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Review Article

Effect of renin-angiotensin system inhibitors on survival in kidney transplant recipients: A systematic review and meta-analysis

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Abstract Renin-angiotensin system inhibitors, specifically angiotensin II converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), have confirmed renoprotective benefits in patients with proteinuria and hypertension. However, it remains controversial whether these agents are beneficial to kidney recipients. We conducted this meta-analysis to evaluate the effects of ACEI/ARB treatment on patient and allograft survival after kidney transplant. The PubMed, Embase and Cochrane Library databases were searched for eligible articles from before May 2016, and we included 24 articles (9 randomised controlled trials [RCTs] and 15 cohort studies with 54,096 patients), in which patient or graft survival was compared between an ACEI/ARB treatment arm and a control arm. Pooled results showed that ACEI/ARB was associated with decreased risks of patient death (relative risk [RR] = 0.64; 95% confidence interval [CI]:0.49–0.84) and graft loss (RR = 0.59; 95%CI:0.47–0.74). Subgroup analysis of the cohorts revealed significantly reduced patient death (RR = 0.61; 95%CI:0.50–0.74) and graft loss (RR = 0.58; 95%CI:0.46–0.73), but this was not seen in RCTs (patient survival: RR = 0.84, 95%CI:0.39–1.81; graft survival: RR = 0.70, 95%CI:0.17–2.79). Significantly less graft loss was noted among patients with biopsy-proved chronic allograft nephropathy (CAN) (RR = 0.26, 95%CI:0.16–0.44). Furthermore, the benefit of ACEI/ARB on patient survival (RR = 0.62; 95%CI:0.47–0.83) and graft survival (RR = 0.58, 95%CI:0.47–0.71) was limited to those with ≥3years' follow-up. ACEI/ARB decreased proteinuria ($P < 0.001$) and lowered haemoglobin ($P = 0.002$), but the haemoglobin change requires no additional treatment (from 119–131 g/L to 107–123 g/L). We therefore concluded that ACEI/ARB treatment may reduce

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patient death and graft loss, but additional well-designed prospective studies are needed to validate these findings.

Introduction

Mounting evidence shows that renin-angiotensin system (RAS) inhibitors, such as angiotensin II converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), can effectively lower blood pressure [1] and proteinuria [2–4] in patients with kidney disease. Indeed, there is evidence that ACEI/ARB use can not only reduce the risk of end-stage renal disease (ESRD) in patients with nondiabetic and diabetic stage 3 chronic kidney disease (CKD) by 56% [5] and 28% [6], respectively, but it can also reduce the risk in those with nondiabetic stage 4 CKD by 40% [7]. Therefore, the Kidney Disease: Improving Global Outcomes (KDIGO) recommendation is to use ACEI/ARBs for blood pressure control in patients with CKD [8] or proteinuric kidney disease without hypertension [9].

Concerning kidney transplant recipients, previous studies have confirmed that ACEI/ARB treatment is beneficial for hypertension and proteinuria [10,11], both of which are risk factors for patient death and graft loss [12]. ACEI/ARB treatment can also reduce the risk of cardiovascular events, which is the major cause of death in kidney recipients [13]. However, there is a lack of consensus on the direct effects of such treatment on patient and graft survival. On the one hand, some studies have confirmed that ACEI/ARB treatment can improve patient and graft survival [14–16], even without increasing the incidence of side effects like anaemia and hyperkalaemia [17,18]. On the other hand, some studies have indicated that ACEI/ARBs do not exert any beneficial effects on patient or graft survival [19,20].

Two systematic reviews have shown the effectiveness of ACEI/ARB treatment on patient and allograft survival. In the review by Cheungpasitporn et al., it reported that no significant reduction was present in the risk of graft loss or patient death among kidney transplant recipients treated with RAS inhibitors [21]. However, that meta-analysis missed many eligible trials, including only five studies (three randomised controlled trials [RCTs] and two cohort studies). More recently, Hiremath et al. found similar results based on RCT data with a pooled sample size of 1502 and a median follow-up of 1.5 years [22]. This study was underpowered by its limited sample size and the follow-up was too short to draw any firm conclusion about the potential survival benefits of RAS inhibitors in kidney recipients. Therefore, it remains unclear whether ACEI/ARB treatment provides survival benefits in kidney recipients and whether they should be routinely recommended after transplantation.

Given the lack of a clear consensus and the limitations of existing analyses, we aimed to conduct a more comprehensive systematic review of whether ACEI/ARB treatment has a positive impact on patient and graft survival.

Methods

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [23] (see Supplementary Table S1 online). Three electronic databases (PubMed, Embase, Cochrane Library) were searched from inception to April 30, 2016, combining the following terms without language limitation: ('Kidney transplantation' or 'Kidney transplant' or 'Renal transplantation' or 'Renal transplant') and ('angiotensin-converting enzyme inhibitors' or 'ACE-inhibitors' or 'angiotensin receptor blockers' or 'ARB' or 'Captopril' or 'Benazepril' or 'Enalapril' or 'Losartan' or 'Valsartan' or 'Lisinopril' or 'ramipril') and ('graft survival' or 'death censored graft survival' or 'graft loss' or 'patient survival' or 'patient death' or 'death' or 'graft dysfunction'). Also, the bibliographies of all eligible studies were screened for potential additional studies.

Inclusion and exclusion criteria

Studies were included for further investigation if they met the following two criteria: 1) they assessed adults who received primary or repeat transplants from a living or deceased donor; and 2) compared ACEI/ARB therapy against a control arm in which active medication, placebo or usual care was used. Studies were excluded if they involved multi-organic transplants or if no patient or graft survival data were available. We included studies with longer follow-up or larger populations from among those with overlapping case series.

Outcomes

Patient and allograft survival were the primary outcomes. Serum creatinine, estimated glomerular filtration rate (eGFR), blood pressure, proteinuria and adverse events were secondary outcomes.

Data extraction

Two authors (YM Jiang and TR Song) extracted the information independently with a standard data extraction table. The following items were extracted: first author's name; publication year; study type; donor and recipient age; duration of follow-up; histological diagnosis after transplant;

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