

DRUG UPDATE

No. 42

May 2005

ANGIOTENSIN II RECEPTOR ANTAGONISTS

Angiotensin II receptor antagonists (ARBs) do not reduce morbidity or mortality more than ACE inhibitors in heart failure or more than calcium channel blockers in hypertension. In heart failure the addition of candesartan (but not valsartan) to an ACE reduces morbidity and mortality but the role of combined therapy has not been defined. ARBs are an appropriate alternative when treatment with an ACE inhibitor is strongly indicated but poorly tolerated (e.g. in patients with diabetic nephropathy or heart failure) but first-line use in hypertension or heart failure is not currently justified.

What are they?

The seven licensed ARBs (candesartan, eprosartan, irbesartan, losartan, telmisartan, olmesartan and valsartan) lower blood pressure by selectively antagonising the type 1 angiotensin receptor. Unlike ACE inhibitors they do not inhibit the breakdown of bradykinin and are therefore associated with a lower incidence of cough.

Since our last review of ARBs¹ several major trials of their use in hypertension, diabetic nephropathy and heart failure have been published.

Hypertension

In a double-blind trial (VALUE), 15,245 patients aged over 50 (mean BP 155/87 mmHg) at high cardiovascular risk were randomised to valsartan 80 - 160 mg/day or amlodipine 5 - 10 mg/day.² More patients taking amlodipine achieved the target blood pressure of <140/<90 mmHg (62% vs. 56%). After a mean of 4.2 years, the incidence of the composite primary endpoint (sudden cardiac death, fatal and non-fatal myocardial infarction, death associated with revascularisation and admission due to heart failure) was similar (valsartan 10.6%, amlodipine 10.4%; hazard ratio 1.04, CI_{95%} 0.94 - 1.15; p=0.49).

Diabetic nephropathy

Irbesartan and losartan are the only ARBs currently licensed for the treatment of renal disease in patients with type 2 diabetes. A systematic review of placebo-controlled trials in patients with diabetic nephropathy concluded that ACE inhibitors and/or ARBs reduced progression of micro- to macroalbuminuria, and increased regression from micro- to normoalbuminuria.³ ACE inhibitors significantly reduced all-cause mortality (relative risk 0.79, CI_{95%} 0.63 - 0.99) but ARBs did not.

Heart failure

Candesartan is the only ARB currently licensed for the treatment of heart failure. Three large trials have recently evaluated the efficacy and safety of combining an ARB and an ACE inhibitor for heart failure.⁴⁻⁶

The ValHeFT study⁴ randomised 5,010 patients with stable heart failure, 93% of whom were taking an ACE inhibitor; treatment was titrated to valsartan 160 mg twice daily or

placebo in addition to standard treatment. After a mean of 23 months, valsartan was associated with 13.2% reduction in the risk of the combined endpoint (mortality, myocardial infarction, admission for heart failure or treatment with inotropic or vasodilator drugs) (28.8% vs. 32.1%; relative risk 0.87, CI_{95%} 0.77 - 0.97; p=0.009) but overall mortality was not significantly affected.

VALIANT compared valsartan (up to 160 mg twice daily) or valsartan plus captopril (up to 50 mg three times daily) with captopril alone in 14,703 patients with heart failure, left ventricular systolic dysfunction or both following acute myocardial infarction.⁵ After a median follow up of 25 months, there were no significant differences in the incidence of primary (all-cause mortality) or secondary endpoints between the three groups.

The CHARM study compared candesartan 32 mg/day with placebo in patients with symptomatic heart failure and left ventricular ejection fraction \leq 40%. Candesartan was associated with a lower incidence of cardiovascular death or admission for heart failure in patients intolerant of an ACE inhibitor (n=2,028)⁶ (33% vs. 40% with placebo; adjusted hazard ratio, HR, 0.70, CI_{95%} 0.60 - 0.81) and when added to established treatment with an ACE inhibitor (n=2,548),⁷ (38% vs. 42% with placebo; HR 0.85, CI_{95%} 0.75 - 0.96).

