

Comparative effectiveness of different antihypertensive agents in kidney transplantation: a systematic review and meta-analysis

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ABSTRACT

Background. We conducted a systematic review and meta-analysis to compare benefits and harms of different antihypertensive drug classes in kidney transplant recipients, as post-transplant hypertension (HTN) associates with increased cardiovascular (CV) morbidity and mortality.

Methods. The Ovid-MEDLINE, PubMed and CENTRAL databases were searched for randomized controlled trials (RCTs) comparing all main antihypertensive agents versus placebo/no treatment, routine treatment.

Results. The search identified 71 RCTs. Calcium channel blockers (CCBs) (26 trials) reduced the risk for graft loss [risk ratio (RR) 0.58 [95% confidence interval (CI) 0.38–0.89]], increased glomerular filtration rate (GFR) [mean difference (MD) 3.08 mL/min (95% CI 0.38–5.78)] and reduced blood pressure (BP). Angiotensin-converting enzyme inhibitors (ACEIs) (13 trials) reduced the risk for graft loss [RR 0.62 (95% CI 0.40–0.96)] but decreased renal function and increased the risk for hyperkalaemia. Angiotensin receptor blockers (ARBs) (10 trials) did not modify the risk of death, graft loss and non-fatal CV events and increased the risk for hyperkalaemia. When pooling ACEI and ARB data, the risk for graft failure was lower in renin-angiotensin system (RAS) blockade as compared with control treatments. In direct comparison with ACEIs or ARBs (11 trials), CCBs increased GFR [MD 11.07 mL/min (95% CI 6.04–16.09)] and reduced potassium levels but were not more effective in reducing BP. There are few available data on mortality, graft loss and rejection. Very few studies performed comparisons with other active drugs.

Conclusions. CCBs could be the preferred first-step antihypertensive agents in kidney transplant patients, as they improve graft function and reduce graft loss. No definite patient or graft survival benefits were associated with RAS inhibitor use over conventional treatment.

Keywords: antihypertensive agents, kidney transplantation, meta-analysis, systematic review

INTRODUCTION

Kidney transplant recipients have a 2-fold risk of cardiovascular (CV) disease compared with the general population [1]. Following transplantation, several factors have the potential to increase CV risk over time, including traditional risk factors [e.g. hypertension (HTN), diabetes], which are highly prevalent [2]. HTN, apart from being a primary CV risk factor, is the most common clinical problem among transplant patients, affecting at least 90% of this population [3]. Inadequate control of post-transplant HTN is associated with an increased risk of CV morbidity and mortality, other than being an independent risk factor for graft loss [4].

Several mechanisms, transplant-specific or not (e.g. elevated renin secretion by the recipients' native kidneys, poor-quality donor kidneys, renal transplant artery stenosis [5]), are implicated in the pathogenesis of post-transplant HTN. In this context, immunosuppressive medications, essential to prevent acute rejection and graft loss, play a key role in promoting post-transplant HTN [6], as demonstrated in particular for calcineurin inhibitor use [7].

Beneficial and adverse effects of blood pressure (BP)-lowering drugs vary among different patient groups, and this problem may be amplified in kidney transplant recipients. Preferred antihypertensive drug classes for patients with chronic kidney disease (CKD) are classically angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics (thiazide or loops) and calcium channel blockers (CCBs) [8, 9]. No ideal single agent for post-transplant HTN management exists and the actual recommendation in kidney transplantation is to use any class of antihypertensive agent that enables BP control [10]. A tailored approach, based on its efficacy and tolerability, should be considered in transplant recipients in order to improve patient or graft survival and reduce CV and renal disease progression risks [11], without overlooking potential drug–drug interactions, especially with immunosuppressive medications.

To explore this issue, we performed an updated comprehensive systematic review and meta-analysis, focusing on randomized clinical evidence, aimed at comparing the relative benefits and harms of different drug classes in kidney transplant patients beyond their BP-lowering action.

MATERIALS AND METHODS

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [12] and was conducted according to a previously published protocol [13].

Major medical databases were searched for randomized controlled trials (RCTs) comparing the effects of different antihypertensive agents (including ACEIs, ARBs, CCBs, diuretics, β -blockers and α -blockers) to placebo/no treatment, routine treatment or any active drug in kidney transplant recipients. The primary endpoints were all-cause mortality, graft failure, acute rejection and/or any rejection episodes and any fatal or non-fatal CV event. Secondary outcomes were a change in kidney function [glomerular filtration rate (GFR)/creatinine clearance, serum creatinine (SCr)], proteinuria/albuminuria, BP control, changes in serum potassium levels and/or hyperkalaemia. The data source and search strategy (see [Supplementary data, Table S1](#)), study selection, data extraction and data analysis and quality and risk of bias assessment are produced in detail as [Supplementary data](#) Materials, Methods and Data analysis.

