<R/Heads>PHARMACOLOGY

# Drugs acting on the heart: antihypertensive drugs

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## Abstract
Antihypertensive drugs are used commonly in anaesthesia and intensive care medicine. Patients might require antihypertensive drugs before surgery for the treatment of essential hypertension, pre-eclampsia or, occasionally for conditions such as phaeochromocytoma; during surgery as part of a deliberate hypotensive anaesthetic technique; or to reduce postoperative cardiovascular complications. Here, we discuss the physiology of blood pressure control, the pharmacology of antihypertensive drugs, current guidelines, and practical applications of antihypertensive therapy.

**Keywords** antihypertensive agents; autonomic nervous system; blood pressure; hypertension; renin–angiotensin system; vasomotor system

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### Learning objectives

After reading this article, you should be able to:
- categorize antihypertensive treatments according to their mechanisms of action
- name the important potential adverse effects associated with specific antihypertensive drugs
- decide when hypertension should be treated, according to recent guidelines

## Introduction
Arterial pressure is modulated by the interactions between vessel tone, blood volume, and cardiac function, which are regulated by local and nervous mechanisms. Local mechanisms include metabolites that influence vascular tone and blood flow within tissues. Nervous mechanisms control the distribution of blood throughout the body, as well as coordination of cardiac output, heart rate, and contractility. The autonomic nervous system (ANS) is controlled by neurones in the spinal cord, brainstem and hypothalamus, which are influenced by higher centres. The renin–angiotensin system (RAS) affects vascular tone and excretion of sodium and water in response to changes in circulating volume and arterial pressure. Blood pressure can be manipulated by drugs acting at several of these sites (Figure 1).

## Autonomic nervous system

**Centrally acting agents**

**Clonidine:** a central $\alpha_2$-agonist that decreases sympathetic tone and is occasionally used for the treatment of hypertension. Premedication (3–5 μg/kg orally or 1-2 μg/kg intravenously) attenuates perioperative sympathetic responses. Clonidine reduces the minimum alveolar concentration (MAC) of anaesthetic agents and has analgesic effects when administered epidurally, being synergistic with opioids. Adverse effects include sedation, bradycardia and rebound hypertension after acute withdrawal of therapy.

**Methyldopa:** a DOPA analogue that is metabolised to α-methylnorepinephrine, which acts as a potent central $\alpha_2$-agonist. Methyldopa is mostly used in the treatment of pregnancy-associated hypertension; the initial dose is 250 mg two or three times daily. Adverse effects include oedema, hepatotoxicity, positive direct Coombs' test (10–20%), and bone marrow suppression.

**Moxonidine:** an imidazoline $I_1$-receptor agonist and a structural analogue of clonidine that acts as a central sympatholytic agent. Moxonidine is used when systemic vascular resistance is high but heart rate and stroke volume are normal. It also can be used in the management of hypertension associated with end-stage renal failure. The main adverse effect is bradycardia.

**General anaesthetic agents:** also cause hypotension, mainly by decreasing central sympathetic tone and lowering the peripheral vascular resistance by causing dose-related vasodilatation.

**Sympathetic outflow**

**Epidural and spinal:** local anaesthetics and opioids inhibit the sympathetic outflow leaving the spinal cord from T1–L2, causing vasodilation and hypotension.

**α-Blockers**

α-Blockers inhibit the action of catecholamines at peripheral α-adrenergic receptors.

**Phentolamine:** a competitive non-selective, short-acting α-blocker used in the treatment of hypertensive crises for example those caused by phaeochromocytoma or cocaine intoxication. An intravenous dose of 1–5 mg causes a rapid reduction in blood pressure for 5–20 minutes.

**Phenoxybenzamine:** a long-acting, non-selective α-blocker that is mainly used in the preoperative management of phaeochromocytoma. Starting dose is 10 mg orally.

