

Chapter 5: Blood pressure management in kidney transplant recipients (CKD T)

Kidney International Supplements (2012) **2**, 370–371; doi:10.1038/kisup.2012.55

INTRODUCTION

This chapter addresses the management of BP in adults with non-dialysis-dependent CKD who have received a kidney transplant (CKD T). There is insufficient evidence to make recommendations specific to children with a kidney transplant.

5.1: We suggest that adult kidney transplant recipients whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. (2D)

RATIONALE

In adult kidney transplant recipients we consider two primary outcomes from the standpoint of BP: graft function and CVD. High BP is well recognized as an important risk factor for both decline in graft function and development of CVD.^{153,284–288} Increased levels of both systolic and diastolic BP are associated with worse graft survival over a 7-year period after transplantation,²⁸⁹ and maintaining a systolic BP <140 mm Hg at 3 years after transplantation is associated with improved graft survival and reduced cardiovascular mortality at 10 years.²⁹⁰ Similarly, high BP is associated with an increased risk of graft loss and all-cause mortality.²⁹¹

Although no RCT defines BP targets in adult kidney transplant recipients for clinically important end points such as graft survival, cardiovascular events, or all-cause mortality, our suggestion is that the BP target should not deviate from the recommended target of ≤130/80 mm Hg as defined in the recent *KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients*,²⁹² since there have been no recent data to contradict this recommendation. Although the European Best Practice Guidelines for Renal Transplantation 2002 recommended a target BP ≤125/75 mm Hg in proteinuric patients, there is no evidence to differentiate BP target based on albumin excretion in renal transplant recipients.²⁹³ Because adult CKD T patients are at high risk for both graft loss and development of CVD,^{284–288} we favor a target of ≤130/80 mm Hg rather than a target of ≤140/90 mm Hg. We recognize that this recommendation is based on observational data and have therefore given it a grade of 2D.

5.2: In adult kidney transplant recipients, choose a BP-lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co-morbid conditions. (Not Graded)

RATIONALE

BP-lowering agents are prescribed in 70 to 90% of kidney transplant recipients, according to both registry reports and RCTs.^{294,295} There are many considerations in choosing antihypertensive drugs for use in adult kidney transplant recipients. These include side effects that are also seen in the general population, side effects particular to kidney transplant patients (e.g., increased propensity to hyperkalemia or anemia with ACE-Is or ARBs), level of urine albumin, degree of hemodynamic stability and the associated potential to alter graft perfusion (especially in a period soon after transplantation), co-morbid conditions that may indicate or preclude certain agents, interactions with immunosuppressive medications or other medications unique to patients with kidney transplant patients, and long-term impact on graft function, CVD, and all-cause mortality.²⁹⁶ Because of these considerations and the absence of large trials with clinically important outcomes, there is marked variability in the prescription of cardioprotective medications after transplantation.²⁹⁴

Short-term RCTs (of duration ≤2 years) suggest a beneficial effect of calcium-channel blockers, as compared with either placebo or ACE-Is, with regard to level of kidney function.^{297–300} In addition, a recent meta-analysis of RCTs indicated that the use of calcium-channel blockers, versus placebo or no treatment (plus additional agents in either arm, as needed) was associated with a 25% lower rate of graft loss (relative risk [RR] 0.75; 95% CI 0.57–0.99) and higher GFR (by 4.5 ml/min; 95% CI 2.2–6.7).³⁰¹ These findings prompted the Canadian Society of Transplantation and Canadian Society of Nephrology to question the recommendation from the 2009 *KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients* to use any class of antihypertensive agent after kidney transplantation.^{292,302} Most transplantation centers prefer to use dihydropyridine calcium-channel blockers for initial therapy after transplantation, since these agents dilate afferent arterioles and counteract the vasoconstrictive effect of CNIs^{298,303} (Supplementary Tables 54–59 online). However, non-dihydropyridines might interfere with the metabolism and excretion of

the CNIs cyclosporine and tacrolimus, as well as the mTOR inhibitors sirolimus and everolimus. When renal transplant recipients are prescribed non-dihydropyridine calcium-channel blockers, careful monitoring of CNIs and mTOR inhibitors blood levels is required if drugs or dosages are changed.

