Commentary for THELANCETDE-D-15-00470R1: Ramipril versus Placebo in Kidney Transplant Patients with Proteinuria: A Multi-Centre, Double-Blind, Randomised Controlled Trial

Title: When evidence doesn't generalise: the case of ACE-inhibition

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Can benefits of interventions observed in the one population be expected in another? Generalisability describes the extent to which findings can be applied in settings other than those in which they were assessed. We rely on generalisabilty in clinical medicine – proven effective treatments are often applied in populations more diverse than those in which they were tested in randomised controlled trials. Treatment benefits are not always consistent across a disease spectrum, and clinical variation may affect the size of observed benefit, but usually not whether benefit exists. [1]

ACE inhibitors (ACEi) have been shown to be effective in reducing proteinuria, progression of kidney disease and death in non-transplant populations with proteinuria.[2, 3] In kidney transplant recipients, ACEi are effective at reducing proteinuria compared to calcium channel antagonists.[4] Proteinuria, in turn, is associated with progression of kidney disease and a return to dialysis or death in kidney transplant recipients.[5] It is tempting therefore to assume kidney transplant recipients with proteinuria would benefit from ACEi. Perhaps these assumptions have contributed to increasingly frequent use of these agents in kidney transplant recipients, despite uncertain comparative benefits from observational data. [6]

In this issue Knoll et al have conducted a well-constructed and carefully described investigator-instigated multicentre randomised trial of ACE-inhibitors (as ramipiril) versus placebo in kidney transplant recipients with proteinuria >=0.2g/d (irrespective of hypertension). Participants in both trial arms could also receive co-interventions of any other non-ACE-inhibitor or angiotensin II receptor blocker measures as required for blood pressure control. The author's conclusions are that despite lowering blood pressure, rampiril did not benefit clinically important outcomes including end stage kidney disease (ESKD), death or doubling of serum creatinine.

What informed this study design? Preliminary work by the investigator team included a systematic review of existing randomised trials in kidney recipients which showed no evidence

of benefit to these clinically important outcomes. [7] A broader-scoped Cochrane review concluded similarly, but also suggested calcium channel blockers might be beneficial. Both reviews were hampered by inconsistent and incomplete outcome reporting by trials; while the Cochrane review included 60 trials overall, with 17 trials on ACEi (10 trials versus placebo, seven trials versus calcium channel blockers) death and graft loss were only reported by three trials each. Overall this selective reporting and the few events prevented firm conclusions about these outcomes.[4] Outcome reporting bias is highly prevalent in randomised trials, with under-appreciated harms and overestimated benefits of treatments the likely consequences.[8, 9]

Well informed design does not guarantee smooth conduct however. The original trial was to run over 4 years, but was extended for a further 4 years, to ensure sufficient participation. Slow recruitment was in part due to increasing usage of ACEi over time in this population, perhaps related to the 2009 publication (while the trial was underway) of international clinical practice guidelines which suggested the use of ACEi in this situation.[10] Knoll et al. claim that diminishing perceived equipoise for their trial hampered recruitment, leading to the need for protocol amendment and extended follow-up. Post hoc protocol amendments can be problematic for randomised trials, because changes may introduce new bias that the original randomised design minimised.[11] In this case authors were adaptive to clinical circumstances, and were explicit; they clearly justified their rationale, did not change the trial outcomes, and changes did not lead to selective reporting of data, or deviation from intention to treat analysis. As such, the impact of the post hoc changes should be small.

This trial makes an important contribution to the literature for two main reasons. Firstly, this trial found that evidence from non-transplant populations of the benefit of ACE-inhibitors in reducing kidney and cardiovascular outcomes is not applicable to kidney transplant recipients with proteinuria, or that any benefit is so small as to be unlikely to be clinically useful. The impact of this finding on clinical practice cannot be under estimated, given ACE-i are widely used and are currently suggested as first line agents by guidelines for hypertensive transplant

recipients with proteinuria. The results of this trial should change these international guidelines, but whether clinical practice change will follow is less clear.

Secondly, this trial specifically recruited transplant recipients at high risk of poor outcomes because of their established proteinuria. As the authors rightly argue, this population was under-represented in many previous trials, despite potentially having most to gain from effective interventions. This trial demonstrates evidence can be generated in populations where it is most needed, by investigator-lead collaborative trials, with minimal potential for commercial bias. In transplantation where new randomised trials are sparse, the scale of this achievement cannot be underestimated. This is principally because of reduced commercial interest as there are few new interventions to test, and because trials are expensive and logistically challenging to manage, needing many geographically separated centres to participate to generate sufficient participants to meet power requirements for patient centred outcomes.

This trial is a timely reminder that while generalisability of treatment benefit can usually be assumed, the size of benefit cannot. True evidence based practice evolves from strategically planned research targeted at evidence gaps, and requires that clinicians are prepared to challenge their own cognitive biases to implement that evidence in their practice.

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