

DRUG UPDATE

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ANGIOTENSIN II RECEPTOR ANTAGONISTS IN THE MANAGEMENT OF HYPERTENSION

Compared with alternative antihypertensive drugs angiotensin II receptor antagonists reduce cardiovascular events in patients with hypertension and left ventricular hypertrophy (losartan vs atenolol), and reduce the progression of renal disease in patients with type 2 diabetes and hypertension (irbesartan vs amlodipine). No similar comparisons between angiotensin II receptor antagonists and ACE inhibitors have been published. Angiotensin II receptor antagonists are more expensive but are a suitable choice for patients with LVH or those with diabetic nephropathy, who are intolerant of an ACE inhibitor.

What are they?

The six licenced angiotensin II receptor antagonists (AIIAs) (candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan) lower blood pressure by selectively antagonising the actions of angiotensin II at the type I angiotensin receptor. Unlike ACE inhibitors they do not block the synthesis of kinins and are therefore less associated with cough or angioedema.

All AIIAs are licensed for the treatment of hypertension; irbesartan was recently licensed for the treatment of renal disease in patients with type 2 diabetes and hypertension.

Mortality and vascular death

In the recent LIFE study, 9193 patients with hypertension and LVH were initially randomised to atenolol 50 mg/day or losartan 50 mg/day.¹ Treatment was titrated to achieve a target blood pressure of less than 140/90, if necessary by the addition of a thiazide, increasing the dose of atenolol or losartan to 100 mg, then adding further antihypertensive drugs. After an average follow-up of 4.8 years, blood pressure reductions were similar with atenolol and losartan. The risk of the primary endpoint (a composite of cardiovascular mortality, stroke and myocardial infarction), was significantly lower with losartan (relative risk 0.87, $p=0.021$). This was due largely to a reduction in the risk of fatal and non-fatal stroke (RR 0.75, $p=0.001$); the risk of cardiovascular mortality or MI was not significantly reduced. Among the secondary endpoints, new onset diabetes was less common among patients treated with losartan (RR 0.75, $p=0.001$). Losartan also reversed LVH significantly more than atenolol.

A subgroup analysis of the 1195 diabetic patients in LIFE reported a greater difference between losartan and atenolol in the primary composite endpoint than in non-diabetic patients (RR 0.76, $p=0.031$).²

Cardiovascular mortality was significantly reduced (RR 0.63, $p=0.028$) but the risks of stroke or MI with atenolol and losartan were similar.

Diabetes and renal disease

Three studies have investigated the potential benefits of AIIAs in the management of patients with diabetic nephropathy. In the first trial, irbesartan demonstrated a dose dependent renoprotective effect on the primary endpoint; time to onset of diabetic nephropathy compared to placebo.³ Two further studies using losartan and irbesartan also showed reductions in progression in renal disease in patients with more advanced diabetic nephropathy (defined as raised serum creatinine plus increased proteinuria) although neither reported a reduction in mortality.^{4,5}

None of the trials used an ACE inhibitor as comparator to the AIIA; therefore comparison in efficacy against ACE inhibitors, also demonstrated to have renoprotective properties, cannot be made.

Adverse effects

Treatment with an AIIA was well tolerated and withdrawals due to adverse events in these trials was comparable with or lower than atenolol^{1,2}, amlodipine or placebo.³⁻⁵

When should they be used?

There is currently inadequate justification for the first-line use of AIIAs in hypertension. However AIIAs are a suitable choice for treating hypertensive patients with LVH or diabetic nephropathy. The alternative is to use ACE inhibitors, which reduce mortality in patients at increased risk,⁶ are as effective as other antihypertensive agents in reducing mortality^{7,8} and also reduce progression of diabetic nephropathy in patients with diabetes.⁹ To date, no published studies have directly compared the long-term renal effects and mortality associated with the ACE inhibitors and AIIAs.

Which AIIA?

