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ORIGINAL ARTICLE

Blood pressure, antihypertensive treatment, and graft survival in kidney transplant patients

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Summary

Whether the use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker inhibitor (ACEI/ARB) is beneficial in renal transplant recipients remains controversial. In this retrospective study on 505 renal transplant recipients, we analyzed blood pressure and graft survival according to antihypertensive treatment with ACE-I/ARB and/or calcium channel blockers (CCB) over a period of 10 years. Patients were stratified according to their blood pressure 1 year after transplantation [controlled (≤130/80 mmHg; CTR, 181 patients) and noncontrolled (>130/80 mmHg; non-CTR, 324 patients)] and according to antihypertensive treatment (ACE-I/ARB and/or CCB taken for at least 2 years). One year after transplantation, 88.4% of CTR and 96.6% of non-CTR received antihypertensive treatment ($P < 0.05$). Graft survival was longer in CTR than in non-CTR ($P < 0.05$). Importantly, graft survival was longer in patients who received long-term treatment with ACEI/ARB, CCB, or a combination of ACEI/ARB and CCB ($P < 0.001$). The beneficial effect of ACEI/ARB therapy was more pronounced in non-CTR compared with that of CTR. We conclude that blood pressure control is a key target for long-term graft survival in renal transplant patients. Long-term ACEI/ARB and CCB therapy is beneficial for graft survival, especially in patients with diabetes and/or albuminuria.

Introduction

Arterial hypertension is common in kidney transplant recipients. More than 80% of these patients develop hypertension during the first year after renal transplantation, according to ISH/WHO criteria [1].

It is well-known that arterial hypertension has adverse effects on kidney graft function and survival [2]. However, the influence of the different antihypertensive agents is less well-understood. In patients with chronic renal failure, blockade of the renin angiotensin system with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB) has been shown to reduce proteinuria and delay the progression of both diabetic and nondiabetic chronic kidney disease [3,4]. In addition, the use of an ACEI is associated with reduced mortality in patients with diabetic nephropathy [4]. The use of ACEI/ARB is now recommended for patients with diabetic nephropathy and nondiabetic kidney disease with proteinuria, even in the absence of hypertension. , However, because of a lack of evidence, the K/DOQI guidelines do not recommend the routine use of ACEI/ARB in renal transplant recipients [5].

Chronic renal failure is a common problem in renal allograft recipients [6]. It strongly influences mortality in these patients [7]. Renal insufficiency in these patients is of multifactorial origin. Immunological (chronic rejection) and nonimmunological (hypertension, hyperlipidemia) factors have been implicated [2,8]. Toxicity of immunosuppressive therapy, recurrent and de novo renal disease also contribute to chronic renal insufficiency [9,10]. Various strategies have been established to delay

the impairment of renal function in kidney transplant recipients, including adjustment of immunosuppressive therapy, treatment of hypertension with ACEI/ARB or calcium channel blockers (CCB), and lipid control [10]. Blockade of the renin angiotensin system and treatment with CCB are commonly prescribed in kidney transplant recipients. However, data that strongly recommend the use of ACEI/ARB in kidney transplant recipients – as established for nontransplant proteinuric kidney disease – are still incomplete and somewhat controversial. To date there are no prospective trials available on the effect of ACEI/ARB therapy in kidney transplantation. A recent retrospective study showed that ACEI/ARB therapy was associated with longer patient and graft survival in renal transplant recipients [11]. However, equivocal data were derived from another retrospective analysis, showing no improvement by ACEI/ARB treatment in renal transplant patients [12]. Moreover, data suggesting a beneficial effect of CCB on long-term graft function are scant [13].

In this study, we present the analysis of 505 renal transplant recipients, who were transplanted between 1993 and 2003 at the transplant unit of the University Hospital of Münster. We conducted a retrospective study to elaborate the influence of blood pressure on graft survival. We further investigated whether long-term graft survival was improved in patients who had received long-term ACE/ARB or CCB therapy for at least 2 years.

Methods

Patients

In this retrospective analysis, we included kidney transplant recipients followed at the renal transplant outpatient clinic of the University Hospital of Münster. Patients had received their graft between 1993 and 2003. Analysis was limited to 505 patients with a functioning graft 12 months after renal transplantation. Follow-up was from 1993 until 2004. Graft function was defined by independency of dialysis. If data collection was incomplete during follow-up, patients were excluded from the study.

