

UCLH GUIDELINES ON ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs) FOR HYPERTENSION AND HEART FAILURE

In March 2010, losartan (Cozaar) lost market exclusivity. This is the first of the angiotensin II receptor blockers (ARBs) to do so. This drug class currently incurs the fourth highest cost to the NHS in terms of drug expenditure. The cost of losartan 50mg and 100mg has fallen to £3.77 (from £12.80) and £4.64 (from £16.18) respectively. Experience with other agents (e.g. ACE inhibitors) suggests the price will fall much further saving the NHS more than £50 million. However the total ARB spend in England was £272 million in England in 2008, with 6 ARBs (candesartan, eprosartan, irbesartan, olmesartan, telmisartan and valsartan) remaining on patent. If losartan were the primary ARB in the NHS more than £200 million could be saved per annum. Locally, NHS London spends £35million a year on ARBs generating potential to achieve a £25 million saving.

Within a class of drugs, all acting in the same way at the same receptor, there can be differences in required dose, dosing frequency, drug interactions, adverse event profiles and the pharmacopolitical environment (cost, licensing etc). For ARBs, which are used in hypertension (usually in combination therapy) and heart failure, these differences are small, almost always clinically insignificant, and reflect minor dosing differences. They are all once a day drugs. In other words, the drugs are more or less clinically indistinguishable. With the recent HEAAL trial publication, a target dose for losartan in heart failure is now available at 150mg [unlicensed] per day. After a UCLH Use of Medicines Committee evidence review of ARBs, and in collaboration with Camden PCT, all ARBs except losartan have been removed from The Formulary. For patients on ARBs for hypertension, a pharmacist-led review policy is to be implemented. For patients on ARBs for stable heart failure where the patient is not on the maximum ARB dose, dose escalation is recommended and achieved by changing to losartan. The exception to this is the [rare] specific situation of prior losartan intolerance. For patients with severe heart failure and prone to frequent decompensations, changing medications could theoretically precipitate decompensation (although there is no published evidence that this is as significant problem). However, for such patients the decision to change will be left to the discretion of the patient's physician.

Recommendations

- New patients: Losartan is the only ARB to be initiated in all patients for both hypertension and heart failure. ARBs should only be prescribed if ACE-inhibitor intolerant.
- Existing patients for hypertension:
 - Patients admitted on branded ARBs will receive and be discharged on losartan (pharmacy-led review). Exceptions: prior documented intolerance to losartan.
- Existing patients for heart failure:
 - Where not already on maximal dose, ARB dose escalation is encouraged. If a patient has the ARB dose escalated, the patient should be changed to losartan (exception: prior documented intolerance to losartan). This should be performed under guidance of the responsible physician. Where the patient is on maximal dose ARB and it is not losartan, the existing ARB is continued and the decision to change left to the responsible physician.
- The losartan dose used in hypertension will be 50mg or 100mg daily depending on whether the existing ARB dose is at the lower or upper end of its dosing schedule (see table). 150mg daily is the target dose for heart failure [unlicensed].

FAQs:

Isn't candesartan more effective than losartan in heart failure and /or have a better evidence-base?

There are no head-to-head studies comparing these agents so there is an absence of robust evidence in terms of ascertaining apparent superiority or inferiority of one agent over another. In terms of evidence base, in 2009, a larger study [involving losartan] with longer follow-up, called the HEAAL study, was published (the HEAAL trial recruited 3,846 patients and followed up for a median of almost 5 years; Charm-Alternative [involving candesartan] recruited 2,028 with a median follow-up of about 3 years) which also demonstrated a reduction in the rate of death or admission for heart failure in patients with heart failure, reduced left-ventricular ejection fraction, and intolerance to ACE inhibitors. It is, however, difficult to compare these two trials directly as Charm-Alternative was merely a placebo-controlled trial and only 55% of patients were taking a β -blocker; baseline β -blocker therapy was much greater (72%) in the active-comparator [low dose losartan] HEAAL study. A recent independent analysis concluded that based on these study differences the findings of HEAAL appear reasonably consistent with those of the CHARM-Alternative study.³

What about the safety issue raised by some commentators of the ELITE II study, where losartan use was associated with increased mortality compared to placebo in patients prescribed beta-blockers. HEAAL had no placebo arm and cannot therefore rule out the possibility that losartan interacts with beta-blockers in patients with heart failure in a negative fashion?

First, this finding was based on exploratory *post-hoc* sub-group analyses in a small (insufficiently powered) group of patients in ELITE II. Such data are interpreted as hypothesis-generating and not policy-defining. Second, this apparent difference was not seen if use was based on **concomitant** treatment with beta-blockers during the study which is more relevant. Third, patients on losartan and captopril also taking beta-blockers did better than most patients not on such treatment at randomisation during ELITE II. Fourth, the "interaction" between treatment effect and **baseline** beta-blocker use should be interpreted with caution given the small absolute number of patients receiving these drugs and potential bias related to the reasons for administering these agents. Fifth, the presence of an interaction was investigated in the subsequent OPTIMAAL study (see below) which showed no interaction between losartan and beta blockers with respect to survival. Sixth, many commentators now agree that these "findings" suggested from ELITE II analyses are likely to be spurious. Seventh, of note, baseline beta-blocker therapy was much greater in the HEAAL and OPTIMAAL studies (72 and 79% respectively) when compared to CHARM-Alternative (55%). Finally, there is no evidence from HEAAL of an inflated mortality rate in either arm.

Wasn't losartan inferior to ACEi for post-MI heart failure (OPTIMAAL study)?