RESULTS

Search results

[Supplementary data, Figure S1](#) shows the flow diagram of the studies selection process. A total of 3503 potentially relevant references were initially found. Six additional citations were added by personal search. By screening titles and abstracts, a total of 3250 citations were excluded for various reasons (search overlap, study population or intervention not pertinent, no RCTs, review articles or experimental studies). Among the 259 studies selected for full-text examination, 147 articles were excluded: (i) no RCTs ($n = 80$); (ii) review articles ($n = 2$); (iii) dealing with the wrong population ($n = 7$); (iv) intervention/outcomes not pertinent to the topic ($n = 58$).

A total of 112 articles, referring to 71 RCTs (6832 individuals), were reviewed in detail and included in the review. Fifty-eight RCTs (6198 individuals), providing suitable numerical data on the outcomes of interest, contributed to pooled meta-analyses.

Study characteristics

The main characteristics of the included studies are detailed as [Supplementary data](#), Study characteristics and summarized in [Supplementary data, Table S2](#). The search identified 71 RCTs [14–84] with a study duration ranging from 2 months [33, 35, 39, 48, 56, 62, 64, 66, 68, 83, 84] to 10 years [79]. Twenty-six RCTs tested CCBs [15–22, 24, 25, 27–29, 34, 36–39, 43, 44, 50, 53, 58, 61, 62, 76], whereas 13 [14, 31, 33, 41, 42, 51, 54, 60, 72, 75, 79, 81, 82] and 10 [63, 64, 69–71, 73, 77, 78, 80, 84] studies, respectively, compared ACEIs and ARBs versus placebo/routine treatment. Among these, 22 trials [24, 25, 28, 29, 31, 37–39, 42, 44, 50, 51, 58, 61, 64, 73, 74, 76, 78, 80–82] compared a single antihypertensive agent to placebo/no treatment, as well as 27 [14–22, 27, 33, 34, 36, 41, 43, 53, 54, 60, 62, 63, 69–72, 77, 79, 84] to routine treatment (e.g. antihypertensive and/or immunosuppressive therapy). Nineteen head-to-head comparisons (single agent versus another active comparator) [23, 26, 30, 32, 40, 45–49, 52, 55, 56, 59, 65–67, 74, 83] were tested, mainly involving CCB and/or ACEI. Three RCTs [35, 57, 68] compared three intervention arms. The final population analysed in the review included 6832 kidney transplant recipients, but the range was highly variable across studies, spanning from 9 [60] to 1640 [76] patients.

The risk of bias

The risk of bias of included studies is detailed in [Supplementary data](#) (Risk of bias) and summarized in [Supplementary data, Table S3](#) and [Supplementary data, Figure S2A](#) and [S2B](#). Overall, the risk of bias was unclear or not assessable for the majority of items/studies.

Main findings

The exhaustive analyses describing comparisons between CCBs, ACEIs or ARBs versus placebo/routine treatment, as well as head-to-head comparisons between active drugs on outcomes, were presented in detail in the related [Supplementary data](#), Effects of single antihypertensive agents on outcomes and [Supplementary data, Figures S3–S14](#). Herein [Table 1](#) summarizes the quality of the body of evidence for every outcome [Grading of Recommendations Assessment, Development and Evaluation (GRADE)] and [Figure 1](#) provides a graphical synthesis of the impact of each drug intervention on the key outcomes of interest.

In CCB versus placebo/routine treatment (26 trials), CCBs reduced the risk for graft loss {1327 patients; risk ratio [RR] 0.58 [95% confidence interval (CI) 0.38–0.89]; [Figure 2](#) (moderate GRADE quality due to study limitations), [Table 1](#)} and increased GFR [2316 patients; mean difference (MD) 3.08 mL/min (95% CI 0.38–5.78); [Figure 3](#) (very low GRADE quality due to presence of study limitations, inconsistency and publication bias)]. Both systolic blood pressure (SBP) [381 patients; MD -7.77 mmHg (95% CI -13.33 to -2.20)] and diastolic BP

Table 1. Summary of findings (GRADE)

