyle changes do not reduce blood pressure to acceptable limits (see Figure 1, overleaf).
- Pursue blood pressure targets (see Table 1) — decreasing blood pressure decreases risk.
- Choose initial therapy according to comorbidity and acceptable adverse effects (see Table 2, overleaf).

Consider poor adherence as a possible cause of treatment failure. Assess adherence routinely to identify patients who warrant intensive efforts to improve adherence. Strategies to improve adherence will be discussed in *NPS Prescribing Practice Review 38* (published July 2007).

Table 1: Clinic treatment goals (mmHg)³

Adults ≥ 65 years (unless there is diabetes and/or renal insufficiency and/or proteinuria ≥ 0.25 g/day)	< 140/90
<ul style="list-style-type: none"> • Adults < 65 years and/or • Adults with diabetes and/or • Adults with renal insufficiency and/or • Adults with proteinuria 0.25–1.0 g/day 	< 130/85 (or < 130/80) ⁴
Adults with proteinuria > 1 g/day (in people with and without diabetes)	< 125/75

Case study 48 — now available online
(see inside for details)



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Figure 1: Treatment of hypertension⁴

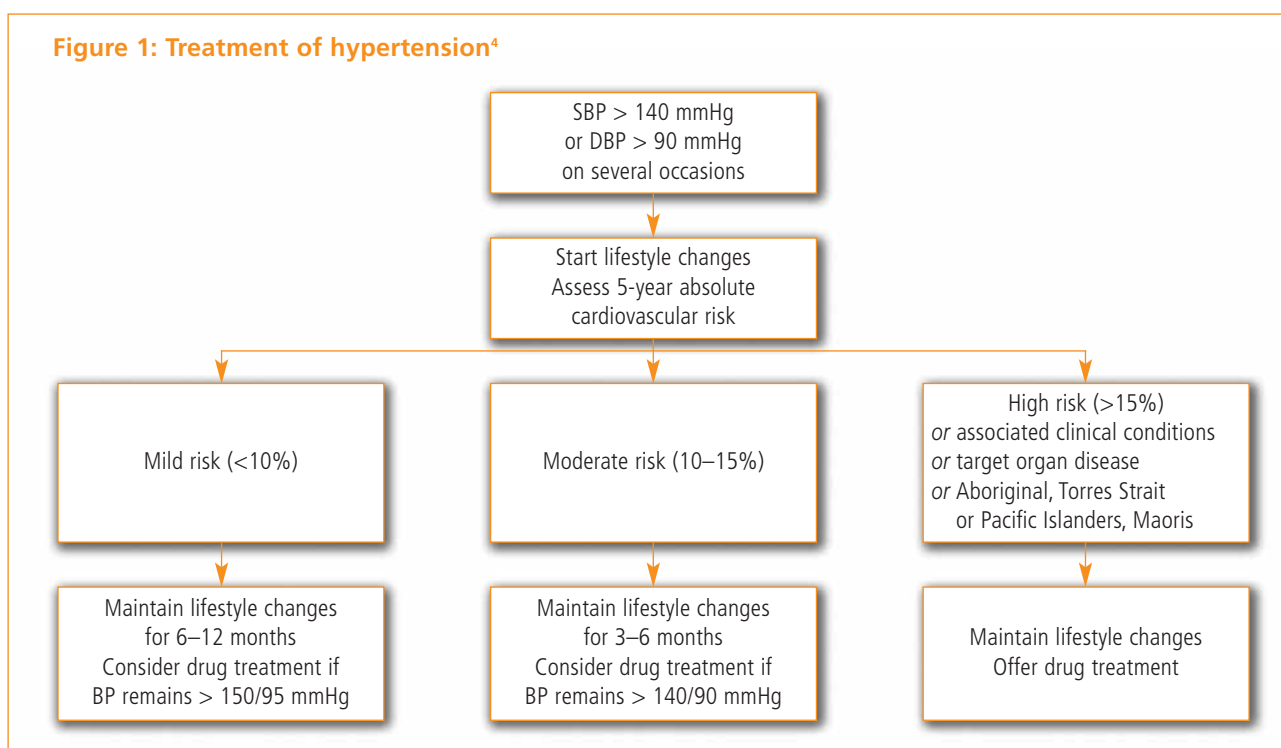


Table 2: Coexisting conditions and antihypertensive choice⁵

Coexisting condition	Drugs with favourable effect
Angina	Beta blockers (except oxprenolol, pindolol), calcium-channel blockers
Heart failure	ACE inhibitors, beta blockers (carvedilol, controlled-release metoprolol, bisoprolol*), thiazide diuretics, angiotensin II-receptor antagonists
Post myocardial infarction	Beta blockers (except oxprenolol, pindolol), ACE inhibitors (left ventricular dysfunction)
Secondary stroke prevention	Low-dose thiazides or thiazide-like diuretics ± ACE inhibitors
Tachyarrhythmias	Beta blockers
Diabetes with microalbuminuria	ACE inhibitors, angiotensin II-receptor antagonists
Non-diabetic nephropathy	ACE inhibitors
Coexisting condition	Drugs with unfavourable effect
Asthma, chronic obstructive pulmonary disease	Beta blockers [†]
Bradycardia, second- or third-degree atrioventricular block	Beta blockers, verapamil, diltiazem
Heart failure	Selective alpha-blockers, verapamil [‡] , diltiazem (other calcium-channel blockers with caution [§])
Gout	Diuretics