**Prazosin and doxazosin:** selective $\alpha_1$-blockers that cause vasodilation. They are also used for benign prostatic hyperplasia (relaxation of urinary tract smooth muscle), congestive heart failure and Raynaud's disease. All α-blockers should be titrated carefully as first-dose hypotension can be severe. They have additional favourable metabolic effects on lipid and glucose metabolism.

**β-Blockers**

β-blockers cause hypotension via several mechanisms: they reduce cardiac output (decreased heart rate and contractility), central sympathetic nervous activity, plasma renin concentrations and peripheral resistance. Hence, they are useful antihypertensive agents in patients with ischaemic heart disease, obstructive cardiomyopathy, congestive heart failure (with caution), arrhythmias, anxiety and thyrotoxicosis. Adverse reactions include worsening of unstable heart failure, bronchospasm, cold extremities and impaired glucose control. β-blockers can be classified according to:

• Cardioselectivity: $\beta_1$-selective drugs (e.g. atenolol, metoprolol, bisoprolol) cause fewer adverse $\beta_2$-mediated effects, such as bronchospasm and hyperglycaemia.

• Intrinsic sympathomimetic activity (ISA): drugs with ISA (e.g. pindolol) are partial agonists that are less likely to cause bradycardia, arteriovenous conduction disturbances or cold extremities.
• Combined α- and β-blockers: (e.g. labetalol, carvedilol) are non-selective β- and $\alpha_1$-antagonists that cause vasodilation and have fewer adverse effects.

**Atenolol** is a cardioselective β-blocker with no ISA. Dose is 25–100 mg per day orally or 2.5–10 mg by slow intravenous bolus, which can be followed by an infusion.

**Labetalol** is a combined $\alpha_1$- and β-blocker (ratio 1:7 intravenous; 1:3 oral). The oral dose is 200–800 mg daily in divided doses. An intravenous bolus of 50–200 mg can be given slowly, or an infusion of 5–150 mg/h can be titrated to effect. It reduces the systemic vascular resistance, while maintaining cerebral, renal, and coronary blood flow.

**Dopaminergic agonists**
**Fenoldopam** is an antagonist at peripheral $DA_1$ receptors that causes vasodilation, primarily of the coronary, renal and mesenteric vasculature. Used in hypertensive emergencies and occasionally used in low doses for renal protection from acute tubular necrosis or acute renal failure, although recent studies suggest this may not be beneficial[1].

## Renin–angiotensin system

The renin–angiotensin system (RAS) is involved in cardiovascular and fluid homeostasis. It can be manipulated at several points to cause hypotension:
• inhibition of renin release (β-blockers or central α-agonists)
• direct inhibition of renin (e.g. aliskiren)
• inhibition of angiotensin-converting enzyme (ACE) (e.g. enalapril, lisinopril) to prevent production of the potent vasoconstrictor angiotensin II
• direct blockade of angiotensin II receptors (AT1) (e.g. losartan, candesartan)
• competitive inhibition of aldosterone (e.g. spironolactone)

**Angiotensin-converting enzyme inhibitors**
Angiotensin-converting enzyme inhibitors (ACEIs) are used in the treatment of hypertension (less effective in the elderly and black populations), heart failure, left ventricular dysfunction and diabetic nephropathy. Adverse effects include profound hypotension (first dose and perioperative), renal insufficiency (contraindicated in renal artery stenosis), hyperkalaemia, cough (increased bradykinin) and angioedema. Several are pro-drugs (e.g. ramipril, enalapril, lisinopril) and should be used with caution in patients with impaired liver function. All should be used with caution in renal impairment and should be avoided in pregnancy due to potential teratogenicity. Ramipril is commenced at 1.25 mg PO and titrated up to 10 mg per day.

**Angiotensin II receptor blockers**
Angiotensin II receptor blockers (ARBs) specifically block the AT1 receptor subtype, leading to a lower incidence of cough and angioedema; hence, compliance is improved compared to ACEIs. The daily dose of losartan is 25–100 mg.