Outcome	Effect estimate (95% CI) ^a	Number of participants (studies)	Quality of the evidence (GRADE) ^b
CCBs versus placebo/routine treatment			
Death	RR 0.79 (0.45–1.40)	1085 (13)	⊕⊕⊕ ^c Moderate
Graft loss	RR 0.58 (0.38–0.89)	1327 (16)	⊕⊕⊕ ^c Moderate
Acute rejection	RR 1.00 (0.81–1.24)	601 (8)	⊕⊕⊕ ^d Low
Any rejection episodes	RR 1.00 (0.88–1.13)	1379 (15)	⊕⊕⊕ ^c Moderate
CV death	RR 0.84 (0.18–3.97)	275 (4)	⊕⊕⊕ ^d Low
eGFR/CrCl (mL/min)	MD 3.08 (0.38–5.78)	2316 (13)	⊕⊕⊕ ^e Very low
SCr (mg/dL)	MD -0.07 (-0.13 to -0.01)	2653 (15)	⊕⊕⊕ ^c Moderate
SBP (mmHg)	MD -7.77 (-13.33 to -2.20)	381 (5)	⊕⊕⊕ ^{c,f} High
DBP (mmHg)	MD -4.75 (-7.43 to -2.07)	381 (5)	⊕⊕⊕ ^{c,f} High
MAP (mmHg)	MD -3.39 (-8.16–1.38)	394 (4)	⊕⊕⊕ ^d Low
AEs: hypotensive episodes	RR 1.20 (0.35–4.11)	301 (3)	⊕⊕⊕ ^g Moderate
ACEIs versus placebo/routine treatment			
Death	RR 1.28 (0.51–3.27)	608 (4)	⊕⊕⊕ ^h High
Graft loss	RR 0.62 (0.40–0.96)	424 (5)	⊕⊕⊕ ^h High
Acute rejection	RR 1.23 (0.44–3.48)	394 (3)	⊕⊕⊕ ^g Moderate
Any rejection episodes	RR 1.34 (0.58–3.09)	394 (3)	⊕⊕⊕ ^g Moderate
eGFR/CrCl (mL/min)	MD -5.82 (-9.94 to -1.70)	409 (6)	⊕⊕⊕ ^c Moderate
SCr (mg/dL)	MD 0.15 (0.01–0.29)	406 (9)	⊕⊕⊕ ^c Moderate
Proteinuria (g/d)	MD -0.18 (-0.40–0.05)	310 (5)	⊕⊕⊕ ^h Moderate
SBP (mmHg)	MD -3.72 (-11.46–4.02)	261 (6)	⊕⊕⊕ ^c Moderate
DBP (mmHg)	MD -2.38 (-6.23–1.47)	261 (6)	⊕⊕⊕ ^c Moderate
MAP (mmHg)	MD -3.79 (-7.03 to -0.56)	450 (10)	⊕⊕⊕ ^c Moderate
Serum potassium (mEq/L)	MD 0.33 (0.10–0.55)	134 (5)	⊕⊕⊕ ^d Low
AEs: proteinuria increase	RR 0.48 (0.23–0.98)	394 (3)	⊕⊕⊕ ^g Moderate
AEs: hyperkalemia episodes	RR 3.66 (1.13–11.80)	418 (5)	⊕⊕⊕ ^g Moderate
AEs: cough episodes	RR 1.91 (1.08–3.38)	666 (5)	⊕⊕⊕ ^d Low
ARBs versus placebo/routine treatment			
Death	RR 0.76 (0.34–1.70)	786 (3)	⊕⊕⊕ ^h High
Graft loss	RR 0.60 (0.15–2.35)	822 (4)	⊕⊕⊕ ^g Moderate
Non-fatal CV events	RR 1.18 (0.63–2.22)	967 (5)	⊕⊕⊕ ^g Moderate
eGFR/CrCl (mL/min)	MD -3.17 (-8.58–2.23)	188 (5)	⊕⊕⊕ ^d Low
SCr (mg/dL)	MD -0.03 (-0.18–0.11)	349 (7)	⊕⊕⊕ ^c Moderate
SCr doubling	RR 0.96 (0.37–2.49)	822 (4)	⊕⊕⊕ ^d Low
SBP (mmHg)	MD -3.17 (-7.25–0.91)	483 (8)	⊕⊕⊕ ^c Moderate
DBP (mmHg)	MD -2.87 (-5.04 to -0.70)	330 (7)	⊕⊕⊕ ^c Moderate
Serum potassium (mEq/L)	MD 0.17 (-0.15–0.49)	283 (6)	⊕⊕⊕ ^d Low
AEs: hyperkalemia episodes	RR 4.10 (1.05–15.95)	281 (4)	⊕⊕⊕ ^d Low
Pooled effect of ACEIs and ARBs versus placebo/routine treatment			
Death	RR 0.95 (0.52–1.74)	1393 (7)	⊕⊕⊕ ^h High
CV death	RR 0.44 (0.10–2.05)	867 (3)	⊕⊕⊕ ^g Moderate
Graft loss	RR 0.62 (0.42–0.92)	1246 (9)	⊕⊕⊕ ^h Moderate
Any rejection episodes	RR 1.15 (0.82–1.62)	613 (5)	⊕⊕⊕ ^h High
Non-fatal CV events	RR 0.82 (0.45–1.49)	1250 (7)	⊕⊕⊕ ^g Moderate
eGFR/CrCl (mL/min)	MD -4.55 (-7.99 to -1.12)	592 (11)	⊕⊕⊕ ^c Moderate
SCr (mg/dL)	MD 0.05 (-0.05–0.14)	727 (15)	⊕⊕⊕ ^c Moderate
SCr doubling	RR 0.77 (0.38–1.56)	1105 (6)	⊕⊕⊕ ^g Moderate
Proteinuria (g/day)	MD 0.07 (-0.39–0.53)	346 (6)	⊕⊕⊕ ^c Moderate
AEs: hyperkalemia episodes	RR 3.42 (1.41–8.29)	681 (8)	⊕⊕⊕ ^g Moderate
CCBs versus ACEIs treatment			
eGFR/CrCl (mL/min)	MD 11.07 (6.04–16.09)	179 (4)	⊕⊕⊕ ^{d,f} Moderate
SCr (mg/dL)	MD -0.12 (-0.22 to -0.03)	287 (5)	⊕⊕⊕ ^c Moderate
SBP (mmHg)	MD -2.65 (-6.46–1.17)	200 (3)	⊕⊕⊕ ^c Moderate
DBP (mmHg)	MD -0.61 (-2.86–1.63)	200 (3)	⊕⊕⊕ ^c Moderate
MAP (mmHg)	MD 0.74 (-1.85–3.34)	206 (4)	⊕⊕⊕ ^c Moderate
Serum potassium (mEq/L)	MD -0.18 (-0.31 to -0.05)	164 (4)	⊕⊕⊕ ^c Moderate
CCBs versus ARBs treatment			
SCr (mg/dL)	MD 0.09 (-0.08–0.26)	194 (3)	⊕⊕⊕ ^d Low
CCBs versus RAS blockade treatment			
Any rejection episodes	RR 0.54 (0.06–5.18)	241 (3)	⊕⊕⊕ ^d Low
eGFR/CrCl (mL/min)	MD 11.07 (6.04–16.09)	179 (4)	⊕⊕⊕ ^{d,f} Moderate
SCr (mg/dL)	MD -0.05 (-0.16–0.06)	427 (7)	⊕⊕⊕ ^c Moderate

