Angiotensin Converting Enzyme Inhibitors – beneficial effects seen in many patient groups may not extend to kidney transplant recipients

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Angiotensin converting enzyme inhibitors (ACEi) have beneficial effects on important clinical endpoints such as mortality, cardiovascular disease events and end stage kidney failure in many patients groups (1,2). Moreover, ACEi are recommended for the treatment of hypertension and proteinuria in patients with chronic kidney disease (3).

Hypertension and proteinuria are common in kidney transplant recipients, as are cardiovascular disease and related adverse outcomes. Despite limited evidence from randomised trials in transplant recipients (4), compelling data of efficacy in non-transplant populations with hypertension and proteinuria have led to clinical practice guidelines recommending preferential use of ACEi in hypertensive proteinuric kidney transplant recipients (5). There has been a measurable practice shift in the use of ACE-I over time; data from the Collaborative Transplant Study show that the proportion treated with ACEi increased from 32% for patients transplanted in 1998-2003 to 44% in patients transplanted in 2004-2010 (6).

A multicentre, double blind, placebo controlled randomised controlled trial lead by Canadian researchers that has recently been published in Lancet Diabetes and Endocrinology, however, challenges these recommendations and current clinical practice. (7)

Following a two week active drug run-in to ensure tolerability, Knoll and colleagues randomised 213 kidney transplant recipients with estimated glomerular filtration rates (GFR) >20ml/min/1.73m2 and proteinuria of > 200mg/d to ramipril 5mg twice daily or placebo, and treated patients for four years. Clinicians were permitted to use any other non-ACEi or angiotensin-2 receptor blocker (ARB) drugs to control blood pressure. The primary outcome was a composite of: doubling of serum creatinine, end stage kidney disease or death, and was experience by 14/103 people on rampiril, and 19/109 on placebo. There was no difference in a range of important secondary outcomes

including overall graft failure (hazard ratio, HR 0.67, 95%CI 0.24-1.9), overall death (HR 1.97, 95%CI 0.66-5.89), and measured GFR (-2ml/min/1.73m2 95%CI -13 to 9ml/min/1.73m2). Side effects were more common in the ramipril group (38%) than the placebo group (22%), p=0.02. Overall, there was no evidence of benefit for the treatment arm (HR 0.76, 95%CI 0.38-1.52).

The trial was well conducted and reported. A number of strengths and some weaknesses were recognized and discussed by the authors. Briefly, Knoll and colleagues assessed clinically relevant outcomes. Selection criteria ensured that transplant patients will most likely benefit from treatment (if the effect of ACEi were similar to that observed in the non-transplant population). Trial design and conduct included elements associated with low risk of bias implemented through rigorous randomisation and allocation concealment practices, blinding of patients, clinicians and trial staff, intention to treat analysis and low loss to follow-up.

Trial recruitment was slow, and the study failed to recruit target numbers, perhaps due to changing clinical practice patterns over time and clinician's reluctance to avoid prescription of ACEi in patients who could potentially be recruited to the study. In addition, the selection of ramipril 5mg BD may be criticised as too low for some patients, although the dose may be reasonable for patient with GFR less 59.8 m/min/1.873m^2, which was the mean GFR of participants.

Evidence context: what does this trial add to what was already known?

We undertook a systematic review in 2009 of randomised trials using antihypertensive agents in kidney transplant recipients and were able to identify 10 trials comparing ACEi to placebo or no treatment (usually with other non-ACEi or ARB co-interventions allowed). (4) Most trials were of much shorter duration than the trial by Knoll et al. and had varied enrolment criteria. All trials were substantially less well conducted or reported with incompletely and variably reported outcomes.

For example, patient death was only reported in a single study of 30 participants (a single death observed in each arm). Two other small studies reported different effects on graft loss but heterogeneity precluded meta-analysis. None of the previous studies reported on cardiovascular outcomes. In comparison, calcium channel antagonists compared to placebo did have moderate amounts of fair quality data suggesting a reduction in risk of graft loss (17 studies, 1255 patients, RR 0.75, 95%CI 0.57-0.99) but no difference in the risk of death after 12 months treatment (12 studies, 792 patients: RR 0.82, 95% CI 0.37 to 1.82).

There is some additional information published subsequent to our review, with one small trial reporting effects on surrogate outcomes and safety endpoints following a six month randomised, placebo controlled trial of low dose (5mg) enalapril in 53 unselected kidney transplant recipients (8). More studies have assessed the effects of ARBs in kidney transplant recipients (9,10,11). A trial comparing losartan 100mg to placebo (9) reached a similar conclusion for the same composite end point as in the Knoll study (HR1.37, 95%CI 0.75 -2.53, p = 0.3). The SECRET trial (comparing candesartan vs placebo) was stopped early due to a lack of difference observed for the primary endpoint (composite of all-cause mortality, cardiovascular morbidity and graft failure).

Knoll and colleague's trial therefore adds high quality information to the growing list of trials that have failed to show significant clinical hard endpoint benefits for kidney transplant recipients when using renin-angiotensin blockade.

What does this mean for clinical management of kidney transplant recipients with hypertension and proteinuria?

Based on the information available now, it is unlikely that ACEi will benefit hypertensive, proteinuric renal transplant recipients in terms of reducing graft loss, mortality or achieving an

improvement of graft outcome. Moreover, there is no information to suggest that these agents should be avoided in these patients (with the exception of registry data suggesting an excess risk of lung cancer in kidney transplant recipients smoking tobacco) (12). ACEi are effective at controlling blood pressure without side effects in many transplant recipients. At the same time, however, their use should not be prioritised over drugs with more data suggesting important beneficial effects, such as calcium channel antagonists – where the evidence of benefit is moderately convincing. ACEi are helpful for treating post transplant polycythaemia, so hypertension in the presence of polycythaemia might make them a good treatment choice.

Where to for research now?

Kidney transplant recipients are at higher risk of adverse cardiovascular outcomes compared to the general population. The assumption that treatments proven in the general population apply to patients who have been treated with dialysis or kidney transplantation continues to require confirmation. This mandates that the transplant community acts to carry out strategic trials in this patient group. Moreover, the utilization of ACEi and/or ARB in kidney transplant recipients post myocardial infarction will need to be confirmed.

Conclusion

Based on current evidence, treatment of hypertension after kidney transplant favours the use of calcium channel antagonists, although the data supporting this approach are of low quality only. In transplant recipients with hypertension and proteinuria data suggest that ACEi and ARBs are unlikely to confer benefits over other agents.

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