Published in final edited form as:

Nat Rev Nephrol. 2016 March ; 12(3): 129–131. doi:10.1038/nrneph.2015.201.

Transplantation:

The role of RAAS blockade in kidney transplantation

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Blockade of the renin–angiotensin–aldosterone system (RAAS) slows the progression of many forms of kidney disease but whether RAAS blockade is beneficial in kidney transplant recipients is unclear. A new randomized controlled trial suggests that RAAS blockade is not beneficial in the transplant setting, but the underpowered nature of this study limits its conclusions.

Kidney transplantation is the optimal mode of therapy for patients with end-stage renal disease (ESRD) and can be life-saving. However, although survival of the transplanted kidney is >90% within the first year of transplantation, graft survival declines over time and is typically <60–70% by 5 years post-transplantation.¹ New findings from a study that assessed the effects of blocking the renin–angiotensin–aldosterone system (RAAS) on transplant outcomes concluded that use of the angiotensin-converting-enzyme (ACE) inhibitor, ramipril, did not reduce the risk of renal dysfunction or death in renal transplant recipients.² This study suffers from several shortcomings, however, including a failure to achieve their target sample size, which limits the conclusions that can be drawn from the study's findings.

The causes of declining graft kidney function after the first year post-transplantation are incompletely understood but include transplant nephropathy, recurrence of the original disease, graft rejection, development of *de novo* disease, and nephrotoxicity from calcineurin inhibitors and other drugs. Transplant nephropathy is a syndrome in which structural damage with scarring of vascular, tubular and interstitial compartments of the allograft lead to a progressive decline in kidney function and is the most common cause of loss of allograft function.

Proteinuria is a well-established marker of risk of disease progression in both native kidneys and in kidney allografts. Many studies indicate that proteinuria is a poor prognostic factor for long-term survival of kidney transplants. Identifying the cause of proteinuria and instituting treatment is therefore prudent. RAAS blockers provide renoprotection in a wide

Competing interests

R.D.T has received honoraria for consulting and advisory board activities from Boehringer–Ingelheim, Amgen, Celgene, Relypsa, and ZS Pharmaceuticals.

Refers to: Knoll, G. A. *et al.* Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial. *Lancet Diabetes Endocrinol.* [http://dx.doi.org/10.1016/S2213-8587\(15\)00368-X](http://dx.doi.org/10.1016/S2213-8587(15)00368-X)

variety of kidney diseases including glomerulonephritides and polycystic kidney disease and those associated with diabetes mellitus and hypertension.^{3,4} Most kidney transplant recipients are hypertensive and receive calcineurin inhibitors, which can raise blood pressure and activate the RAAS, providing a rationale for the use of RAAS blockade in this patient population. Whether RAAS blockade benefits kidney transplant recipients has, however, been difficult to demonstrate, and their use in this population is therefore controversial. The overall findings from randomized controlled trials, observational studies and meta-analyses of RAAS blockade in kidney transplant recipients are inconclusive.^{5–8} However, these studies have been limited by small sample sizes, use of surrogate outcomes, observational designs, retrospective analyses, and most importantly a lack of long-term clinical end points including ESRD.

Knoll *et al.* have now reported the findings of a multi-centre, multinational controlled trial designed to resolve this controversy.² They performed a double-blind randomized controlled trial in which 213 kidney transplant recipients were randomly assigned to receive placebo or 5 mg ramipril once daily for up to 4 years. Participants were then followed for an extended period of up to 4 years. The primary end point was the composite of a doubling of serum creatinine level, ESRD or death. They also performed repeated measurement of glomerular filtration rate (GFR) using radiolabelled ^{99m}technetium- diethylene-triamine-pentaacetate (^{99m}Tc-DTPA) clearance at 6 monthly intervals during the initial 4-year follow up period. The researchers found no difference in the primary composite outcome, death or rate of decline in GFR between the placebo and ramipril groups.

This study has many strengths including its randomized, placebo-controlled and multicentre design, the use of a composite outcome, the use of a target blood pressure of 130/80 mmHg for all patients, the inclusion of patients with proteinuria, and use of an intention-to-treat analysis. Additional strengths include the extended follow-up observational phase in which data were collected for up to 4 years. The researchers are to be congratulated for designing and conducting this multicentre outcomes trial in this patient population. Unfortunately, however, the study failed to show an improvement in outcomes in patients treated with ramipril.

So why did this study fail? This study suffered from a major problem that is commonly encountered in clinical trials—namely, it was too underpowered to detect a potentially important treatment effect. As indicated in the methods section of the report, the trial required 528 participants to have 80% power to detect a 12% difference in the primary outcome; however, the trial only included 213 participants. Although the researchers made a valiant attempt to identify a potential benefit of ramipril by extending follow up, they were doomed to fail by the low recruitment. Although estimated event rates were not reported by the researchers, lower than anticipated event rates plagued the largest randomized controlled trial of RAAS blockade in which Philipp *et al.* failed to show a benefit of candesartan on ESRD and cardiovascular events among transplant recipients.⁷ Additional potential confounders in the report by Knoll *et al.* include important imbalances in comorbidities between the two treatment groups, for example, in the proportion of participants with diabetes and heart failure at baseline.

