

CALCIUM CHANNEL BLOCKERS (CCBs)

Calcium channel blockers (CCBs) or calcium antagonists, are among the most widely used drugs in cardiovascular medicine with roles not only in hypertension but also in angina and (for some CCBs) tachyarrhythmias.

Examples	Amlodipine
	Diltiazem
	Felodipine
	Isradipine
	Lacidipine
	Lercanidipine
	Nicardipine
	Nifedipine
	Nisoldipine
	Verapamil

Mechanism of action

CCBs promote vasodilator activity (and reduce blood pressure) by reducing calcium influx into vascular smooth muscle cells by interfering with voltage-operated calcium channels (and to a lesser extent receptor-operated channels) in the cell membrane. Interference with intracellular calcium influx is also important in cardiac muscle, cardiac conduction tissue and gastrointestinal smooth muscle. In cardiac tissues, CCBs have potential for negative inotropic, chronotropic and dromotropic activity while the gastrointestinal effects predispose to constipation. These effects vary with different agents according to ability to penetrate cardiac and other tissues, relative affinity for calcium channels in different tissues and the influence of reflex cardiac stimulation secondary to peripheral vasodilation.

Although often considered as a single class, CCBs can be subdivided according to structural and functional distinctions.

- Dihydropyridine derivatives : amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nisoldipine
- Phenylalkylamine : verapamil
- Benzothiazepine derivative : diltiazem

Dihydropyridine derivatives have pronounced peripheral vasodilator properties and intense reflex cardiac stimulation overcomes any direct cardiac effects. Verapamil and diltiazem are also vasodilators but the balance of actions is such that these drugs have noticeable cardiac effects including reduced heart rate (**rate-limiting CCBs**).

Pharmacokinetics

Most CCBs have low and variable oral bioavailability because of extensive first-pass metabolism. Half-life is relatively short (≤ 12 hours). The exception is amlodipine which, although extensively metabolised, has a substantially longer half-life (> 40 hours). Diltiazem and verapamil tend to inhibit drug metabolism. This enzyme inhibitory effect is a potential source of drug interactions e.g. with cyclosporin.

Adverse effects

- Dihydropyridines
 - headache and flushing due to peripheral vasodilation
 - tachycardia and palpitation secondary to reflex activation of the sympathetic nervous system
 - **Particularly with rapid-onset and short-acting agents** (usually declines with time)
 - swelling of ankles and occasionally hands due to disturbance of haemodynamics of microcirculation (preferential pre-capillary arteriolar vasodilation)
 - gum hypertrophy
 - **Long-term effects** (can arise many months after treatment initiated and may be more common with long-acting agents)
 - Rate-limiting CCBs
 - bradycardia and atrio-ventricular conduction delay due to direct cardiac effects
 - constipation with verapamil
- Early onset vasodilator effects less than with dihydropyridines

Practical issues

All CCBs are effective antihypertensive agents because of peripheral vasodilator activity. Blood pressure reduction appears to be more marked in those with low renin hypertension such as the elderly and those of Afro-Caribbean descent. Earlier formulations of some dihydropyridines, such as nifedipine capsules, have a rapid onset of action, unpredictable effects on blood pressure and are accompanied by reflex tachycardia and activation of the renin-angiotensin system. Angina can be precipitated. These formulations have no place in the management of hypertension even in the emergency setting. Long-acting dihydropyridine drugs, such as amlodipine, or other CCBs in once-daily formulations are preferred. CCBs combine well with drugs which block the renin-angiotensin system (ACE inhibitors and angiotensin receptor blockers) to produce overall antihypertensive effects which are at least additive.

Side effects can limit the utility of CCBs. Vasodilator effects of dihydropyridines are less marked with naturally long-acting drugs or sustained release formulations. Since peripheral oedema is a consequence of disturbance of the microcirculation, prescription of a diuretic is not helpful. The combined pre-capillary and post-capillary action of lercanidipine may reduce the frequency of this side effect. Peripheral oedema may also be reduced by co-administration of an ACE inhibitor or angiotensin receptor blocker, drugs which cause post-capillary vasodilation. Non-dihydropyridines cause less peripheral oedema but are negatively inotropic and chronotropic, and should therefore be avoided in patients with compromised left ventricular function and should be used with extreme caution in combination with beta-blockers. However, the negative cardiac effects of diltiazem and verapamil reduce myocardial oxygen demand such that these drugs are the preferred form of CCB as monotherapy in angina. Rate-limiting CCBs also have a role in the management of tachyarrhythmias such as atrial fibrillation.

Dihydropyridine calcium channel blockers are available in single pill combinations with beta-blocker or angiotensin receptor blocker; verapamil is available in combination with an ACE inhibitor. These preparations may improve compliance, and should be considered, provided there is no cost disadvantage.

Large scale prospective outcome studies have demonstrated benefits in cardiovascular protection with CCBs at least equivalent to those with other antihypertensive agents. Dihydropyridine CCBs may be particularly useful in elderly patients with isolated systolic hypertension. Rate-limiting CCBs have benefits similar to those of beta-blockers post-myocardial infarction.

Compelling indications include hypertension in the elderly and isolated systolic hypertension (dihydropyridines), and angina (rate-limiting CCBs).

Possible indications include angina (dihydropyridines) and post myocardial infarction (rate-limiting CCBs).

Caution is advised with concomitant beta-blocker (rate-limiting CCBs).

Compelling contraindications are heart block and heart failure (rate-limiting CCBs).

In the absence of a compelling indication for another drug or contraindication to a CCB, these drugs should be used as recommended in the NICE/BHS algorithm.

- **step 1** in people aged 55 years or over, or of Afro-Caribbean descent
- **step 2** option with an ACE inhibitor or angiotensin receptor blocker
- **step 3** therapy with an ACE inhibitor or angiotensin receptor blocker plus a thiazide or thiazide-like diuretic