

## DRUG CLASSES

### ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

ARBs have haemodynamic properties similar to those of ACE inhibitors but are better tolerated.

**Examples**

- Axilsartan
- Candesartan
- Eprosartan
- Irbesartan
- Losartan
- Olmesartan
- Telmisartan
- Valsartan

#### **Mechanism of action**

ARBs antagonise the action of angiotensin II in a highly selective manner at the angiotensin II AT<sub>1</sub>-receptor. Angiotensin II receptors are subclassified into AT<sub>1</sub> and AT<sub>2</sub> receptors. The AT<sub>1</sub>-receptor mediates all the classical effects of angiotensin II e.g. vasoconstriction, aldosterone release, sympathetic activation and other potentially harmful effects on the cardiovascular system. The functional role of the AT<sub>2</sub>-receptor is less well understood but broadly this receptor mediates effects opposite to the AT<sub>1</sub>-receptor. Because many tissues contain enzymic pathways capable of converting angiotensin I to angiotensin II independent of angiotensin converting enzyme (ACE), there are theoretical advantages in blocking the renin-angiotensin system via the AT<sub>1</sub>-receptor compared with ACE inhibition. Many ARBs or active metabolites bind to the AT<sub>1</sub>-receptor in a manner which is competitive but slowly surmountable, so that duration of action is prolonged.

Reduction in blood pressure secondary to vasodilation following angiotensin receptor blockade is greatest when the renin-angiotensin system is activated (e.g. following self restriction, diuretic therapy or renal artery stenosis) but ARBs also lower blood pressure when there is normal or low activity of the renin-angiotensin system. Nevertheless, Afro-Caribbeans and elderly individuals, who tend to have low renin hypertension, respond less well to ARBs.

### **Pharmacokinetics**

All ARBs are well absorbed after oral administration but differ slightly in metabolism and pharmacokinetics. Losartan is converted to an active metabolite, EXP 3174, and candesartan is the active constituent of the pro-drug, candesartan cilexetil.

### **Adverse effects**

ARBs are reported to have a side effect profile indistinguishable from that of placebo but adverse reactions can occur rarely.

- Hyperkalaemia due to potassium retention mediated by reduction of aldosterone.  
**Rare except in renal impairment.**
- Impairment of renal function. **Caution if bilateral renal artery stenosis suspected.**

### **Practical issues**

ARBs produce blood pressure reductions similar to those seen with ACE inhibitors and other antihypertensive classes. These drugs vary in efficacy and duration of action but all are recommended for once daily dosing. Like ACE inhibitors, duration of antihypertensive effects is dose-dependent; therefore, smooth blood pressure control over 24 hours is most likely at the maximum recommended dose. To avoid precipitous initial fall in blood pressure or decline in renal function, it is generally advised to start therapy with low dosages in the elderly, and in patients with compromised renal function or heart failure.

These drugs are particularly well tolerated with very few side effects. Because ARBs do not influence kinin metabolism, dry cough and angioedema are not seen. Impairment in renal function may arise in patients with bilateral renal artery stenosis, which should be suspected if there is evidence of peripheral vascular disease. Renal failure, reversible on discontinuation of ARB, may be precipitated. To avoid the risk of abrupt reduction in renal function and hyperkalaemia, serum creatinine and potassium should be measured before and soon after starting an ARB. Only if serum potassium rises above the reference range or serum creatinine rises by more than 20% (and is above the reference range), need the ARB be discontinued and further investigations of renal structure and function should be considered. In addition, patients should be advised to consult with

their GP during dehydrating illnesses such as diarrhoea and vomiting to consider temporarily suspending the use of ARBs to avoid postural hypertension and acute kidney injury. ARBs should be avoided in women of child bearing potential because of the danger of foetal maldevelopment. Like ACE inhibitor treatment, regimens based on ARBs reduce the risk of new onset diabetes.

Since adverse effects are not dose-related while duration of antihypertensive effect is dose-dependent, doses higher than those previously recommended are now advised e.g. candesartan 32 mg daily, losartan 100 mg daily, valsartan 320 mg daily. ARBs combine well with thiazide and thiazide-like diuretics, and with calcium channel blockers to produce overall antihypertensive effects which are at least additive. However, care should be taken when these drugs are co-administered with potassium supplements and potassium sparing diuretics because of the risk of hyperkalaemia, especially if there is pre-existing renal impairment. Similar caution is advised if non-steroidal anti-inflammatory drugs are prescribed with ARBs.

ARBs are available in fixed-dose combinations with a thiazides diuretic or a calcium channel blocker. These preparations may improve compliance and should be considered, provided there is not a cost disadvantage.

Large-scale prospective outcome trials have demonstrated benefits in cardiovascular protection with ARBs equivalent to those with ACE inhibitors and other antihypertensive drugs. ARBs may also offer additional benefits in patients with type 2 diabetes complicated by hypertension and nephropathy, and in heart failure.

**Compelling indications** include ACE inhibitor intolerance, hypertension with left ventricular hypertrophy, heart failure in ACE inhibitor-intolerant patients and post myocardial infarction.

**Possible indications** include left ventricular dysfunction post myocardial infarction, intolerance of other antihypertensive drugs, proteinuric renal disease, chronic renal failure and heart failure. ARBs may be beneficial in chronic renal failure but should only be used with caution, close supervision and specialist advice when there is established and significant renal impairment. ARBs can be useful in subjects who have headaches or migraine.

**Caution** is advised in renal impairment and in peripheral vascular disease because of the association with renovascular disease.

**Compelling contraindications** are pregnancy and renovascular disease, ARBs are sometimes used in patients with renovascular disease under specialist supervision. ARBs should not be combined with direct renin inhibitors and not with ACE inhibitors. [They are also contra-indicated with sacubitril/valsartan.](#)

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

- **step 1** in Caucasian people aged less than 55 years who are intolerant of an ACE inhibitor
- **step 2** with a calcium channel blocker or thiazide-like diuretic if intolerant of an ACE inhibitor
- **step 3** with a calcium channel blocker plus a thiazide-like diuretic if intolerant of an ACE inhibitor