Continued

Table 1. Continued

Outcome	Effect estimate (95% CI) ^a	Number of participants (studies)	Quality of the evidence (GRADE) ^b
MAP (mmHg)	MD 1.76 (−1.96–5.48)	273 (5)	⊕⊕○○ ⁱ Low
Serum potassium (mEq/L)	MD −0.24 (−0.38 to −0.10)	274 (5)	⊕⊕⊕○ ^c Moderate
ACEIs versus ARBs treatment			
SCr (mg/dL)	MD −0.02 (−0.13–0.08)	173 (3)	⊕⊕⊕○ ^c Moderate
Serum potassium (mEq/L)	MD 0.02 (−0.09–0.13)	173 (3)	⊕⊕⊕○ ^c Moderate

^aEffects of antihypertensive agents on outcomes.

^bGRADE Working Group grades of evidence. High quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate.

^cDowngraded for study limitations (risk of bias).

^dDowngraded for study limitations and imprecision.

^eDowngraded for study limitations–inconsistency and publication bias.

^fUpgraded for magnitude of effect.

^gDowngraded for imprecision.

^hDowngraded for indirectness.

ⁱDowngraded for study limitations and indirectness.

AEs, adverse events; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; RoB, risk of bias.

(DBP) [381 patients; MD −4.75 mmHg (95% CI −7.43 to −2.07)] were reduced; the quality of the evidence for these outcomes was high. No differences were observed in all-cause [1085 patients; RR 0.79 (95% CI 0.45–1.40)] and CV mortality [275 patients; RR 0.84 (95% CI 0.18–3.97)] or rejection episodes [1379 patients; RR 1.00 (95% CI 0.88–1.13)]. The GRADE quality of these analyses was moderate due to study limitations.

Comparing ACEIs versus placebo/routine treatment (13 trials), ACEIs reduced the risk for graft loss [424 patients; RR 0.62 (95% CI 0.40–0.96); Figure 4 (high GRADE quality of the evidence)] but decreased renal function [409 patients; GFR: MD −5.82 mL/min (95% CI −9.94 to −1.70); Figure 5; SCr: MD 0.15 mg/dL (95% CI 0.01–0.29) (moderate GRADE quality for study limitations)]. In such comparisons, ACEIs increased serum potassium [134 patients; MD 0.33 mEq/L (95% CI 0.10–0.55) (low GRADE quality due to study limitations and imprecision)] as well as hyperkalaemia episodes [418 patients; RR 3.66 (95% CI 1.13–11.80) (moderate GRADE quality for imprecision)]. ACEIs did not affect risk for death [608 patients; RR 1.28 (95% CI 0.51–3.27) (high quality of the evidence)] or rejection events [394 patients; RR 1.34 (95% CI 0.58–3.09) (moderate GRADE quality due to imprecision)] and no benefit on proteinuria [310 patients; MD −0.18 g/day (95% CI −0.40–0.05) (moderate GRADE quality due to indirectness)] or BP reduction [261 patients; SBP: MD −3.72 mmHg (95% CI −11.46–4.02); DBP: MD −2.38 mmHg (95% CI −6.23–1.47)] was found.