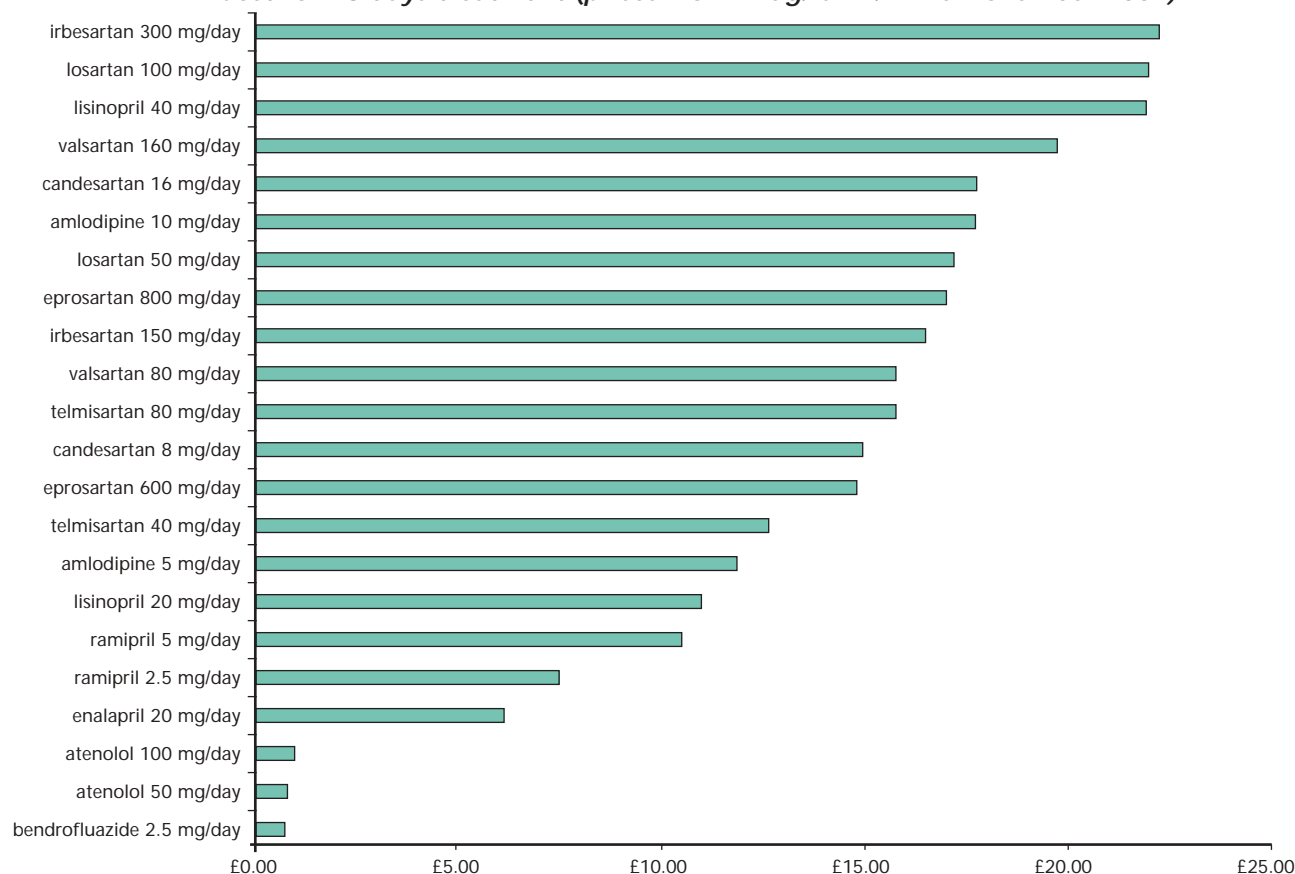
In the treatment of hypertension, the effects of losartan are probably a class effect.¹⁰ At present, only irbesartan is licensed for the treatment of renal disease. Dose equivalence for the AIIAs is uncertain; at recommended maintenance doses, telmisartan is the least expensive.

How much is prescribed?

In 2001/02, almost £12 M was spent on AIIAs in the former Northern and Yorkshire Region, an increase of 44% on the previous year. Prescribing of ACE inhibitors rose by 10% in the same period to just over £18 M.

How much do they cost?

Cost for 28 days treatment (prices from Drug/Tariff/MIMS November 2002)



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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial, CC-case control study, C-cohort study, L-letter

NHS Northern & Yorkshire
Regional Drug & Therapeutics Centre
Wolfson Unit, Claremont Place, Newcastle Upon Tyne NE2 4HH
Tel: 0191 232 1525 Fax: 0191 261 9359
e-mail: nyrdtc.di@ncl.ac.uk website: www.nyrdtc.nhs.uk