5477 patients 50 years of age or older with confirmed acute myocardial infarction and heart failure during the acute phase or a new Q-wave anterior infarction or reinfarction, were randomly assigned and titrated to a [low] target dose of losartan (50 mg once daily) or [proven] captopril (50 mg three times daily) as tolerated in the OPTIMAAL study. The primary endpoint was all-cause mortality. There were 946 deaths during a mean follow-up of 2.7 years: 499 (18%) in the losartan group and 447 (16%) in the captopril group (relative risk 1.13 [95% CI 0.99—1.28], $p=0.07$) i.e. a non-significant difference in the primary endpoint (total mortality) was observed. The incidence of reinfarction, revascularisation, and all-cause hospital admission were essentially identical between the two groups. The upper one-sided 95% confidence margin (1.25) for the relative risk of death from any cause was above the pre-specified margin of 1.10 resulting in failure to satisfy the non-inferiority criterion.

Valsartan and candesartan lose exclusivity within 2 years, is this worth all the effort?

Patents are often extended and there is often a delay between total expiry and generic availability. Regardless, savings of several hundred million pounds that could be achieved during this time are far from insignificant.

It would be easier to apply these guidelines for new patients only, won't changing patients stabilized on treatment be too time consuming and risky?

For patients treated for hypertension, no experts consulted at UCL Hospitals thought this unreasonable especially considering the wide inter- and intra-day variations in physiological blood pressure; most use will be as combination therapy as well. For patients with heart failure the guideline allows for clinical discretion and only suggests change during up-titration to target dose; a practice that is universally encouraged in heart failure.

Why don't you recommend changing all heart failure patients?

The evidence for all ARBs in heart failure is robust, including evidence for losartan. The effect of ARBs in heart failure is a class effect. There are no head-to-head studies indicating superiority or inferiority of one agent over another. Also, losartan is the only ARB where high dose has been shown to be more effective than low dose. Nevertheless, despite all the pharmacological data of equivalence, there may be small 'dosology' differences between ARBs. Some heart failure patients are very unwell with short life expectancy. It is possible that even slight changes such as may occur during an ARB change could tip patients into decompensation – or, of course, decompensation episodes could occur anyway and be blamed on the ARB change, preventing disclosure of other causes.

High dose losartan for heart failure is not licensed.

This is true, but sometimes the regulatory environment lags the evidence, and sometimes, such as when the drug is off patent, it may never catch up. Doctors use unlicensed drug/dose/indications frequently (such as generic clopidogrel in acute coronary syndrome), provided the reasons are sensible and robust. The UCLH Use of Medicines Committee has also advocated the use of 150mg losartan in heart failure.

Are there any significant differences in drug-drug or drug-food interactions?

No although aliskiren levels may be reduced by irbesartan.

What about combination drugs?

Patients appreciate combination drugs (ARB+diuretic) as it reduces the total number of tablets per day to be taken. However, the price premiums for combination drugs are too high so it is not cost-effective to prescribe them. Any individuals on combination treatment will be changed to losartan plus equivalent dose diuretic.

What are the precise dose comparisons with losartan?

All 7 drugs are marketed in 3 doses (low, medium, high dose). We recommend changing to low, medium or high dose losartan (see table). During changing, there may be the opportunity to uptitrate the dose because higher doses of losartan are better in heart failure.

Limiting medical prescribing is a threat to doctor autonomy.

NHS resources are limited and getting more so. Optimising cost-effective prescribing of ARBs will free up resources for other areas where there may be no alternatives, particularly new, expensive but effective treatments.

What will the saving be?

The savings of an England-wide change are in the region of £200 million per year, and £25million in London. This saving will not, however, be sustained long term as other ARBs lose their patent (e.g. candesartan 2012) – but in an environment of fiscal tightening, this will free up resources for other essential services and drugs over the next few years.

Will patients want to change?

There is extensive experience of changing similar drugs both locally and nationally, e.g. in statins. We have also developed a patient information leaflet to explain the justification and reasons for changing. When conducted sensitively, patients almost universally approve and consent to changing.

Who contributed to these guidelines?

Dr James Moon & Dr Simon Woldman, both Consultant Cardiologists; Dr Anthony Grosso & Mr Pritesh Bodalia, both Pharmacists; and Prof Raymond MacAllister & Prof Aron Hingorani, both Consultant Clinical Pharmacologists, drafted these guidelines which were approved by the multidisciplinary Use of Medicines Committee (Drugs and Therapeutics Committee).

Appendix

Table 1: Dose comparisons of ARBs in heart failure

ARB	Lower dose	Intermediate dose	Target dose
Losartan	50mg	100mg	150mg [unlicensed]
Candesartan	4mg	8-24mg	32mg
Valsartan	80mg	120-280mg	320mg

Table 2: Dose comparisons of ARBs in hypertension

ARB	Lower dose	Intermediate dose	Upper dose
Losartan	50mg	50-100mg	100mg
Candesartan	4mg	8-24mg	32mg
Eprosartan	600mg	600mg	800mg
Irbesartan	150mg	150mg	300mg
Olmesartan	10mg	20mg	30-40mg
Telmisartan	20mg	40mg	80mg
Valsartan	80mg	120-280mg	320mg

Note: These are not exact dose equivalent tables and lower doses may be appropriate for the elderly, patients with renal or hepatic impairment or if on concomitant diuretic treatment (see current British National Formulary or Summary of Product Characteristics for prescribing information).

References

1. McKelvie, R. Compared with low-dose losartan, high-dose losartan decreases risk of death or hospital admission for heart failure in people with heart failure who are intolerant to ACE inhibitors Evidence-Based Medicine April 2010 | volume 15 | number 2.