

Which **Antihypertensive?**

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Choosing an antihypertensive medicine

The main benefit of any antihypertensive treatment is lowering of blood pressure and this is largely independent of the class of medicine used.¹ Once the decision has been made to initiate antihypertensive treatment, choice of medicine should be based on individual patient characteristics including age and co-morbidities.

The main classes of antihypertensive medicines are; thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blocker [ARB] for those who are not able to tolerate an ACE inhibitor), calcium channel blockers and beta blockers.

There is much debate on which antihypertensive medicine is the most appropriate first choice. In practice, combination treatment is ultimately needed to control blood pressure in the majority of patients so it is less important which antihypertensive is used initially.² Some patients may respond well to one medicine but not to another.¹

Beta blockers are not usually considered for first line treatment of hypertension, except when used for their protective effect in ischaemic heart disease and heart failure, and for their rate-controlling effect in atrial fibrillation.³ The effectiveness of beta blockers in reducing major cardiovascular events (stroke in particular) compared to other antihypertensive agents is currently under review.

Key concepts

- In patients with uncomplicated, mild hypertension and in elderly people, initiating a single antihypertensive medicine is appropriate first-line treatment
- Selecting which antihypertensive to use can be based on co-morbidities and individual patient characteristics
- Thiazide diuretics, ACE inhibitors and calcium channel blockers are all appropriate initial choices and beta blockers may be used first line in selected groups of patients
- In general, an ACE inhibitor may be selected for a younger patient (<55 years) and a diuretic or calcium channel blocker selected for an older patient, if there are no compelling indications for another choice
- If blood pressure targets are not achieved with monotherapy, consider initiating combination therapy - the majority of people with hypertension will require at least two antihypertensive medicines to achieve recommended targets
- In patients with moderate to severe hypertension or high to very high cardiovascular risk, combination therapy can be initiated as first-line treatment
- The choice of antihypertensive combination can be based on selecting medicines with different actions and on individual patient characteristics. An ACE inhibitor plus a diuretic or calcium channel blocker is a commonly used regimen.
- “Start low, go slow” unless otherwise indicated
- If patients experience adverse effects, changing early to a more tolerated medicine will improve adherence


Monotherapy is a practical starting point

“Monotherapy is recommended initially, especially for patients with mildly elevated blood pressure and low to moderate total cardiovascular risk. A low dose thiazide diuretic is recommended as first-line treatment, unless contraindicated or if indications are present for one of the other treatment options.”

In patients with uncomplicated, mild hypertension and in elderly people, antihypertensive therapy can be initiated gradually after a period of life style changes, e.g. three to six months. Monotherapy is recommended initially, especially for patients with mildly elevated blood pressure (140 – 159/90 – 99 mmHg), and low to moderate total cardiovascular risk.²

The New Zealand Guidelines recommend a low dose thiazide diuretic as first-line treatment, unless contraindicated or if indications are present for one of the other treatment options.⁴ For example, a beta blocker may be appropriate as a first-line treatment when there are co-existing cardiac problems such as ischaemic heart disease and heart failure. ACE inhibitors or calcium channel blockers can also be used initially. Choice is based on individual patient characteristics, including age, ethnicity, contraindications or compelling indications for specific medicines, adverse effects and relative cost effectiveness (Table 1).⁵

Treatment should be initiated at a low dose. If blood pressure is not controlled after six weeks, either a full dose of the initial medicine can be given, or patients can be switched to a medicine of a different class (starting at a low dose and then increasing). If blood pressure control is not reached, low doses of two medicines is preferable to increasing to a maximum dose of a single medicine. This approach maximises efficacy while minimising adverse effects.⁶

 **Best Practice Tip:** Starting with even a low dose of an antihypertensive medicine can cause an exaggerated

response in some people. Inform patients of the signs of hypotension especially in the early stages of treatment.