Definition of variables

Blood pressure

According to the ISH/WHO criteria, controlled blood pressure (CTR) in renal transplant recipients was defined as blood pressure <130/80 mmHg. Noncontrolled blood pressure (non-CTR) was defined accordingly as blood pressure ≥130/80 mmHg. Blood pressure obtained 12 months after renal transplantation was used to stratify patients into CTR or non-CTR. Blood pressure measurements were performed by well-instructed study nurses, with an automatic sphygmomanometer (Dinamap Pro 100; Johnson&Johnson, Tampa, FL, USA), after patients had been at rest for 5 min in an upright position. Blood pressure measurements were performed in both arms, unless patients were still having an av fistula. If blood pressure readings were available for both arms, the higher values were taken. All measurements were performed in the same quiet, air-conditioned (stable temperature of 20–22 °C) room in the transplant outpatient clinic.

In the first year after transplantation, outpatient visits in our department were performed at 1, 3, 6, and 12 months; in the second year at 18 and 24 months; and thereafter once a year.

Acute rejection

Acute rejection was diagnosed clinically and proven by biopsy in accordance with the BANFF classification in most cases [4,14]. Patients who showed an improvement of kidney function after initiation of rejection therapy were also classified as having acute rejection.

Laboratory findings

Blood and urine (24 h) for analysis of leukocytes, hemoglobin, creatinine, BUN, glucose, cholesterol, triglycerides, uric acid, and albuminuria were obtained at inclusion (12 month after transplantation) in the study. During follow-up, blood and urine samples were analyzed annually for leukocytes, creatinine, BUN, and albuminuria.

Antihypertensive therapy

Patients with at least 2-year graft survival were stratified according to their antihypertensive therapy: ACEI/ARB (treatment with either ACEI or ARB for at least 2 years), CCB (treatment with CCB for at least 2 years), and treatment with a combination of ACEI/ARB and CCB for at least 2 years. The patients fulfilling these criteria were compared with the remaining patients. The remaining patients are referred to in the results section and in the figures as controls (receiving no antihypertensive therapy, other antihypertensives, or short-term therapy with ACE/ARB or CCB, for <2 years).

Outcomes

Primary and combined endpoints

The primary endpoint was defined as graft loss with permanent return to dialysis. For the calculation of functional graft survival, patients who died with a functioning graft were censored.

The combined endpoint was defined as graft loss and death with a functioning graft. Patient survival time was defined as the time from kidney transplantation until death or study termination/loss to follow-up.

Statistical analysis

All analyses were performed with SPSS (SPSS Inc., Chicago, IL, USA). For descriptive purposes, values are presented as mean with the corresponding standard error. Actuarial survival curves were created using the Kaplan–Meier method. Comparisons between groups were performed using the log rank test. In certain cases, for stronger weighting of earlier events, statistical significance was evaluated using the Breslow (Gehan-Wilcoxon) test. Adjustment for potential confounders was performed by multivariate analysis using the Cox proportional hazards model. The model was adjusted for potential confounders, i.e., age, gender, body-mass index, diabetes, time period studied (1993–1998 and 1999–2004), ACEI/ARB or CCB stratification, statin therapy, HLA mismatch, donor-age, number of transplantation, acute rejection, and cytomegalo virus infection. Additionally, the following measures obtained 12 months after transplantation were included: hemoglobin, uric acid, glucose, cholesterol, triglycerides, creatinine, albuminuria, systolic and diastolic blood pressure, heart rate and pulse pressure. Based on the full model, backward elimination was applied to create a reduced model. Results are presented by mean values of Hazard ratios with 95% CI. Any two-sided P value less than 0.05 was considered to reflect statistical significance.

Results

The patient characteristics are listed in Table 1. A total of 505 renal transplant recipients were included in this study. At 5 years of follow-up, the study population was reduced to a total of 273 patients; at 10 years of follow-up the study population consisted of 87 patients. 83.5% ($n = 431$) received their first allograft, 12.9% ($n = 65$) received their second, 1.6% ($n = 8$) their third, and 0.2% ($n = 1$) their fourth allograft. There were 35.8% ($n = 181$) females and 64.2% ($n = 324$) males. The mean age of patients was 46.7 ± 0.6 years at the time of transplantation (range: 16.0 to 75.3 years). The mean age of the donors was 43 ± 1 years, the average follow-up was 63 ± 2 months. A total of 118 patients (21.5%) were diabetic.

