

DRUG UPDATE

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ACE INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS IN COMBINATION

There is a lack of evidence to support the use of ACE inhibitor/ARB combination therapy in hypertension. Optimal blood pressure control is important and should be achieved using the treatment algorithm proposed in the NICE hypertension guidelines. Beneficial effects on morbidity and mortality of ACE inhibitor/ARB combination therapy in the treatment of renal disease have not been consistently demonstrated. Routine use of ACE inhibitor/ARB combination therapy is not recommended and should be reserved for patients with resistant congestive heart failure or renal disease, or severe unresponsive hypertension, following specialist advice.

What are they?

Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs) work at different steps of the renin-angiotensin system. Angiotensin II has numerous effects, including stimulation of the sympathetic nervous system, vasoconstriction, increasing aldosterone release and sodium retention, which can result in hypertension.¹ Although angiotensin II formation is facilitated by ACE, non-ACE dependent pathways have also been identified.² Blockade of ACE with an ACE inhibitor has been shown to reduce blood pressure in hypertensive patients.³ ARBs antagonise the binding of angiotensin II to the AT₁ receptor which mediates most of the effects usually associated with angiotensin II.² Currently, 11 ACE inhibitors and seven ARBs are licensed in the UK.⁴

What is the rationale for the use of combination therapy?

Congestive heart failure (CHF)

Standard initial treatment of CHF consists of an optimal dose of an ACE inhibitor plus a beta blocker (+/- diuretic).⁵ Two large randomised controlled trials (CHARM-added⁶ and ValHeFT⁷) were conducted to evaluate the benefits of adding an ARB to ACE inhibitor therapy. In the CHARM-added study the addition of candesartan produced a statistically significant reduction in cardiovascular (CV) death in patients with NYHA functional class II-IV CHF (n = 2,548, mean follow up = 41 months).⁶ In the candesartan group 23.7% reached this endpoint compared with 27.3% of the placebo group (adjusted hazard ratio (HR) = 0.83

[95% confidence intervals (CI) 0.71 to 0.97], p = 0.021).⁶ However, in the ValHeFT study (mean duration of follow up = 23 months, n = 5,010), where 93% of the population were taking concurrent ACE inhibitor treatment, no significant difference in mortality between the placebo and valsartan groups was demonstrated (19.4% vs. 19.7%, relative risk (RR) = 1.02 [95%CI 0.88 to 1.18]).⁷ Candesartan is the only ARB licensed as add-on therapy to ACE inhibitors in patients with CHF and left ventricular systolic dysfunction (LVSD).⁴

The benefits of combination treatment in patients with a recent (within 10 days) myocardial infarction (MI) with LVSD and clinical evidence of CHF (or both) were examined in the VALIANT trial (n = 14,703).⁸ No significant differences in CV mortality or morbidity were demonstrated with combination treatment (valsartan plus captopril) compared with captopril alone.

The combination of telmisartan and ramipril on the composite endpoint of CV death, MI, stroke or hospitalisation for CHF is being evaluated in the ONTARGET trial.⁹ Results from this trial are expected in early 2008.¹⁰

Chronic kidney disease

No long-term clinical trials have assessed mortality and morbidity with ACE inhibitor/ARB combination therapy in diabetic and non-diabetic kidney disease. It is unclear whether benefits that have been shown in the smaller, shorter-term trials are due to effective blood pressure lowering or additional benefits from treatment with the ACE inhibitor/ARB combination. NICE guidance on the treatment of chronic kidney disease is due in September 2008.¹¹

Hypertension

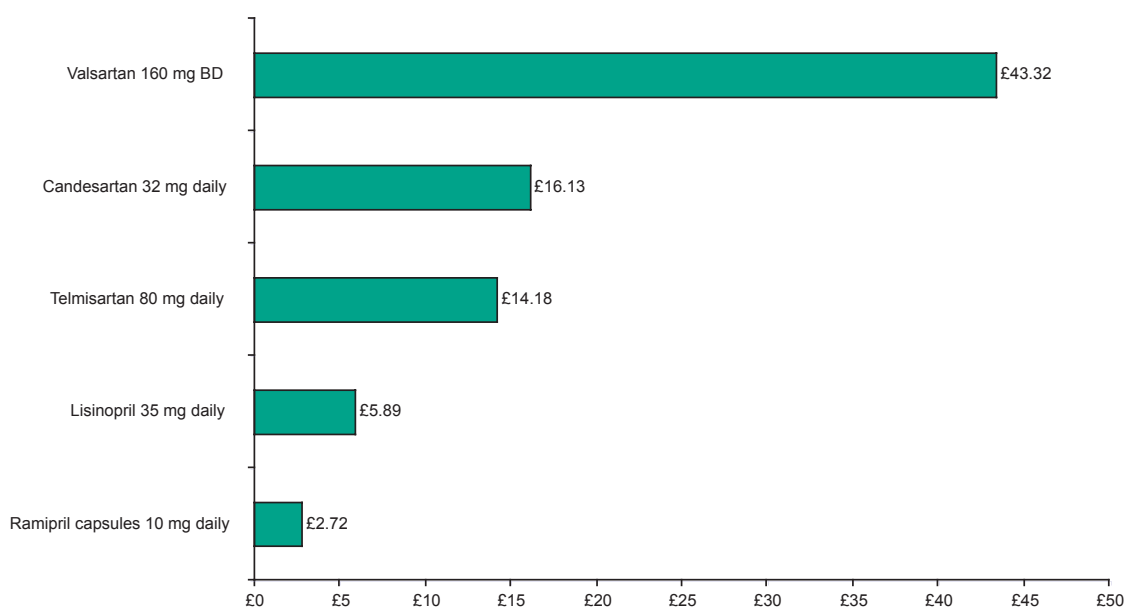
Additional blood pressure lowering effects have been seen in trials comparing combination therapy with single agents in patients with CHF.⁶⁻⁸ It is not clear whether any benefits seen in these trials were solely due to the effect on blood pressure.

How safe are they?

The CHARM-added study demonstrated an increased incidence of hyperkalaemia in the combination group (3.4% vs. 0.7% in the placebo group, $p < 0.0001$).⁶ Increases in serum creatinine levels have also been seen with combination treatment.^{6,7} Regular monitoring of urea and electrolytes is especially important in patients treated with combination therapy irrespective of the indication.

How much do they cost?

Cost of 28 days treatment (Drug Tariff June 2007)



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

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Key: RCT - randomised controlled trial, G- guidelines, R-review

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