Patient co-morbidity influences antihypertensive choice

There are specific indications, limitations or contraindications for each of the antihypertensive medicine classes for individual patients, depending on their co-morbidities.⁷

Compelling indications include the use of ACE inhibitors or ARBs in patients with nephropathy and beta blockers in patients who have had a myocardial infarction.⁴ Equally, there may be clinical reasons to avoid a particular class of antihypertensive (Table 1).

Age influences antihypertensive choice

Unless a patient has a specific indication for a particular antihypertensive class, there are some medicines which may be best suited to them based on their age.

ACE inhibitors for younger patients: Treatment guidelines from the United Kingdom recommend that ACE inhibitors or ARBs are initiated for younger patients (aged under 55 years) with hypertension.³

In practice, many younger patients are started on an ACE inhibitor. Special Authority criteria apply for the prescription of an ARB. A limited number of studies have found ACE inhibitors and beta blockers to be more effective at lowering blood pressure in younger people compared to calcium channel blockers or thiazide diuretics.⁸ One study found significantly greater responses in blood pressure levels in a group of younger patients (age 22 to 51 years) when treated with an ACE inhibitor and also when treated with a beta blocker, compared to when they were treated with a calcium channel blocker or a diuretic.⁹ In the absence of a compelling indication, beta blockers are not commonly used for initial monotherapy.

Thiazide diuretics and calcium channel blockers for older patients: United Kingdom guidelines recommend diuretics

Table 1: Choice of antihypertensive in patients with co-morbidities^{6, 10}

Condition	Potentially beneficial	Cautions
Angina	Beta blockers (without ISA)* Calcium channel blockers ACE inhibitors	No specific cautions
Post myocardial infarction	Beta blockers (without ISA)* ACE inhibitors	No specific cautions
Atrial fibrillation	Rate control: beta blockers Verapamil, diltiazem	No specific cautions
Heart failure	ACE inhibitors, ARBs Thiazide diuretics Beta blockers e.g. carvedilol, metoprolol controlled release	Caution: Calcium channel blockers (especially verapamil, diltiazem) Contraindicated: Alpha blockers in aortic stenosis, beta blockers in uncontrolled heart failure
Chronic kidney disease	ACE inhibitors, ARBs	
Post stroke	ACE inhibitors, ARBs Calcium channel blockers Low dose thiazide diuretics	Thiazides in very elderly people or those with poor fluid intake could contribute to hypoperfusion
Diabetes	ACE inhibitors, ARBs Calcium channel blockers	Beta blockers Thiazide diuretics (risk of metabolic adverse effects mainly associated with high doses)
Symptomatic benign prostatic hypertrophy	Alpha blockers (add-on) e.g. doxazosin, prazosin	Alpha blockers could lead to postural hypotension in elderly people
Asthma/COPD	No specific recommendations	Beta blockers Cardioselective beta blockers e.g. metoprolol, atenolol, can be used cautiously in stable COPD, especially if specifically indicated, e.g. in heart failure Beta blockers are generally contraindicated in asthma
Gout	No specific recommendations	Thiazide diuretics: precipitation of gout unlikely especially if controlled with allopurinol

* ISA = intrinsic sympathomimetic activity. Beta blockers with ISA are: pindolol, oxprenolol and celiprolol, all other beta blockers are without ISA

or calcium channel blockers for older patients (aged 55 years or older) with hypertension.³ Australian guidelines recommend thiazide diuretics as first line treatment in patients aged 65 years and older.⁶ In very elderly or frail patients the decision to treat hypertension should be made on a case by case basis.

Older patients often respond best to a thiazide diuretic or calcium channel blocker and therefore these may be more effective initial choices in this group.¹ The use of thiazide diuretics and calcium channel blockers in older patients may have the additional benefit of managing isolated systolic hypertension. This is more prevalent in elderly people due to large vessel stiffness associated with ageing.¹⁰ Older patients usually have lower plasma renin activity than younger patients, therefore ACE inhibitors and beta blockers may not be as effective.¹

Hypertension in pregnancy

Suitable first line medicines for women with hypertension who are planning a pregnancy include labetalol, methyldopa and clonidine.⁶

ACE inhibitors, ARBs and diuretics are contraindicated at all stages of pregnancy. Calcium channel blockers are contraindicated in early pregnancy but have been shown to be safe and effective in the late second and third trimesters. Specialist referral is recommended for all pregnant women with hypertension.⁶

Combination diuretic therapy

“Most patients will require more than one antihypertensive medicine to reach their treatment target.”