Patients treated with tacrolimus (TAC) had a significantly higher prevalence of diabetes than those treated with cyclosporine A (21% diabetics in the CSA group versus 31% diabetics in the TAC group; $P < 0.05$).

Data on blood pressure control and therapy in the cohort of patients with controlled blood pressure (CTR) and noncontrolled blood pressure (non-CTR), respectively, are shown in Table 1.

Graft survival was significantly longer in CTR (106 ± 2.4 months) than in non-CTR (100 ± 2.2 months; $P < 0.05$, Fig. 1). Regarding the combined endpoint of graft survival and death, again there was a significant difference between CTR and non-CTR (93 ± 2.3 months with 101 events in non-CTR compared to 99 ± 2.7 months with 45 events in CTR, respectively; $P < 0.05$ for the comparison between CTR and non-CTR, respectively).

Long-term ACEI/ARB therapy prolonged graft survival (105 ± 1.8 months for ACEI/ARB, $n = 261$ vs. 99 ± 3.2 months for controls, respectively, $n = 244$; $P = 0.002$, Fig. 2). Regarding the combined endpoint of graft loss and death with a functioning graft, long-term ACEI/ARB therapy significantly prolonged survival (98 ± 1.9 months for ACEI/ARB, $n = 261$ vs. 91 ± 3.3 months for controls, $n = 244$; $P = 0.002$).

As antihypertensive treatment in transplant patients is often an add-on treatment, we were concerned that the effect of RAS inhibition was mainly related to the number of drugs applied. However, the beneficial effect of ACE/ARB therapy was independent of the number of antihypertensive drugs given, as shown in a Cox proportional hazard analysis (data not shown).

Long-term CCB therapy improved graft survival in patients not receiving ACEI/ARB (104 ± 1.8 months for CCB vs. 100 ± 3.7 months for controls, respectively; $P = 0.03$).

We could show that albuminuria was an independent risk factor for graft survival (Fig. 3).

Concerning the primary endpoint graft survival (101 ± 4.0 months in ACEI/ARB vs. 81 ± 9.1 months in controls; $P = 0.0005$) and the combined endpoint graft survival and death (93 ± 4.2 months in ACEI/ARB vs. 70 ± 7.8 months in controls; $P = 0.0001$, Fig. 4), our data show a strong benefit of long-term ACEI/ARB therapy in albuminuric renal transplant recipients. Albuminuria in ACEI/ARB was 111 ± 40 mg/day compared to 59 ± 19 mg/day in controls (P = NS). Serum–creatinine was 1.58 ± 0.05 mg/dl vs. 1.57 ± 0.05 mg/dl in patients treated with ACEI/ARB and controls, respectively (P = NS), indicating that the positive effect of long-term ACEI/ARB on graft survival was not confounded by better graft function at inclusion. Furthermore, we analyzed the data concerning the role of RAS inhibition for graft survival in patients without significant (<30 mg/day) albuminuria. Of note, even in this subgroup, ACEI/ARB inhibition significantly prolonged graft survival (107 ± 2 months in ACEI/ARB vs. 103 ± 3 months in controls, respectively; $P < 0{,}01$).

Furthermore, pulse pressure (PP) was as strong as systolic blood pressure in predicting graft survival as shown by multivariate analysis (Fig. 3). Data were analyzed using a cut-off value of 60 mmHg (106 ± 2 months for patients with PP < 60 mmHg vs. 97 ± 3 months for patients with PP > 60 mmHg, $P < 0.006$).

Table 1. Demographic data of all kidney transplant recipients enrolled in the study.

