ACE inhibitors, Angiotensin Receptor Blockers or their combination

There is insufficient evidence to support the use of combination therapy to treat chronic kidney disease.

Overview: There is strong evidence that lowering blood pressure in patients with chronic kidney disease (CKD) reduces cardiovascular risk and the progression of CKD. In general, different classes of antihypertensives reduce blood pressure and hence end-stage kidney disease (ESKD) and cardiovascular disease to a similar degree, regardless of the class of drug used. However, particular benefits for renin-angiotensin system drugs (ACE inhibitors or angiotensin receptor blockers [ARBs]) seem clearer for patients with, rather than without, diabetes, and for patients with higher levels of proteinuria.

It has been proposed that in patients with CKD, more complete blockade of the renin-angiotensin system with combination therapy i.e. an ACE inhibitor plus an ARB could be more beneficial than monotherapy. However, it is important to know how combination therapy affects patient-oriented, clinical renal outcomes, such as the initiation of dialysis or survival, not just proteinuria, which is a disease-oriented, surrogate renal outcome (Kunz et al, 2008 and ONTARGET Investigators, 2008).

Current advice: NICE recommends offering most patients with CKD an ACE inhibitor (or an ARB if the ACE inhibitor is not tolerated) to control blood pressure. The guideline development group found no evidence that ARBs have any advantage over ACE inhibitors in CKD, and no evidence to suggest combination therapy is more effective than the maximum recommended dose of each individual drug. An update of the NICE clinical guideline on CKD is in the early stages of development.

New evidence: A systematic review and meta-analysis included 85 RCTs involving 21,708 people which compared ACE inhibitors, ARBs or their combination in people with micro or macroalbuminuria and one or more cardiovascular risk factor (Maione et al, 2011). The meta-analyses were dominated by a few larger RCTs reporting patient-oriented outcomes, such as ONTARGET.

Both ACE inhibitors and ARBs reduced the risk of progression of kidney disease compared with placebo or no treatment by around 20-30% in relative terms. Compared with placebo, both classes of drug also reduced the risk of non-fatal cardiovascular events. However, neither ACE inhibitors nor ARBs reduced the risk of fatal cardiovascular events or all-cause mortality compared with placebo or no treatment. Head to head trials of ACE inhibitors vs. ARBs found no significant differences between these classes of drugs with regard to cardiovascular or renal outcomes.

Combination therapy with an ACE inhibitor plus an ARB was no more effective than either drug alone on cardiovascular or renal outcomes. With regard to ESKD, the 95% confidence intervals around these figures indicate that combination therapy could be either beneficial or indeed harmful.

The authors suggest the results raise concerns about a reduction in proteinuria being a valid surrogate marker for cardiovascular and renal protection. Although superior antiproteinuric effects of
combination therapy versus monotherapy have previously been shown (Kunz et al, 2008), this did not translate into improved patient oriented outcomes in this systematic review (which was heavily dominated by ONTARGET). Even in high-risk patients with albuminuria and at least one cardiovascular risk factor, no beneficial effects from combining an ACE inhibitor with an ARB were seen.

Commentary: "Currently, there is little primary evidence to refute the suggestion that ACE inhibitors and ARBs are equivalent, and inter-changeable in clinical practice due to reductions in all-cause mortality, cardiovascular outcomes and progression of CKD. Combined therapy with an ACE inhibitor and an ARB has not been recommended, and one of the largest trials of combination therapy, COOPERATE (in non-diabetic renal disease), was withdrawn due to irregular practices. This systematic review shows that the evidence for relative risk reduction in these endpoints can only be assessed in data from the ONTARGET study. This was primarily focused on vascular events, and combination therapy was associated with a higher incidence of acute dialysis and hence a worsening of renal outcomes. At present, the recommendation should remain cautious about the use of combined therapy, although there is a definite need for a well-designed RCT.

"The major limitation of this systematic review is the small number and overall poor quality of most of the included studies. Few of the studies had a 'hard' endpoint such as patient survival or initiation of dialysis, and instead have primary outcomes of changes in continuous surrogate markers, or a composite outcome. It remains unproven that reduction in these surrogate endpoints will be followed by reduction in the incidence of events, or improved patient survival, especially in the more heterogeneous populations with CKD risk factors" - Dr Edward Sharplles, Consultant in Nephrology and Transplant Medicine Knowledge Adviser to NHS Evidence.

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