An estimated 50–75% of patients with hypertension will not achieve blood pressure targets with monotherapy.⁶ Most patients will require more than one antihypertensive medicine to reach their treatment target.⁴

A combination of two medicines at low doses may also be used as initial therapy in patients with moderate to

Recommended doses for commonly used antihypertensives^{6,11}

Class	Commonly used medicines	Usual dose range
Thiazide diuretics	Bendrofluazide	2.5 mg once daily
ACE inhibitors	Cilazapril	0.5–5 mg once daily
	Quinapril	2.5–40 mg once daily or in two equally divided doses
	Enalapril	2.5–20 mg once daily or in two equally divided doses
ARBs	Candesartan	4–8 mg once daily (maximum 32 mg)
	Losartan	25–50 mg once daily
Calcium channel blockers (dihydropyridine)	Felodipine	2.5–10 mg once daily (controlled release)
	Amlodipine	2.5–10 mg once daily
Beta blockers	Metoprolol tartrate	50–100 mg twice daily
	Metoprolol succinate	23.75–190 mg once daily (controlled release)
	Atenolol	25–50 mg once daily
ACE Inhibitor with diuretic	Cilazapril (5 mg) with hydrochlorothiazide (12.5 mg)	
	Quinapril (10 mg or 20 mg) with hydrochlorothiazide (12.5 mg)	

Notes:

- Initial doses in older people or in those with renal impairment should be at the lowest end of the dose range.
- Atenolol is recommended only in combination with other agents. For patients on atenolol monotherapy, consider substituting for another beta blocker or another medicine class (due to adverse outcomes in meta-analyses of monotherapy clinical trials).¹²

Adherence to antihypertensive therapy

International studies suggest that up to one quarter of patients discontinue their antihypertensive treatment after six months, and this is associated with increased risk of hospitalisation for cardiovascular problems. In a recent large Canadian study, 22% of patients stopped their treatment completely within the first six months. Factors associated with an increased

likelihood of continuing treatment were; better medical management and communication by the prescriber, early changes in treatment (if adverse effects are experienced), more follow up visits and non-diuretics as initial choice of therapy.¹³ This study emphasises the importance of monitoring treatment and adverse effects, and making appropriate changes promptly to improve adherence.

highly elevated blood pressure or high to very high total cardiovascular risk.²

There is an additive effect when two antihypertensives from different classes are combined, and this is greater than the effect of increasing the dose of a single medicine.⁴ The most effective combinations involve medicines that act on different physiological systems.² Most guidelines recommend renin angiotensin system inhibitors i.e. ACE inhibitors or ARB, in combination with a diuretic or calcium channel blocker as the preferred combination therapy.^{3, 6, 14}

The combination of a thiazide diuretic and a beta blocker, although still effective, is not routinely recommended in people with glucose intolerance, metabolic syndrome or established diabetes.^{2, 6} This is because of the additive combination of metabolic adverse effects,

An ACE inhibitor or ARB is likely to be less effective when used in combination with a beta blocker, since beta blockers reduce renin secretion and therefore angiotensin II formation.¹

Occasionally a combination of more than three antihypertensive drugs may be required to achieve adequate blood pressure control. If patients continue to have an elevated blood pressure despite triple therapy, the possibility of secondary hypertension should be considered, although factors such as non-compliance, non-steroidal anti-inflammatory use or alcohol misuse may contribute to resistance.⁴ Patients with suspected secondary hypertension need to be further investigated for the cause e.g. sleep apnoea, chronic kidney disease, Cushing's syndrome, phaeochromocytoma.

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