	CTR *n* = 181 36%	Non-CTR *n* = 324 64%	Significance *P*
Age (years)	44.7 ± 1	47.9 ± 0.7	<0.01
Male/Female, *n* (%)	116(64)/65(36)	208(64)/116(36)	NS
Body mass index (kg/m^2)	22.9 ± 0.2	23.4 ± 0.2	NS
Age of donor (years)	39.7 ± 1.4	44.9 ± 1.1	<0.003
Mismatches (*n*)	2.3 ± 1	2.4 ± 0,8	NS
No. kidney transplantations, *n* (%)	1(83)	1. = 86	NS
	2(15)	2. = 12	NS
	3(1)	3. = 2	NS
	4(1)	4. = 0	NS
Immunosuppression (*n*)			
Steroids	181	324	NS
CYA	35	65	NS
TAC	38	62	NS
AZA	61	114	NS
MMF	64	134	NS
Follow-up (months)	66 ± 3	61 ± 2	NS
Systolic blood pressure* (mmHg)	124 ± 0.5	147 ± 0.7	<0.001
Diastolic blood pressure* (mmHg)	76 ± 0.3	90 ± 0.4	<0.001
Pulse pressure (mmHg)	48 ± 0.2	58 ± 0.3	<0.001
No. antihypertensive drugs (%)			
0	4	2	NS
1	6	7	NS
2	10	19	<0.05
3	11	23	<0.05
4	5	10	<0.05
5	1	2	NS
Serum-creatinine (mg/dl)	1.39	1.68	<0.001
Albuminuric patients (*n*/%)			
30–300 (mg/day)	33/18	85/26	<0.001
>300 (mg/day)	5/3	28/9	<0.001
Total cholesterol* (mg/dl)	247 ± 5	257 ± 5	NS
Triglycerides* (mg/dl)	213 ± 9	267 ± 30	NS
Acute rejection† (%)	40	41	NS
Diabetes mellitus (%)	20	25	NS
CMV infection (%)	30	35	NS
Causes of death (*n*)			
Infectious diseases	1	5	NS
Cardiovascular events	8	19	NS
Malignancies	1	6	NS
Unkown	7	5	NS
Graft loss (*n*)	28	66	NS

Patients are categorized based on blood pressure control. In the CTR group, blood pressure was <130/80 mmHg; in the non-CTR group ≥130/80 mmHg.

*12 months after transplantation.

†clinical diagnosis during the first 12 months after kidney transplantation.

Diabetes emerged as a potent factor reducing graft survival (Fig. 3). Diabetics had a strong benefit from long-term ACEI/ARB therapy, as graft survival was prolonged profoundly in this group (99 ± 4.1 months vs. 89 ± 7.8 months in controls, $P = 0.0046$). There was no difference in serum-creatinine and in proteinuria between groups.

Discussion

In this retrospective single-center analysis, we investigated the effect of blood pressure, renal function, albuminuria, and antihypertensive therapy on long-term renal graft survival. We confirm here that blood pressure is a strong determinant of long-term graft survival in renal trans-

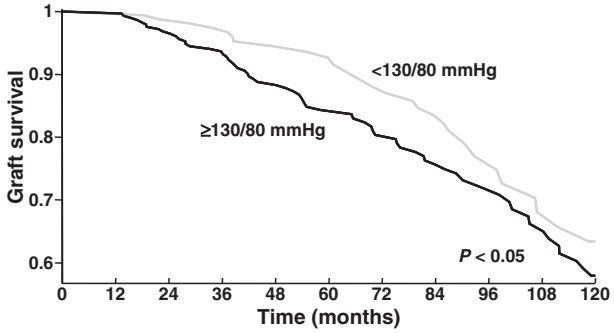

Figure 1 Kaplan–Meier estimates of the primary endpoint kidney graft survival. Cumulative graft survival in CTR (blood pressure <130/80 mmHg; $n = 181$, 28 events) and non-CTR (blood pressure ≥130/80 mmHg; $n = 324$, 66 events) kidney transplant recipients is shown. Statistical significance was indicated using the Breslow test.

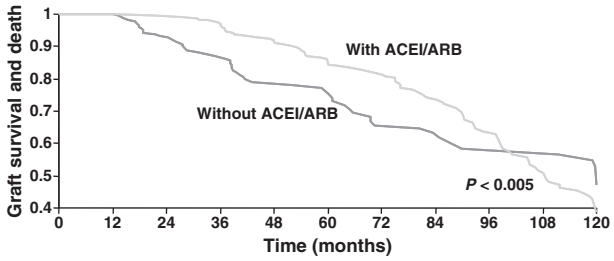

Figure 2 Kaplan–Meier estimates of the combined endpoint kidney graft survival and death. Patients were stratified according to antihypertensive therapy: long-term angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy (ACEI/ARB; $n = 261$, 95 events) versus controls (without ACEI/ARB; $n = 244$, 58 events). Statistical significance was calculated using the Breslow test.