In ARB versus placebo/routine treatment (10 trials), no difference in the risk of death [786 patients; RR 0.76 (95% CI 0.34–1.70) (high quality of the evidence)], graft loss [822 patients; RR 0.60 (95% CI 0.15–2.35) (moderate GRADE quality due to imprecision)] and non-fatal CV events [967 patients; RR 1.18 (95% CI 0.63–2.22) (moderate GRADE quality due to imprecision)] was observed. The effect of ARBs was inconclusive for GFR [188 patients; MD −3.17 mL/min (95% CI −8.58–2.23) (low GRADE quality due to study limitations and imprecision)], SCr [349 patients; MD −0.03 mg/dL (95% CI −0.18–

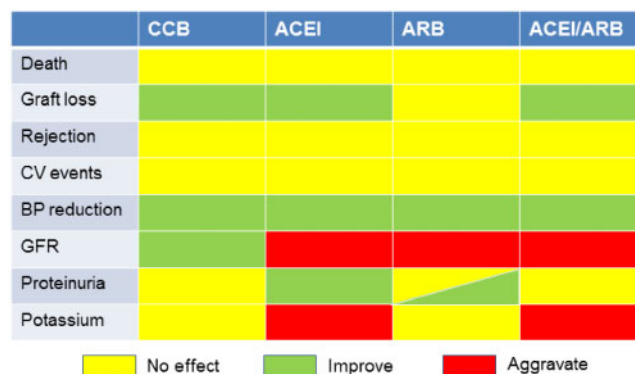


FIGURE 1: Summary of effects of different drug interventions on key outcomes.

0.11) (moderate GRADE quality for study limitations)] and BP reduction [SBP: 483 patients; MD −3.17 mmHg (95% CI −7.25–0.91); DBP: 330 patients; MD −2.87 mmHg (95% CI −5.04 to −0.70) (moderate GRADE quality for study limitations)]. In contrast, ARBs increased the risk for hyperkalaemia episodes [281 patients; RR 4.10 (95% CI 1.05–15.95) (low GRADE quality due to study limitations and imprecision)].

When pooling ACEIs and ARBs data, the risk for graft failure was significantly reduced with respect to placebo/routine treatment [1246 patients; RR 0.62 (95% CI 0.42–0.92) (moderate GRADE quality due to indirectness)], but the risk of hyperkalaemia was maintained [681 patients; RR 3.42 (95% CI 1.41–8.29) (moderate GRADE quality due to imprecision)].

In direct comparison with ACEIs or ARBs (11 trials), CCBs increased GFR [179 patients; MD 11.07 mL/min (95% CI 6.04–16.09); Figure 6 (moderate GRADE quality of the evidence), see Table 1]. Furthermore, CCBs reduced SCr [287 patients; MD −0.12 mg/dL (95% CI −0.22 to −0.03) (moderate GRADE quality due to study limitations)] and serum potassium levels [274 patients; MD −0.24 mEq/L (95% CI −0.38 to −0.10) (moderate GRADE quality due to study limitations)] but were

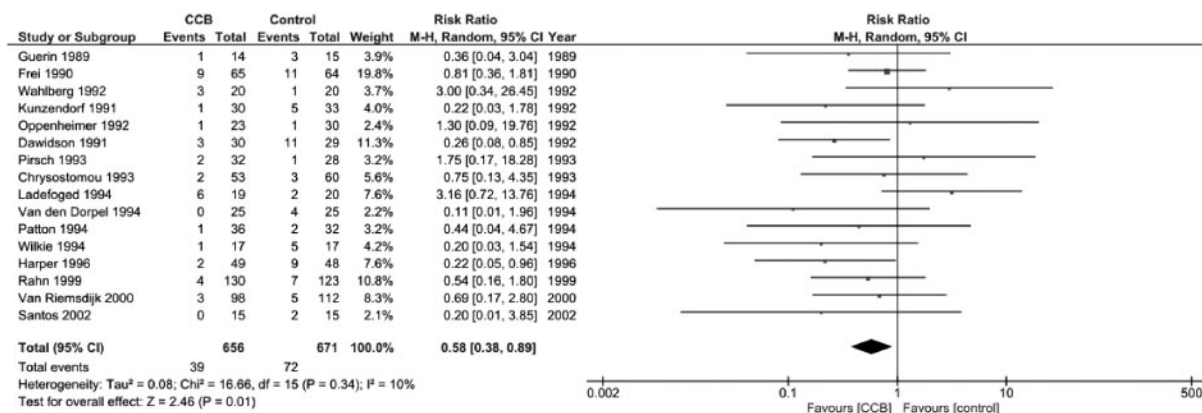


FIGURE 2: Effects of CCBs versus control treatment on graft loss.

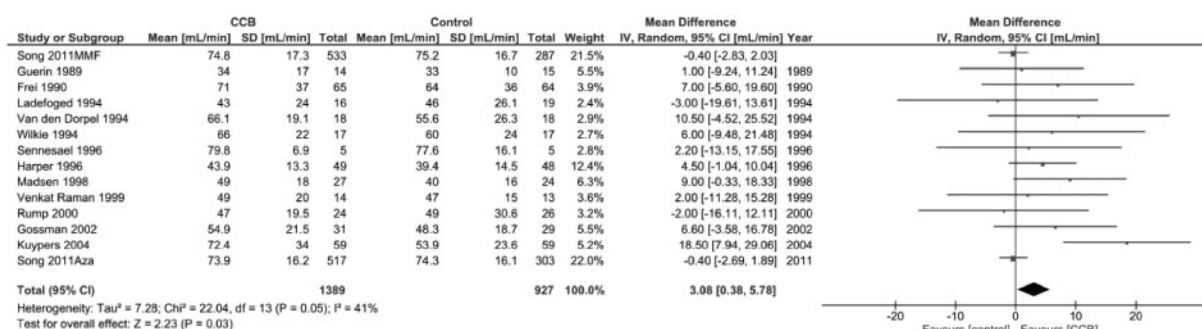


FIGURE 3: Effects of CCBs versus control treatment on estimated GFR/creatinine clearance.