How safe are they?

In patients with hypertension, valsartan was associated with a higher incidence of myocardial infarction than amlodipine (11.4% vs. 9.6%; hazard ratio, HR, 1.19; CI_{95%} 1.02 - 1.38, p=0.02) but a lower incidence of new-onset diabetes (13.1% vs. 16.4%; odds ratio 0.77; CI_{95%} 0.69 - 0.86, p<0.0001).²

However the frequency of hypotension and renal dysfunction was greater among patients taking valsartan or candesartan plus an ACE inhibitor compared with an ACE inhibitor alone.⁵⁻⁷ Renal function and serum potassium should be monitored.

When should they be used?

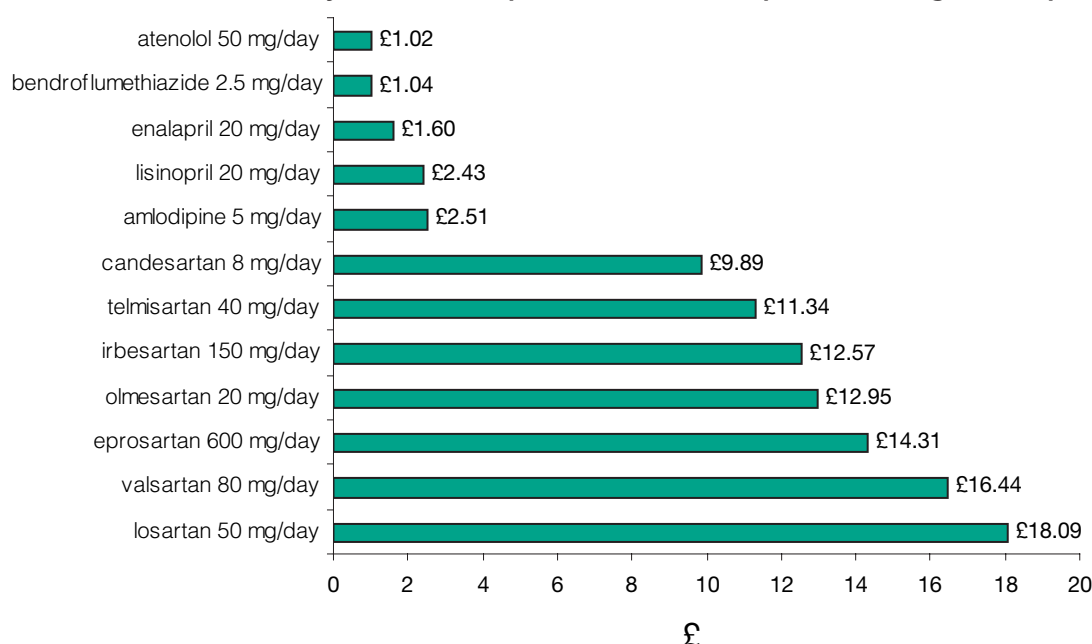
An ARB should be considered when an ACE inhibitor is strongly indicated but not tolerated. According to NICE,⁹ ACE inhibitors are second-line agents (after a thiazide diuretic) for uncomplicated hypertension; they are the agents of choice for patients with heart failure, left ventricular dysfunction or diabetes with microalbuminuria or nephropathy. In patients

of African descent they are less effective unless combined with a thiazide.⁹ Approximately 10% of patients taking an ACE inhibitor develop cough. A drug from a different class (e.g. a calcium channel blocker) should be considered before prescribing an ARB for those who are affected, unless there is a compelling indication for blockade of the renin-angiotensin-aldosterone cascade.

ACE inhibitors are the drugs of choice for renal protection in patients with type 2 diabetes and microalbuminuria or proteinuria.¹⁰ There is insufficient evidence to support the use of combined treatment with an ACE inhibitor and an ARB.

How much do they cost?

Cost for 28 days treatment (prices from MIMS April 2005/Drug Tariff April 2005)



NB Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, R - review, G - guideline

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