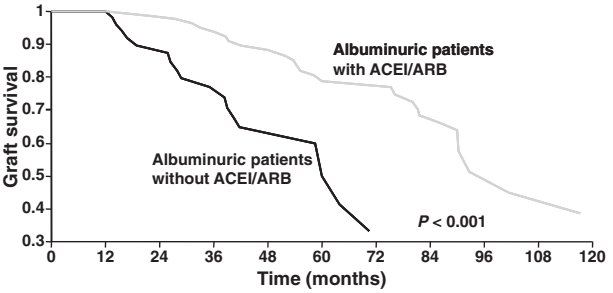

Figure 4 Kaplan–Meier estimates of the combined endpoint of kidney graft survival and death. In the subgroup of patients with albuminuria >30 mg/d, patients were stratified according to their antihypertensive therapy: long-term angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy (ACEI/ARB; $n = 84$, 26 events) versus controls (without ACEI/ARB; $n = 62$, 19 events). Statistical significance was indicated using the Breslow test.

plant patients [2]. Randomized, prospective trials for the definition of target blood pressure in kidney transplant recipients will probably never be conducted because of the limited number of patients. In this context, the SECRET trial, which investigated whether the ARB candesartan is superior to placebo in reducing graft failure and cardiovascular morbidity, has to be mentioned. However, candesartan was not beneficial. Of note, the observed event rate was far lower than expected, thereby reducing the significance of the study [15].

In our retrospective analysis, we divided patients into those who met the WHO/ISH criteria for the control of blood pressure and those who did not [16]. Although limited by its retrospective design, our data support that

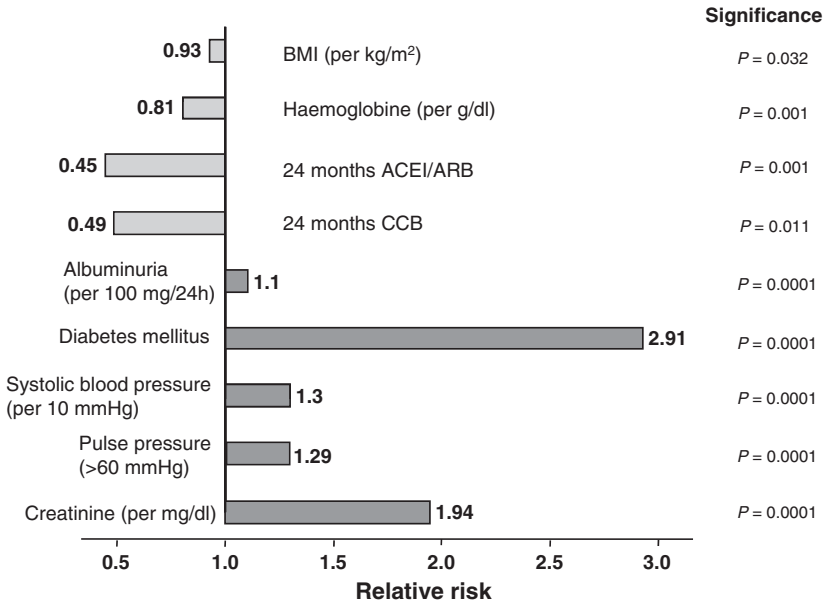

Figure 3 Cox proportional hazard analysis of factors influencing the primary endpoint of graft survival.

WHO/ISH criteria for blood pressure control should also be targeted in renal transplant recipients.

Data on the use of ACEI/ARB in diabetic and nondiabetic proteinuric kidney diseases are compelling regarding preservation of kidney function and patient survival [17–19]. With respect to the differences in pathogenesis between chronic graft failure and the progression of chronic renal insufficiency in native kidney disease, data obtained in the latter cannot be easily translated into kidney transplantation. Moreover, there are no randomized trials on the effect of long-term RAS inhibition in renal transplant recipients. Data derived from prospective short-term trials are equivocal [20–23].

In our patient cohort, long-term, i.e., >2 years, antihypertensive therapy with ACEI/ARB or CCB improved graft survival. Concerning the beneficial effect of ACEI/ARB therapy, our data are in line with observations by Heinze *et al.* They showed in a retrospective analysis of 2031 patients that therapy with ACEI/ARB improved patient and graft survival [11]. Contradicting data from the Collaborative Transplant Study presented by Opelz showed no benefit of this therapy in renal transplant recipients [12]. Of note, there are certain differences in the study design. Heinze *et al.* included patients as early as 3 months after transplantation, whereas Opelz included patients not before 1 year after transplantation. With regard to the results of Opelz, Heinze *et al.* speculated that the time point of inclusion of transplant recipients (i.e., 3 months vs. 1 year after transplantation) explains the difference [24]. Interestingly, in our study we used a protocol comparable with that of Opelz as we also included patients at 1 year after transplantation. However, our results are in line with data obtained by Heinze *et al.* Several studies revealed a favorable effect of short-term CCB treatment on graft function [13,25]. The effect might be caused by a reduction of calcineurin-inhibitor toxicity. Our data support these findings as long-term CCB treatment improved graft and patient survival in patients receiving calcineurin inhibitors.