**Aliskiren**
The first non-peptide, oral, direct renin inhibitor that reduces plasma renin activity. It can be given alone or in combination with other antihypertensive medications, although combination with ACEis and ARBs is not recommended[2]. It may cause hyperkalaemia, hypotension and renal dysfunction. Long-term safety data are lacking to date and it is not widely used.

**Mineralocorticoid receptor antagonists**
The mineralocorticoid receptor antagonists, spironolactone and eplerenone, inhibit the reabsorption of sodium in the distal convoluted tubule and collecting duct of the kidney, lower. The recent PATHWAY-2 study[3] demonstrated spironolactone (25-50 mg OD) to be a useful adjunct in treatment resistant hypertension. Side effects include hyperkalaemia and gynaecomastia.

## Vasodilators

**Calcium channel blockers**
Calcium channel blockers (CCBs) block the entry of calcium through L-type (long-lasting) channels. The effects are negative myocardial inotropy, reduced excitability in nodal cells and peripheral vasodilation. The degree of each effect depends on the class of calcium channel blocker:
• phenylalkylamines (e.g. verapamil) act primarily on cardiac conducting tissue, so they are used mostly as antiarrhythmic agents
• dihydropyridines (e.g. nifedipine, nimodipine, nicardipine, amlodipine) mostly cause vasodilation and are used for treatment of hypertension. Nicardipine can be given as an intravenous infusion in the acute management of hypertensive crises.
• benzothiazepines (e.g. diltiazem) act preferentially on coronary vessels, so they are used as antiarrhythmic and anti-anginal drugs.

Adverse effects of CCBs include reflex tachycardia, bradycardia (verapamil should not be given with β-antagonists), headache, flushing and potentiation of neuromuscular blockers.

**Nitric oxide donors**
**Glycerine trinitrate (GTN):** used for the treatment of hypertension (venodilation) and angina (reduced myocardial oxygen demand). It can be administered sublingually, as an oral modified release tablet, transdermally or intravenously (10–200 µg/min). Adverse effects include tachycardia, tolerance (within 48 hours), postural hypotension, platelet dysfunction and headache.

**Sodium nitroprusside (SNP):** causes dilation of arteries and veins. SNP can be used in a hypertensive crisis and for deliberate hypotensive anaesthesia. It has fast onset and offset times, but it is photosensitive, so the infusion should be protected from light. Typical dose range is 0.5–8 µg/kg/min. Adverse effects are similar to GTN, but with the additional risk of cyanide poisoning, myocardial ischaemia and rebound hypertension. Tachyphylaxis may occur.

**Potassium channel activators**
**Hydralazine, minoxidil and diazoxide:** cause arterial vasodilatation. Hydralazine is used in hypertensive crises in doses of 5–10 mg by slow intravenous bolus or as an infusion of 50–150 µg/min. Adverse effects include reflex tachycardia and fluid retention.

## Diuretics

Diuretics can be used to reduce blood pressure by reducing plasma volume and producing vasodilation. Low doses of diuretic produce the maximal blood pressure lowering effect whilst reducing biochemical disturbance. The thiazide-like diuretics chlortalidone and indapamide are the preferred diuretic for the management of hypertension. Bendroflumethiazide continues to be used in the management of heart failure but is no longer considered the first-line diuretic for the management of hypertension. Adverse effects include hyperglycaemia (especially with co-administered β-blockers), electrolyte disturbances, and gout. If increased diuresis is required, a loop

diuretic (furosemide) can be added; if potassium loss is a problem, a potassium-sparing diuretic (amiloride) can be given.