Renovascular disease	ACE inhibitors, angiotensin II-receptor antagonists
Severe peripheral vascular disease	Beta blockers
Pregnancy	ACE inhibitors, angiotensin II-receptor antagonists

* may have unfavourable effect in uncontrolled heart failure

[†] cardioselective beta blockers (e.g. atenolol, metoprolol) may be used cautiously in mild-to-moderate reactive airways diseases

[‡] verapamil may be used in hypertrophic cardiomyopathy

[§] calcium-channel blockers are associated with an increased risk of heart failure compared with other agents and with placebo¹

Reproduced, with modification, from the *Australian Medicines Handbook*, 2006

Antihypertensives in diabetes: which outcomes matter?

Many prescribers cite 'renoprotection' as their rationale for choosing ACE inhibitors first line for most patients. While this approach is justified in patients with diabetes-related kidney disease, the evidence is less clear for people without diabetes-related renal impairment or who do not yet have diabetes.

In diabetic nephropathy ACE inhibitors are recommended to slow the progression of renal disease.^{3,6}

In people with diabetes and microalbuminuria drugs that act on the renin–angiotensin system (ACE inhibitors and angiotensin II-receptor antagonists) delay the progression of renal disease.⁷

In people with diabetes without microalbuminuria:

- There is some evidence that ACE inhibitors reduce the risk of developing new microalbuminuria (compared with placebo or calcium-channel blockers), but there was no reduction in mortality.⁸
- Low-dose thiazides have substantive evidence for reducing cardiovascular events in people with diabetes^{9,10}; they are recommended for people with diabetes on this basis.⁴ Thiazide diuretics were not associated with worse renal outcomes in people with hypertension, diabetes and reduced glomerular filtration rate (GFR) in the ALLHAT* study; unfortunately baseline microalbuminuria and proteinuria were not measured¹¹, nor are these data available elsewhere.⁷

Monotherapy will be inadequate for many people with diabetes. The UKPDS[†] study showed that tight blood pressure control in people with diabetes significantly reduced the incidence of microalbuminuria¹², but around one-third of patients required three or more antihypertensives to achieve this.