ACE-Is and ARBs are known to have acute hemodynamic effects, resulting in an increase in SCr level, and are therefore frequently avoided within the first 3 to 4 months after transplantation, when acute rejection is a strong possibility, and an increase in creatinine level can be difficult to interpret.^{298,304,305} Side effects of ACE-Is and ARBs when used soon after transplantation include increased creatinine levels, hyperkalemia, and anemia. One study showed that although 44% of patients were receiving ACE-Is or ARBs at the time of transplantation, the proportion dropped to 12% at 1 month and subsequently increased to 24% at 6 months.²⁹⁴

In the longer term, especially in kidney-transplant patients with persistent albuminuria, ARBs and ACE-Is should be considered. Two analyses of registry data have been published, with one showing a benefit and the other no benefit with the use of ACE-Is or ARBs for graft and patient survival.^{306,307} Small trials have examined various agents to lower BP in kidney-transplant patients. One examined losartan, captopril, and amlodipine and noted no change in BP or kidney function between baseline and end of follow-up. ACE-Is and ARBs did, however, reduce the risk of proteinuria, as compared with a calcium-channel blocker³⁰⁸ (Supplementary Table 60 online).

The Study on Evaluation of Candesartan Cilexetil after Renal Transplantation (SECRET) was an RCT of candesartan versus placebo.³⁰⁹ The primary outcome was all-cause mortality, cardiovascular morbidity, or graft failure. Enrollment of 700 patients was planned, but unfortunately, the study was terminated prematurely due to lower-than-expected event rates after enrollment of 502 participants because only 26 events took place in the 20 months of follow-up (with no difference in frequency between the two arms), whereas 210 events had been predicted over 3 years. Although there was slightly better BP control in the active group versus the control group (mean BP, 131/80 mm Hg vs. 137/83 mm Hg, respectively), the relatively tight BP control in both arms might have contributed to the low event rate. The protein excretion rate decreased in the ARB arm and increased in the placebo arm, but this difference may have been influenced by the different achieved BP levels (Supplementary Tables 61–62 online).

A large Canadian RCT of ramipril versus placebo is ongoing.³¹⁰ It will enroll 528 kidney-transplant patients who underwent transplantation >6 months previously, have protein excretion of >0.2 g per 24 hours, and have a GFR 20–55 ml/min/1.73 m². Outcomes will include doubling of SCr level, kidney failure, and death.

Because no large studies with clinically important outcomes have been completed, we have chosen to follow the

recommendations of the *KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients*²⁹² and to provide an ungraded statement.

RESEARCH RECOMMENDATIONS

RCTs are needed to determine:

- The optimal target BP for adult patients with kidney transplants with a focus on clinically important outcomes such as graft survival, CVD, and mortality.
- The effects of ACE-Is and ARBs versus placebo, ACE-Is and ARBs versus calcium-channel blockers, and calcium-channel blockers versus placebo regarding long-term graft survival, CVD, and patient survival.

DISCLAIMER

While every effort is made by the publishers, editorial board, and ISN to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor, copyright holder, or advertiser concerned. Accordingly, the publishers and the ISN, the editorial board and their respective employers, office and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

SUPPLEMENTARY MATERIAL

Supplementary Table 54. Evidence profile of RCTs examining the effect of ACEI or ARB vs. CCB in transplant recipients without DM.

Supplementary Table 55. RCTs examining the effect of ACE or ARB vs. CCB in transplant recipients with CKD without DM [categorical outcomes].

Supplementary Table 56. RCTs examining the effect of ACE or ARB vs. CCB in transplant recipients with CKD without DM [continuous outcomes].

Supplementary Table 57. Evidence profile of RCTs examining the effect of CCB vs. placebo in transplant recipients without DM.

Supplementary Table 58. RCTs examining the effect of CCB vs. placebo in transplant recipients [categorical outcome].

Supplementary Table 59. RCTs examining the effect of CCB vs. placebo in transplant recipients without DM [continuous outcome].

Supplementary Table 60. RCTs examining the effect of ACE vs. ARB in hypertensive transplant recipients without DM [continuous outcomes].

Supplementary Table 61. RCTs examining the effect of ARB vs. placebo in transplant recipients [categorical outcome].

Supplementary Table 62. RCTs examining the effect of ARB vs. placebo in transplant recipients without DM [continuous outcome].

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/bp.php