Beta-blockers have been widely used in the management of angina, certain tachyarrhythmias and heart failure, as well as in hypertension.

**Examples**
- Acebutolol
- Atenolol
- Bisoprolol
- Carvedilol
- Celiprolol
- Labetalol
- Metoprolol
- Nadolol
- Nebivolol
- Oxprenolol
- Pindolol
- Timolol

**Mechanism of action**
Beta-blockers antagonise the effects of sympathetic nerve stimulation or circulating catecholamines at beta-adrenoceptors which are widely distributed throughout body systems. Beta$_1$-receptors are predominant in the heart (and kidney) while beta$_2$-receptors are predominant in other organs such as the lung, peripheral blood vessels and skeletal muscle.

- **Kidney**: Blockade of beta$_1$-receptors inhibit the release of renin from juxta-glomerular cells and thereby reduce the activity of the renin-angiotensin-aldosterone system.
- **Heart**: Blockade of beta$_1$-receptors in the sino-atrial node reduces heart rate (negative chronotropic effect) and blockade of beta$_1$-receptors in the myocardium decrease cardiac contractility (negative inotropic effect).
- **Central and peripheral nervous system**: Blockade of beta-receptors in the brainstem and of prejunctional beta-receptors in the periphery inhibits the release of neurotransmitters and decreases sympathetic nervous system activity.

The mode of action in lowering blood pressure remains controversial. Conventionally, the antihypertensive action of beta-blockers is attributed to cardiac effects (decreased heart rate and
cardiac output). However, long-term reductions in blood pressure appear greater in individuals with high renin forms of hypertension, suggesting that renal actions are important.

Many beta-blockers have ancillary properties which influence choice in hypertensive individuals.

- **Selectivity**: Since the desired effects of beta-blockers are mediated by blockade of beta₁-receptors which predominate on the heart, “cardioselective” agents with relative selectivity for this receptor are generally preferred. However, receptor selectivity is not absolute and is lost at high doses. Examples of “cardioselective” beta-blockers include atenolol, bisoprolol and metoprolol. Beta-blockers with selectivity rates > 50, e.g. bisoprolol and nebivolol, are least likely to lose selectivity at high doses.

- **Partial agonist activity (intrinsic sympathomimetic activity)**: This manifests as a beta-stimulant effect when background adrenergic activity is low (e.g. during sleep) but beta-blockade occurs when adrenergic activity is increased (e.g. during exercise). Beta-blockers with partial agonist activity include pindolol.

- **Membrane-stabilising activity**: This confers a local anaesthetic and anti-arrhythmic effect e.g. sotalol.

- **Other properties**: Some beta-blockers also block effects mediated at peripheral alpha-adrenoceptors (e.g. carvedilol and labetalol), stimulate beta₂-adrenoceptors (e.g. celiprolol) or have direct vasodilator activity (e.g. nebivolol).

**Pharmacokinetics**

Beta-blockers vary in the degree of elimination by the kidney or the liver, usually with extensive first-pass metabolism. Lipid-soluble beta-blockers, e.g. labetalol, metoprolol, pindolol and propranolol, typically depend upon hepatic metabolism for clearance, whereas water soluble beta-blockers e.g. atenolol are cleared by the kidney. Drugs eliminated by the liver tend to exhibit wide inter-individual variability in bioavailability. The half-life of most beta-blockers is relatively short; those eliminated by the kidney tend to have longer half-life.

**Adverse effects**

Most are predictable

- Bronchospasm in susceptible individuals due to blockade of beta₂-receptors which mediate dilation in the bronchi. **Asthma is an absolute contraindication for all beta-blockers.**

- Bradycardia and impairment of myocardial contractility. **Common but seldom symptomatic.**

- Peripheral vasoconstriction due to reduced cardiac output and possibly blockade of beta₂-receptors which subserve vasodilatation in blood vessels supplying skeletal muscle beds typically resulting in cold hands and feet, and possibly exacerbation of Raynaud’s phenomenon. **Mainly non-selective agents.**
- CNS effects due to reduced sympathetic outflow e.g. malaise; vivid dreams, nightmares and, rarely, hallucinations with highly lipid soluble beta-blockers which have greater penetration into the CNS.
- Tiredness and fatigue due to reduced cardiac output exacerbated by blockade of beta_2_-receptors in skeletal muscle associated with increased muscle activity. Mainly non-selective agents.
- Masking of hypoglycaemia in insulin-dependent diabetes because of blunting of sympathetic nervous activation. Mainly non-selective agents.
- Hyperglycaemia Risk of new onset diabetes