In people without diabetes no class has been proven superior. Thiazide diuretics slightly increase the risk of new-onset diabetes compared with other antihypertensives (at most, by 3.5% over 5 years compared with an ACE inhibitor⁹); there is some evidence that this is particularly so when used in combination with a beta blocker.¹³ While it may be prudent to avoid thiazides in people who are at risk of type II diabetes^{14,15}, for most people the benefits from BP-lowering and cardiovascular protection probably outweigh any adverse metabolic effects (these are less likely at the low doses of thiazides currently recommended for treatment^{4,5}). There is debate about whether thiazide-induced glucose increases have the same adverse outcomes as diabetes in other circumstances. In both the ALLHAT study and a 14-year follow-up of the SHEP[‡] study (in isolated systolic hypertension), people who developed new diabetes while on diuretic therapy did not have worse cardiovascular outcomes.^{9,16,17}

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

† United Kingdom Prospective Diabetes Study

‡ Systolic Hypertension in the Elderly Program

Be aware of drug and dose in fixed-dose combinations

While fixed-dose combination preparations may be cost-saving for patients and may aid adherence, dosing can be problematic.

- Check the components and doses of combination preparations and the implications for dose adjustments. Some combinations are only available at higher doses than would normally be prescribed. For example, there is no candesartan 8 mg strength available in the combination with hydrochlorothiazide. Avoid preparations that increase the dose of either component if this has not been proven necessary.

- Avoid starting with fixed-dose combinations — titration is difficult, and the source of adverse events may be difficult to identify. Trial the second agent as a separate drug before prescribing a combination preparation.
- Using fixed-dose combination preparations for initiation is outside PBS restrictions, which require inadequate control with one antihypertensive before a second is added.

Which combination and when?

Fewer than 50% of patients achieve satisfactory blood pressure with a single antihypertensive³, and many will need combination therapy. In particular, people with diabetes often need more two (or more) drugs to reach target blood pressure.

The common benefit of all combination therapy is a greater reduction in blood pressure than with monotherapy.¹⁸ Start with a single antihypertensive chosen according to favourable effects on the patient's comorbidity or risk profile.

When adding a second antihypertensive, choose the drug and dose being added using a similar rationale. Use low — that is, the usual recommended doses — of two drugs from different classes in preference to maximum doses of a single agent. A regimen with minimal adverse effects should aid compliance.³ A thiazide will be an appropriate choice in combination with most other antihypertensives.

Useful combinations include:

- ACE inhibitor with calcium-channel blocker (in diabetes or lipid abnormalities)³
- beta blocker with dihydropyridine* calcium-channel blocker (coronary heart disease)³
- beta blocker with ACE inhibitor (heart failure or post myocardial infarction)
- thiazide[†] with beta blocker (mortality and cardiovascular benefits; but may impair glucose tolerance [see, 'Antihypertensives in diabetes'])³
- thiazide with ACE inhibitor (or angiotensin II-receptor antagonist) (heart failure or secondary

stroke prevention).¹⁹ **Note:** risk of renal failure if an NSAID is added to this combination ('triple whammy').²⁰

Combinations to avoid or use with caution include:

- beta blocker with verapamil or diltiazem (non-dihydropyridine calcium-channel blockers)
- ACE inhibitor or angiotensin II-receptor antagonist with potassium-sparing diuretic (increases risk of hyperkalaemia)³
- ACE inhibitor with angiotensin II-receptor antagonist; may adversely affect renal function — reserve for use in diabetic nephropathy or diabetes with proteinuria.

Some data show that using two antihypertensives doubles blood pressure-lowering effects (about 10–20 mmHg) — but does not double adverse effects, compared with single drug therapy (increased from 5.2% to 7.5%).¹⁸ There is little evidence to guide combinations of three or more antihypertensives, but combining drugs from different classes is preferred (for example, ACE inhibitor, calcium-channel blocker and thiazide diuretic).