## Guidelines for treatment of hypertension

According to the most recent guidance from the National Institute for Health and Care Excellence (NICE), there is a 7% increased risk of mortality from ischaemic heart disease and a 10% increase in death from stroke with each 2-mmHg rise in systolic pressure[4]. Patients should be assessed for the possible causes of hypertension, for organ damage caused by hypertension and for other cardiovascular risk factors (Table 1)[5]. NICE has outlined a guide for the drug treatment of hypertension, summarised in Figure 2. The presence of other diseases can be a compelling indication for additional or alternative therapy (e.g. angina, CCB or β-blocker; heart failure/diabetic nephropathy, ACEI or ARB). Antihypertensive drugs are often combined in lower doses to cause additive or synergistic effects with fewer adverse effects than with monotherapy (e.g. ACEI or β-blockers with CCB or diuretic; AB/CD algorithm).
Secondary prevention (aspirin and statins) should be considered for all patients with hypertension complicated by cardiovascular disease.

## Antihypertensive drugs and anaesthesia

Fluctuations in heart rate and arterial pressure during anaesthesia and surgery are exaggerated in patients with hypertension. Uncontrolled preoperative hypertension is associated with worse perioperative cardiac outcomes (odds ratio 1.35)[6,7], but this association might not be clinically significant. The absolute risk depends on the degree of hypertension and the presence of end-organ damage. Arterial pressures of <180 mmHg systolic or <110 mmHg diastolic do not increase perioperative risk substantially and surgery should be cancelled only in order to treat hypertension in patients with stage 3 hypertension with organ damage or those with other significant risk factors. Antihypertensive medications should usually be continued throughout the perioperative period to help attenuate cardiovascular responses, with the possible exception of ACEIs and ARBs, which can be associated with refractory perioperative hypotension.

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## Further reading

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| Other risk factors, asymptomatic organ damage or disease | High normal<br>SBP 130-139<br>Or DBP 85-89 | Grade 1 HT<br>SBP 140-149<br>Or DBP 90-99 | Grade 2 HT<br>SBP 160-179<br>Or DBP 100-109 | Grade 3 HT<br>SBP ≥180<br>Or DBP ≥110 |
|---|---|---|---|---|
| No other RF | No BP intervention | Lifestyle changes for several months<br>Then add BP drugs targeting <140/90 | Lifestyle changes for several weeks<br>Then add BP drugs targeting <140/90 | Lifestyle changes<br>+<br>Immediate BP drugs targeting <140/90 |
| 1-2 RF | Lifestyle changes<br>No BP intervention | Lifestyle changes for several weeks<br>Then add BP drugs targeting <140/90 | Lifestyle changes for several weeks<br>Then add BP drugs targeting <140/90 | Lifestyle changes<br>+<br>Immediate BP drugs targeting <140/90 |
| ≥3 RF | Lifestyle changes<br>No BP intervention | Lifestyle changes for several weeks<br>Then add BP drugs targeting <140/90 | Lifestyle changes<br>+<br>BP drugs targeting <140/90 | Lifestyle changes<br>+<br>Immediate BP drugs targeting <140/90 |
| OD, CKD stage 3 or diabetes | Lifestyle changes<br>No BP intervention | Lifestyle changes<br>+<br>BP drugs targeting <140/90 | Lifestyle changes<br>+<br>BP drugs targeting <140/90 | Lifestyle changes<br>+<br>Immediate BP drugs targeting <140/90 |
| Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs | Lifestyle changes<br>No BP intervention | Lifestyle changes<br>+<br>BP drugs targeting <140/90 | Lifestyle changes<br>+<br>BP drugs targeting <140/90 | Lifestyle changes<br>+<br>Immediate BP drugs targeting <140/90 |

Table 1. Please add caption at proof stage

<Footnotes>

Risk Factors: Male sex, Age (men ≥55 years; women ≥65 years), Smoking, Dyslipidaemia, Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL), Abnormal glucose tolerance test, Obesity [BMI ≥30 kg/m2 (height2)], Abdominal obesity (waist circumference: men ≥102 cm;

women ≥88 cm) (in Caucasians), Family history of premature CVD (men aged <55 years;

women aged <65 years)

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension;

OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

From Mancia, Giuseppe, et al. "2013 ESH/ESC Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)." *European Heart Journal* 34.28 (2013): 2159-2219.