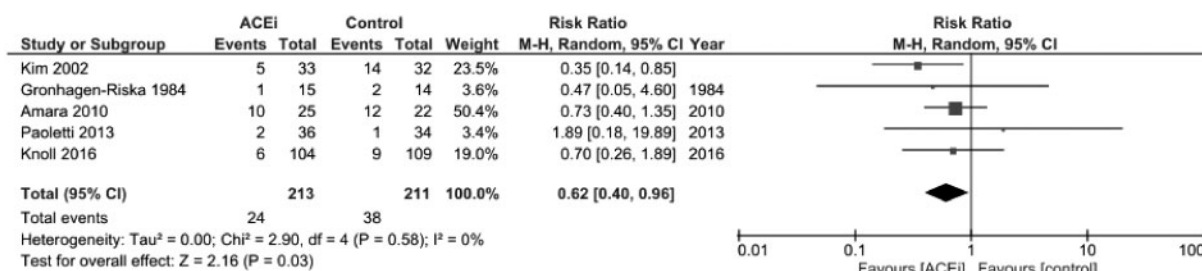


FIGURE 4: Effects of ACEIs versus control treatment on graft loss.

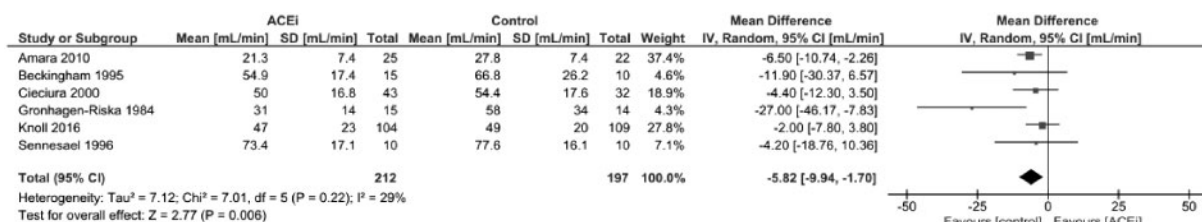


FIGURE 5: Effects of ACEIs versus control treatment on estimated GFR/creatinine clearance.

not more effective in reducing BP. There are few available data on mortality, graft loss and rejection.

In ACEIs versus ARBs comparisons (four trials), no study reported on death, graft loss or CV events. Regarding secondary endpoints, no difference between groups was observed in SCR [173 patients; MD -0.02 mg/dL (95% CI -0.13-0.08)] and serum potassium [173 patients; MD 0.02 mEq/L (95% CI -0.09-

0.13)]. GRADE quality of the evidence for both outcomes was moderate due to study limitations.

Very few studies (seven trials) performed head-to-head comparisons involving α - and β -blocking agents, as well as diuretics.

Publication bias was virtually absent in all but one (GFR-CCBs versus placebo/routine treatment) meta-analyses, as

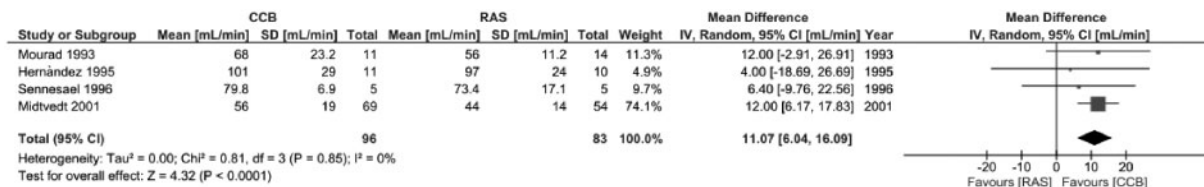


FIGURE 6: Effects of CCBs versus RAS blockade on estimated GFR/creatinine clearance.

suggested by visual inspection of funnel plots and results from the Egger's regression test (Supplementary data, Figure S15).

DISCUSSION

Until now there have been no RCTs specifically performed in kidney transplant recipients that clearly identify the ideal target BP or the combination of antihypertensive agents in order to improve long-term patient or graft survival and minimize CV risk in this population. Different guidelines on post-transplant HTN management have been published in recent decades [6, 10, 85, 86] based on the efficacy and tolerability of individual antihypertensive agents.

Recently three systematic reviews examining renin-angiotensin system (RAS) blockade in kidney transplantation have been published [87–89]. To date only one Cochrane review [90], published in 2009, tested the effects of different antihypertensive drug classes on patient and graft survival as well as on renal function. This analysis concluded that CCBs may be preferred as first-line agents for hypertensive kidney transplant recipients and that ACEIs had some detrimental effects in kidney transplant recipients. However, the authors called for more high-quality studies in this field [90]. Given the lack of a clear consensus on the benefits these agents may offer and the limitations of existing analyses, we felt it was necessary to conduct a new, updated systematic analysis of the available evidence, as well as in light of a series of new RCTs finalized in recent years on the same topic. Our systematic review, to the best of our knowledge, has the largest sample size (6832) and study number (71 RCTs) included to date.