Note: consider secondary causes of hypertension in treatment failure. For example, use of drugs with prohypertensive effects, such as some antidepressants (e.g. venlafaxine, reboxetine), NSAIDs, sibutramine, steroids, amphetamines.³

* dihydropyridine calcium-channel blockers are amlodipine, felodipine, lercanidipine, nifedipine

† includes thiazide-like diuretics

Reserve ACE inhibitor–angiotensin II-receptor antagonist combination for proteinuria in people with diabetes

For most patients, the combination of an ACE inhibitor and an angiotensin II-receptor antagonist achieves little additional benefit in blood pressure lowering (about 4/3 mmHg, systolic/diastolic, overall compared with either drug alone), with the possibility of additive adverse effects.²¹ There is some evidence that the combination causes clinically significant reductions in proteinuria in people with chronic renal disease and diabetes, and independent of blood pressure-lowering effects.²¹ Theoretically, the combination could potentiate inhibition of angiotensin II, which is thought to occur less effectively with ACE inhibitors in the long term.

However, additional BP reduction in studies of combination therapy may have reflected differences in pharmacokinetics rather than a synergistic effect.

In the studies, most ACE inhibitors were shorter-acting but given once daily, so the combined effect may have been no greater than would have occurred with an additional ACE inhibitor dose. Additive effects were not seen in trials using longer-acting ACE inhibitors (trandolapril) or higher doses of ACE inhibitors.²¹

The combination may adversely affect renal function and cause hyperkalaemia.^{21,22} An increased risk has not been seen in studies to date, but these have been small (fewer than 500 people), short term and offer less certainty regarding safety.²¹ Seek specialist advice before prescribing, and closely monitor renal function and electrolytes in people using this combination.

Role of beta blockers in hypertension

The role of beta blockers in treating hypertension was challenged recently after combined analyses (meta-analyses) suggested that they provide less protection from stroke than other antihypertensive drug classes.

Overall, when used as monotherapy or as the dominant drug in a regimen, beta blockers (particularly atenolol) may reduce the risk of stroke less than other antihypertensives as a group^{23,24}; this may be particularly so for older patients and those with overt cardiovascular risk factors. However, if patients currently prescribed beta blockers have satisfactory blood pressure control and/or are prescribed beta blockers because of a favourable effect on comorbidity (e.g. heart failure, previous MI), there is no need to change treatment.^{15,25}

Beta blockers reduced the risk of stroke compared with placebo^{23,26}, but had a higher risk of stroke than other antihypertensives combined.^{23,24,26} Beta blockers did not reduce the risk of mortality or myocardial

infarction compared with placebo, but were not different for these outcomes compared with other antihypertensives.²³

Questions remain. None of the combined analyses accounted for differences in actual blood pressure achieved — yet blood pressure directly affects stroke risk and explains much of the difference in event rates in antihypertensive drug trials.^{1,18} Similarly, differences in cardiovascular risk in the individual trials were not accounted for.

Two trials in high-risk populations carried particular weight in the meta-analyses — the LIFE* study (in which all patients had left ventricular hypertrophy) and the ASCOT† study. In ASCOT, patients had 3 or more risk factors, including diabetes (22%), previous stroke (11%), and microalbuminuria/proteinuria (62%), which may have made a beta blocker-based regimen inappropriate for many patients.²⁷

* Losartan Intervention For Endpoint reduction

† Anglo-Scandinavian Cardiovascular Outcomes Trial

Older antihypertensives — not all the same

Although thiazides and beta blockers are often described together as 'older antihypertensives', low-dose thiazides are not affected by the doubts raised about beta blockers.¹⁴ Thiazides reduce the risk of cardiovascular morbidity and mortality, including stroke, and have yet to be proven inferior to calcium-channel blockers, ACE inhibitors or angiotensin II-receptor antagonists for these outcomes.^{1,28} Although data were limited, trials of mixed thiazide–beta blocker regimens did not show an increased risk of stroke relative to other antihypertensives, though this was shown with beta blockers alone.²³

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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 clinical circumstances of each patient.



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