**Practical issues**
All beta-blockers, irrespective of ancillary properties, lower blood pressure to a similar extent. Beta-blockers which undergo hepatic metabolism require a wide range of doses and usually multiple daily dosing. Drugs eliminated via the kidney may be suitable for once daily administration, particularly at high doses. Beta_1_-selective (cardioselective) beta-blockers which can be administered once daily tend to be preferred e.g. atenolol 25 – 100 mg daily, bisoprolol 5 - 10 mg or nebivolol 5 mg daily. Blood pressure reductions appear to be less marked in those with low renin hypertension such as the elderly and people of Afro-Caribbean descent. Beta-blockers combine well with thiazide and thiazide-like diuretics, and with dihydropyridine type calcium channel blockers to produce overall antihypertensive effects which are at least additive. However, beta-blockers should be used with extreme caution in combination with rate-limiting calcium channel blockers (diltiazem and verapamil) because of the risk of heart block and potentially fatal bradyarrhythmias and should not be used routinely with thiazide or thiazide-like diuretics because of the high risk of new-onset diabetes.

Irrespective of apparent beta_1_-selectivity, beta-blockers are contraindicated in people with asthma. All beta-blockers should be used with caution in chronic obstructive pulmonary disease with significant reversibility. In patients with less severe pulmonary disease, beta-blockers can be used without concern. Rarely, excessive reductions in inotropic activity may precipitate or exacerbate cardiac failure in susceptible individuals. While these depressant effects on cardiac function are occasionally deleterious, reduction in cardiac work and reduction in myocardial oxygen demand contribute to the antianginal effects of these agents. Sudden withdrawal of beta-blocker may provoke worsening angina or myocardial infarction. Beta-blockers should be introduced with caution in patients at risk of heart failure. Although acutely beta-blockers can worsen left ventricular dysfunction, under specialist supervision, beta-blockers can improve symptoms and prolong survival in patients with congestive heart failure. Worsening of peripheral vascular flow due to vasoconstriction is usually only important in critical ischaemia. Masking of hypoglycaemia is marginal with beta_1_-selective beta-blockers. Many patients are denied the benefits of beta-blockers because of unnecessary concerns.
In addition to use in hypertension, beta-blockers are used to treat supraventricular cardiac arrhythmias (including atrial fibrillation), angina, post myocardial infarction, heart failure, anxiety neurosis, thyrotoxicosis, migraine and glaucoma. Prophylactic treatment with non-selective beta-blockers appears to reduce the risk of gastrointestinal bleeding in patients with chronic liver disease complicated by oesophageal varices.

Beta-blockers are available in single pill combinations with thiazide and thiazide-like diuretics, and with dihydropyridine calcium channel blockers. These preparations may improve compliance, and should be considered, when compelling indications apply and there is no cost disadvantage.

There is accumulating evidence for outcome benefits with beta-blockers in the management of heart failure and in patients post myocardial infarction. Beta-blockers were included in the therapeutic regimens which established the benefits of treating hypertension. However, recent data indicate that treatment based on beta-blockers is inferior to that based on other antihypertensives in cardiovascular protection. This evidence, together with the increased risk of new onset diabetes associated with these drugs, especially in combination with diuretics, has resulted in the recommendation that beta-blockers are no longer appropriate first-line agents, except where there are compelling indications for this form of treatment.

**Compelling indications** are myocardial infarction, angina and tachyarrhythmias.

**Possible indications** include stable heart failure.

**Caution** is advised in unstable heart failure, peripheral vascular disease, diabetes (except those with coronary heart disease), with concomitant rate-limiting calcium channel blockers (diltiazem and verapamil) and with thiazide or thiazide-like diuretics (unless there is a compelling indication).

**Compelling contraindications** are asthma, chronic obstructive pulmonary disease with significant reversibility and heart block.

In the absence of a compelling indication or contraindication for a beta-blocker, these drugs should be used as recommended in the NICE/BHS ACD algorithm i.e. as a step 4 therapy option in individuals with blood pressure above target despite treatment with an ACE inhibitor or angiotensin receptor blocker (A), a calcium channel blocker (C) and a thiazide or thiazide-like diuretic (D) each at full dose, in combination.

**NB :** Beta-blockers may be considered as a first-line option in women of child-bearing potential because of concern about foetal renal maldevelopment with ACE inhibitors or angiotensin receptor blockers.