Overall, none of the antihypertensive agents evaluated in our meta-analysis demonstrated a significant reduction of death or the occurrence of fatal or non-fatal CV events in the kidney transplant population, and this despite a reduction in BP. In this respect, our data contrast with the risk reduction for death and CV events reported in patients with advanced CKD [91, 92]. Among the reasons why neither total nor CV mortality were significantly reduced under antihypertensive therapy, one could mention the low percentage of transplant patients being adequately treated and reaching the recommended BP targets (<130/80 mmHg) [93, 94]. In the Folic Acid for Vascular Outcome Reduction in Transplantation trial, 69% of hypertensive renal transplant patients were not on target [93]. Yet one has to acknowledge that the optimal BP target to be reached in this population has not been defined adequately so far.

Nevertheless, in the present meta-analysis, data from 16 RCTs involving 1327 kidney transplant recipients suggest that the administration of CCBs, as compared with placebo or routine therapy, reduces the risk of graft loss by at least 40%. The

beneficial effects of CCB on graft loss did not vary by indication for therapy, suggesting that these medications could benefit patients irrespective of baseline HTN. Although the quality of the evidence for this outcome was moderate due to study limitations (risk of bias), a reduction in graft loss was more apparent in studies with longer follow-up (≥ 1 year) and in patients with a lower (≤ 2 agents) immunosuppressive regimen (see Supplementary data, Effects of single antihypertensive agents on outcomes).

Results from our meta-analysis reported improvements in renal function, as assessed by two pooled analyses of 13 and 15 RCTs on GFR and SCr, respectively. These analyses, however, remain questionable given the low GRADE quality of the body of evidence for study limitations and inconsistency. We speculate that variable estimates of renal function (estimated/measured GFR and creatinine clearance) across studies and low-quality RCTs retrieved may be the main factors responsible of this condition.

BP (SBP and DBP) reported by five studies was lower on CCB than on placebo/routine treatment. These findings were in line with those by Cross *et al.* [90] suggesting that CCBs could be the ideal treatment for hypertensive kidney transplant recipients, although there are very few data on adverse and CV events. In our analysis, CCBs had no impact on CV mortality and morbidity.

Calcium antagonists appeared significantly superior to placebo as well as to ACEIs or ARBs for several outcomes. In head-to-head comparisons, subjects randomized to CCB had improved renal function, showing higher GFR (+11 mL/min) and lower levels of SCr (-0.12 mg/dL) as compared with the ACEI group. This effect can be clearly explained by the different action on glomerular haemodynamics of the dihydropyridine CCB class (i.e. vasodilation of the afferent arteriole and increase in intraglomerular pressure and GFR) as compared with ACEIs/ARBs (i.e. vasodilation of the efferent arteriole and a decrease in intraglomerular pressure, GFR and proteinuria) [8, 95]. According to this mechanism, ACEIs and ARBs have been shown to reduce the progression of renal injury in renal outcome trials involving patients with proteinuric nephropathies, despite a functional initial dip in GFR [95–97], and are currently recommended as first-step antihypertensive agents in CKD with micro- or macro-albuminuria [8, 98]. However, there are currently no renal outcome studies suggesting a benefit of RAS blockers in patients with normoalbuminuria and relatively preserved renal function [8]; in contrast, dihydropyridine CCBs may be associated with preserved renal function in such individuals [99, 100]. Furthermore, whether the same mechanism applies to renal transplant patients has not been demonstrated so far.

The Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension study was the only study testing two combination treatments for HTN, benazepril plus amlodipine versus benazepril plus hydrochlorothiazide, but was prematurely terminated because of superior efficacy of the ACEI/CCB combination on the primary outcome. Use of an ACEI plus a dihydropyridine CCB, besides the overall optimal BP control, slowed significantly the progression of CKD, with an impressive 48% reduction in SCr doubling, thus indicating that this combination may be ideal for the general hypertensive population [100].

We speculate that the relevant differences in baseline urine protein excretion in studies included in this meta-analysis may explain our findings favouring CCB use. CCB treatment is associated with lower serum potassium levels of ~ 0.2 mEq/L. In these comparisons, effects on other outcomes, particularly on death and graft loss, were inconclusive due to scant data, although the point estimate was in favour of CCB treatment.

Many studies have investigated the possible benefits of RAS inhibitor treatment in the non-transplant population and in other patients with CKD [91, 92, 101–104], as well as in renal transplant recipients [72, 79, 81, 105, 106], particularly for their role in reducing proteinuria and managing CV events, besides controlling HTN. Despite this, there are conflicting data on the benefits they offer in clinically meaningful outcomes such as patient or graft survival [87, 89, 90, 107].

