

ACE inhibition after renal transplantation: the effect on persistent left ventricular hypertrophy

Original article Paoletti E *et al.* (2007) ACE inhibitors and persistent left ventricular hypertrophy after renal transplantation: a randomized clinical trial. *Am J Kidney Dis* 50: 133–142

SYNOPSIS

KEYWORDS ACE inhibitor, blood pressure, left ventricular hypertrophy, renal transplantation

BACKGROUND

Left ventricular hypertrophy (LVH) is associated with poor prognosis in renal transplant recipients.

OBJECTIVE

To assess the effect of angiotensin-converting-enzyme (ACE) inhibition on LVH at 18 months after renal transplantation.

DESIGN

Consecutive nondiabetic recipients of a single deceased-donor kidney were recruited for this randomized trial at the Azienda Ospedaliera Universitaria San Martino in Genova, Italy, over a 3-year period, starting from 1 January 2001. Inclusion criteria were stable graft function (serum creatinine $<221 \mu\text{mol/l}$ [$<2.5 \text{ mg/dl}$]) and proteinuria $\leq 1 \text{ g/24 h}$ within 3–6 months of transplantation. Second, pre-emptive transplantation, prior use of drugs acting on the renin-angiotensin system (RAS), and acute rejection during the previous 3 months were among the exclusion criteria. Echocardiography was performed at baseline (3–6 months after transplantation) and 18 months later; echocardiograms were reviewed by a single, blinded cardiologist.

INTERVENTION

Patients with a left ventricular mass index (LVMI) greater than the upper limit of normal ($49.2 \text{ g/m}^{2.7}$ for men; $46.7 \text{ g/m}^{2.7}$ for women) at baseline underwent a 2-week antihypertensive washout period. They were then randomized on a 1:1 basis to receive either the ACE inhibitor lisinopril (starting dose 5 mg/day;

titrated to between 2.5 mg/day and 20 mg/day) or no RAS-blocking treatment (controls). Blood pressure was measured weekly, and antihypertensive drugs not acting on the RAS were used in both groups as necessary to maintain the target blood pressure of $\leq 130/80 \text{ mmHg}$.

OUTCOME MEASURE

The primary end point was the change in LVMI between baseline and month 18.

RESULTS

Of the 74 patients who were randomized, 4 did not undergo echocardiography at 18 months. Thus, a total of 70 patients (67% male; aged 30–68 years) were available for analysis. Most baseline demographic, echocardiographic and clinical characteristics (including LVMI and blood pressure) were comparable in the lisinopril group ($n=36$) and the control group ($n=34$). Immunosuppression comprised ciclosporin ($n=38$) or tacrolimus ($n=32$), plus mycophenolate mofetil and prednisone. From baseline to 18 months, there were significant decreases in systolic and diastolic blood pressure in the lisinopril group (-5 mmHg , $P<0.01$; and -7 mmHg , $P<0.001$; respectively) and the control group (-4 mmHg , $P<0.001$ for both). These changes were not significantly different between the two groups. LVMI decreased by $9.1 \text{ g/m}^{2.7}$ in the patients randomized to receive lisinopril ($P<0.001$), but remained almost unchanged in the patients randomized to receive no RAS-blocking antihypertensive treatment (increase of $1 \text{ g/m}^{2.7}$). In a post hoc multivariate regression analysis, the beneficial effect of lisinopril on the change in LVMI was significant in patients who received ciclosporin ($P<0.001$), but not in those who received tacrolimus ($P=0.2$).

CONCLUSION

Treatment with an ACE inhibitor reverses LVH in renal transplant recipients receiving ciclosporin, partly, it seems, via a mechanism that is independent of blood-pressure lowering.

COMMENTARY

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The study by Paoletti *et al.* indicates that the ACE inhibitor lisinopril reverses post-transplantation LVH, in a manner seemingly independent of its antihypertensive action. This finding implies that ACE inhibitors should be the first choice of treatment for hypertensive renal transplant recipients with LVH. The study does, however, have several limitations. The number of patients included was rather small, and the patients were highly selected. Diabetes mellitus was an exclusion criterion; thus, patients with diabetic nephropathy—which is the most frequent cause of end-stage renal disease (ESRD) in many countries—were not included. Acute rejection during the 3 months preceding study entry was a further exclusion criterion. Patients had to have very good graft function in order to be eligible for the study, and those who were included also had relatively well controlled blood pressure. In addition, the interval of 3–6 months between renal transplantation and study recruitment is likely to have been too short to allow the authors to achieve their aim of studying transplant recipients who had LVH that did not result from ESRD during dialysis. Finally, the 18-month follow-up period was insufficient to allow conclusions to be drawn about clinical outcomes (e.g. myocardial infarction, stroke and ESRD).

Despite the above-mentioned limitations, the data reported by Paoletti *et al.* are compatible with those from a number of other studies. Antihypertensive drugs acting on the RAS are more effective than β -blockers at reducing LVH in patients with hypertension.¹ In one study, the ACE inhibitor perindopril reduced left ventricular mass in patients with ESRD, whereas the calcium-channel blocker nitrendipine did not.² Data also imply that ACE inhibitors provide greater renoprotection than β -blockers in renal transplant patients. In hypertensive renal allograft recipients, the ACE inhibitor quinapril significantly decreased urinary protein excretion, but the β -blocker atenolol had no effect on this parameter.³ In a retrospective analysis, long-term patient and graft survival were better in renal allograft recipients treated with an ACE inhibitor or an angiotensin-receptor

blocker than in those who did not receive an antihypertensive drug acting on the RAS.⁴ Finally, a meta-analysis showed that ACE inhibitors slow the progression of chronic renal insufficiency more effectively than do other antihypertensive agents.⁵

Interestingly, levels of intact parathyroid hormone at the end of the treatment period in the Paoletti study were about 30% higher in the control group than in the lisinopril group. As a result of the small number of patients studied, this difference was not statistically significant; however, it did imply that there was more-effective prevention of secondary hyperparathyroidism in the lisinopril group.

It seems appropriate, in the context of the findings reported by Paoletti *et al.* and those of previous studies, to use ACE inhibitors as the first-line antihypertensive drugs for renal transplant recipients with LVH—particularly those who are receiving ciclosporin. In order to achieve the generally accepted blood pressure target of <130/80 mmHg, most patients require a combination of two or more antihypertensive agents. Prospective long-term studies are needed to confirm the beneficial effects of ACE inhibitors on clinical end points (e.g. mortality, myocardial infarction, stroke and ESRD) in the transplantation setting.

References

- 1 Mancia G *et al.* (2007) 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* **25**: 1105–1187
- 2 London GM *et al.* (1994) Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease: comparative effects of ACE inhibition and calcium channel blockade. *Circulation* **90**: 2786–2796
- 3 Hausberg M *et al.* (1999) ACE inhibitor versus beta-blocker for the treatment of hypertension in renal allograft recipients. *Hypertension* **33**: 862–868
- 4 Heinze G *et al.* (2006) Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol* **17**: 889–899
- 5 Jafar TH *et al.* (2003) Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* **139**: 244–252

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Acknowledgments

The synopsis was written by Chloë Harman, Associate Editor, Nature Clinical Practice.

Competing interests

The author declared no competing interests.

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Received 30 August 2007

Accepted 1 October 2007

Published online

30 October 2007

www.nature.com/clinicalpractice
doi:10.1038/ncpneph0663

PRACTICE POINT

Angiotensin-converting-enzyme inhibitors should be the first choice antihypertensive drug in renal transplant recipients with left ventricular hypertrophy, particularly in those who are receiving ciclosporin