Clinical trials that have demonstrated the ability of RAAS blockade to prevent ESRD in patients with diabetes mellitus were much larger than the study by Knoll *et al.*, with number of participants ranging from 419 to 1,715. In addition, although the dose response of blood pressure to ACE inhibition is relatively flat, the antiproteinuric effect is dose dependent, particularly in populations administered calcineurin inhibitors.^{9,10} It is unfortunate that Knoll *et al.* did not use a higher dose of ramipril in their study, as it could have important effects on the study outcome. Also, one-third of participants assigned to receive ramipril discontinued the drug permanently about 1 year after randomization. This high proportion of drug discontinuations could have contributed to the null result of the study. Finally, the trial protocol was modified to increase recruitment and the study took 4 years to recruit 213 participants, an excessive period of time for a relatively small sample size.

In my opinion, the study by Knoll *et al.* is therefore not definitive. A properly powered study with sufficient participants is needed to provide definitive evidence of the efficacy and safety of RAAS blockade in renal transplant recipients. Although well designed, this aspirational study failed to move the field forward in a meaningful way and is therefore unlikely to result in changes to clinical practice guidelines or clinical practice. A study with a larger sample size and a more homogenous risk factor profile, for example a minimum of 300 mg/g of albuminuria might have increased the likelihood of detecting a difference in important clinical outcomes. In addition, the researchers' assertion that it is improbable that ramipril would benefit a lower risk kidney transplant population is not well founded. The fact that their study was underpowered—recruiting less than half of the calculated sample size needed for a meaningful effect—makes this conclusion untenable. To the contrary, a large, properly powered study in a lower risk population might indeed demonstrate a benefit of ramipril. Such a trial, using a surrogate end point such as a 40% decline in estimated GFR or a substantive increase in serum creatinine, should be considered for the kidney transplant population.

To answer the important question of whether RAAS blockade can improve outcomes in kidney transplant populations the nephrology community must unite to develop and implement successful recruitment methodologies to definitively answer the question of whether RAAS blockade improves outcomes in this population. Unfortunately, the study by Knoll *et al.* does not provide new insights into, nor settles the controversy surrounding the use of RAAS blockade in the renal transplant population. Until firm evidence is available to the contrary, RAAS blockers will therefore continue to be used to manage hypertension and proteinuria in renal transplant recipients.

Acknowledgments

R.D.T. is supported by the National Center for Advancing Translational Sciences of the NIH under award Number UL1TR001105. The content is solely the responsibility of the author and does not necessarily represent the official views of the NIH.

References

1. Gondos A, Dohler B, Brenner H, Opelz G. Kidney graft survival in Europe and the United States: strikingly different long-term outcomes. *Transplantation*. 2013; 95:267–74. [PubMed: 23060279]

2. Knoll, GA., et al. Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial. *Lancet Diabetes Endocrinol.* [http://dx.doi.org/10.1016/S2213-8587\(15\)00368-X](http://dx.doi.org/10.1016/S2213-8587(15)00368-X)
3. Lewis EJ, Hunsicker L, Bain R, et al. The Effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *The New England journal of medicine.* 1993; 329:1456–1462. [PubMed: 8413456]
4. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *The New England journal of medicine.* 2001; 345:851–60. [PubMed: 11565517]
5. Heinze G, Mitterbauer C, Regele H, Kramar R, Winkelmayr WC, Curhan GC, Oberbauer R. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *Journal of the American Society of Nephrology : JASN.* 2006; 17:889–99. [PubMed: 16481415]
6. Ibrahim HN, Jackson S, Connaire J, Matas A, Ney A, Najafian B, West A, Lentsch N, Ericksen J, Bodner J, Kasiske B, Mauer M. Angiotensin II blockade in kidney transplant recipients. *Journal of the American Society of Nephrology : JASN.* 2013; 24:320–7. [PubMed: 23308016]
7. Philipp T, Martinez F, Geiger H, Moulin B, Mourad G, Schmieder R, Lievre M, Heemann U, Legendre C. Candesartan improves blood pressure control and reduces proteinuria in renal transplant recipients: results from SECRET. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2010; 25:967–76.
8. Mariat C. Early use of renin-angiotensin-aldosterone system inhibitors after renal transplantation. *Nature clinical practice Nephrology.* 2008; 4:306–7.
9. Rossi AP, Vella JP. Hypertension, living kidney donors, and transplantation: where are we today? *Advances in chronic kidney disease.* 2015; 22:154–64. [PubMed: 25704353]
10. Prokai A, Csohany R, Sziksz E, Pap D, Balicza-Himer L, Boros S, Magda B, Vannay A, Kis-Petik K, Fekete A, Peti-Peterdi J, Szabo AJ. Calcineurin-Inhibition Results in Upregulation of Local Renin and Subsequent Vascular Endothelial Growth Factor Production in Renal Collecting Ducts. *Transplantation.* 2015