In agreement with a recent meta-analysis [89], we showed that RAS blockade, particularly ACEI use, was associated with a decreased risk of graft loss of $\sim 40\%$ in renal transplant recipients. Nevertheless, we found ACEI administration associated with a lower GFR (-5.82 mL/min) and an increase in SCr (0.15 mg/dL) compared with controls, which is in keeping with previous meta-analyses [88, 108], although the presence of limitations in study design and execution (risk of bias) downgraded the quality of the body of evidence on outcomes. In addition, as expected, ACEI and/or ARB treatments were associated with an increase in serum potassium ($+0.33$ mEq/L), as well as a significantly increased risk for hyperkalaemia (at least 3-fold). Several studies have shown moderate hyperkalaemia to be related with RAS inhibitors in patients with CKD [109, 110] and other meta-analyses have found a moderate and manageable (0.1 – 0.5 mEq/L) elevation of serum potassium, also accompanied by episodes of hyperkalaemia [87, 88, 90].

In contrast with other meta-analyses [88, 89], we observed that the effect of RAS inhibitors on proteinuria was inconclusive in renal transplant recipients. Beneficial effects may not have been observed, probably due to a lack of reported data or heterogeneity in population characteristics (mostly related to baseline levels of protein excretion reflecting the severity of underlying renal injury), precluding the identification of statistically significant results. In summary, RAS inhibitors have contrasting effects in renal transplantation, which may explain the reluctance of many physicians to use them more frequently. On one hand, they provide benefits (e.g. increased graft survival, reduction of BP and, in most cases, reduced proteinuria), but these may be outweighed by competing harms (e.g. increased risk of hyperkalemia, reduction in GFR).

Very few RCTs performed placebo or head-to-head comparisons involving α - or β -blocking agents, although a recent retrospective study showed an intensification of HTN treatment in renal transplant patients treated with β -blockers [111]. Some observational reports have shown that therapy with β -blockers is associated with better long-term survival of this population [112], despite evidence about possible metabolic side effects of this drug class, such as alterations in glucose metabolism and dyslipidaemia, to which these patients are prone. We identified six studies involving β -blockers [26, 30, 49, 56, 59, 66]. Currently there are insufficient data to determine the relative benefits and harms of this antihypertensive class. However, data from these trials indicate that β -blockers have no appreciable detrimental impact on BP, renal function or proteinuria [26, 59, 66] (see [Supplementary data](#), Effects of single antihypertensive agents on outcomes). They might be helpful to control BP and prevent CV events, in particular in transplant patients with coronary heart disease or congestive heart failure.

Our work has a series of strengths and limitations that deserve mentioning. Strengths include a pre-published protocol, a thorough literature search of different medical databases and a systematic approach to study selection, data extraction, analyses and trial quality assessment by two independent reviewers. Moreover, the large number of studies included in several meta-analyses allowed the performance of exhaustive investigations, such as additional subgroup analyses, in order to explain major sources of heterogeneity for relevant outcome analyses (see [Supplementary data](#), Effects of single antihypertensive agents on outcomes).

The key limitation of this meta-analysis mostly relies on the robustness of information available from the majority of the included studies. RCTs were of variable methodological quality and risks of bias were low or unclear for the majority of the items analysed, hence partially limiting the overall quality of evidence available. Furthermore, the large heterogeneity of the available studies, particularly due to the short follow-up period, prevented drawing definite conclusions for long-term outcomes and hampered the generalizability of findings to the whole kidney transplant population. No less important, clinically relevant outcomes (such as CV events) were omitted by different studies.

Treatment of HTN in transplant patients requires a tailored approach based on the individual risk profile. Although the data are not definitive, it appears that CCB and/or RAS blockers should be included in an effective antihypertensive regimen. Subjects at risk for coronary disease may also benefit from β -blocker administration.

The findings from this meta-analysis suggest that CCBs could be first-line antihypertensive agents in kidney transplant patients, as they improve graft function and reduce graft loss, beyond their unquestionable effect on reducing BP. Since RAS blockers also reduce graft loss but have some detrimental effects on clinically relevant transplant parameters such as renal function and serum potassium, clinicians should consider the prescription of ACEIs/ARBs more carefully in situations where any potential advantage to the patient outweighs the detrimental effects. In many cases, however, owing to the difficulty in

controlling HTN in renal transplant, patients should probably start on a single-pill combination containing a CCB and an RAS blocker, as recommended by the recent European Society of Cardiology/European Society of Hypertension HTN guidelines [113]. Larger RCTs are warranted to provide stronger evidence for the differential use of antihypertensive agents in renal transplant recipients.

FUNDING

This paper has not received financial support from any institution and represents an original work of the authors.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt](http://ndt.oxfordjournals.org/) online.

AUTHORS' CONTRIBUTIONS

All authors participated in the critical revision of the article for important intellectual content. F.M., J-M.H., A.Pe., G.W., P.S., B.W., M.B. and C.Z. contributed to the study concept and design. A.Pi. and D.B. developed and ran the search strategy and were responsible for data acquisition, interpretation and analysis. G.D. contributed to the data analysis. C.Z., A.Pi. and D.B. drafted the manuscript.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part. All authors declare no conflicts of interest related to the present work.

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Received: 4.10.2018; Editorial decision: 11.4.2019