Proteinuria is associated with poor graft survival [26]. Proteinuria >500 mg/day at 1 year after transplantation is frequently associated with glomerular pathology, indicating limited prognosis [27]. The MDRD and the REIN study strongly correlated proteinuria to a decline of renal function in diabetic and nondiabetic native kidney disease [25,28]. In nondiabetic kidney disease, combined blockade of the RAS with ACEI/ARB is superior to monotherapy independent of blood pressure, as shown by the COOPERATE Study [18]. However, very recently published data do not support this view. The ONTARGET study did not find a benefit for combined RAS blockade in a group at high risk for vascular events [14,29]. Data in kidney transplant recipients are incomplete. In our cohort, albuminuria was a strong independent risk factor for graft survival. Proteinuric patients with long-term ACEI/ARB therapy had an even greater benefit from this therapy than nonproteinuric renal transplant recipients.

In our patients, diabetes was an independent risk factor for graft survival. This is in accordance with work from other groups [30,31]. Long-term ACEI/ARB therapy profoundly improved graft survival in these patients, suggesting that the pathogenesis of diabetic nephropathy in the transplant setting is comparable with that in native kidneys.

Arterial stiffness, as determined by pulse pressure and pulse wave velocity, has been shown to be a strong predictor of cardiovascular outcome in different study populations [32–34]. Indeed, we could confirm in this study that pulse pressure was independently associated with graft survival.

Our data confirmed that acute rejection is associated with impaired graft survival [35]. The rejection rate within the first year was 40% in our patient cohort and appears to be rather high. Indeed, in the recently published ELITE-Symphony Study, rejection rates for a calcineurin inhibitor-based immunosuppressive therapy were 17–33% within the first year [36]. However, patients included in our study did not receive an IL-2Rα antibody, as was used in the ELITE-Symphony Study. This might explain the difference as IL-2Rα antibody induction therapy reduces the acute rejection rate [37].

Limitations of our study include the retrospective design. Patients were not randomized to therapy with different antihypertensive drugs. The medication was chosen at the discretion of the physicians of the transplant outpatient clinic. In the first line diuretics, beta blocking agents and CCB were used. The therapy with ACEI/ARB was started not before 3 months after transplantation. It was started preferably in diabetics and in proteinuric patients. However, over the years, physicians became more liberal in commencing ACEI/ARB therapy also in nonproteinuric and nondiabetic kidney transplant recipients. As shown in the results section, there were no differences in proteinuria and in serum-creatinine between long-term ACEI/ARB therapy and the alternatively treated diabetic and nondiabetic renal transplant recipients. This indicates that patients in the different strata were comparable. This is confirmed by the Cox hazard analysis, which showed that long-term ACEI/ARB therapy had an independent and positive effect on graft survival. Unfortunately, we did not analyze our data with respect to the smoking status.

In conclusion, our data show that blood pressure control in accordance with the WHO/ISH criteria improves graft survival. Our data support the view that in terms of graft survival, long-term treatment with ACEI/ARB is

superior to therapy with drugs from other classes. Proteinuria reduces graft survival and patients strongly benefit from long-term ACEI/ARB therapy. Of note, even in nonproteinuric patients, treatment with ACEI/ARB exerts a beneficial effect on graft survival. We confirm that diabetes is a potent risk factor for graft survival and that diabetics benefit from long-term ACEI/ARB therapy. In accordance with previous studies, calcineurin-inhibitor treated kidney transplant recipients benefit from CCB treatment. Our data support the need of rigorous blood pressure control and encourage the use of ACEI/ARB and CCB in the management of post-transplant hypertension.

Authorship

EB: designed study. UH and BMS: designed study and wrote the paper. UH, BMS, DL, SR, HP, MH and EB: performed study. KL: collected data. SA: analyzed data.

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