Angiotensin-Converting Enzyme Inhibitor or Angiotensin II Type 1 Receptor Antagonist Therapy Is Associated with Prolonged Patient and Graft Survival after Renal Transplantation

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Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II type 1 receptor blockers (ARB) reduce cardiovascular death in the general population, but data for renal transplant recipients remain elusive. Similarly, ACEI/ARB have been shown to reduce proteinuria, but data on graft survival are lacking. Therefore a retrospective open cohort study was conducted of 2031 patients who received their first renal allograft at the Medical University of Vienna between 1990 and 2003 and survived at least 3 mo. Patient and graft survival was compared between patients with *versus* without ACEI and/or ARB therapy. Data were analyzed with and without propensity score models for ACEI/ARB therapy. Medication and comorbidities were analyzed as time-dependent variables in the Cox regression analyses. Ten-year survival rates were 74% in the ACEI/ARB group but only 53% in the noACEI/ARB group ($P < 0.001$). The hazard ratio (HR) of ACEI/ARB use for mortality was 0.57 (95% confidence interval [CI] 0.40 to 0.81) compared with nonuse. Ten-year actual graft survival rate was 59% in ACEI/ARB patients but only 41% in nonusers ($P = 0.002$). The HR of actual graft failure for ACEI/ARB recipients was 0.55 (95% CI 0.43 to 0.70) compared with nonusers; the HR of functional graft survival was 0.56 (95% CI 0.40 to 0.78). Ten-year unadjusted functional graft survival rates were 76% among ACEI/ARB patients and 71% in noACEI/ARB recipients ($P = 0.57$). In summary, the use of ACEI/ARB therapy was associated with longer patient and graft survival after renal transplantation. More frequent use of these medications may reduce the high incidence of death and renal allograft failure in these patients.

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The effectiveness of angiotensin converting enzyme inhibitors (ACEI) or angiotensin II type 1 (AT1) receptor blockers (ARB) for primary and secondary prevention of cardiovascular (CV) outcomes has been documented in several trials of patients with high CV risk (1–3). No such data exist for renal transplant recipients because such patients were excluded from these studies. To extrapolate these trial results to kidney transplant recipients may not be appropriate. It was shown recently that some of the factors that are positively associated with CV risk in the general population, such as hypercholesterolemia, arterial hypertension, and elevated body mass index, are in fact negatively associated with CV events and overall mortality in patients who have ESRD and are treated by dialysis (4,5).

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Similarly, the effectiveness of ACEI and ARB on the progression of kidney disease has been documented in a variety of native kidney diseases and in transplant nephropathy (6–8). It remains unknown, however, whether these protective effects on GFR and proteinuria translate into prolonged transplant survival.

So far, only one randomized, controlled, multicenter trial was designed to address prospectively the effectiveness of ARB use on CV mortality and transplant survival in renal allograft recipients. Although as of 2003 all of the 700 planned patients in >30 centers had been enrolled and randomly assigned to either candesartan or placebo, the trial was stopped early because the observed event rate was only one quarter of the expected rate that was used for planning of the study. Thus, no statistically valid information is available on the utility of ARB to prolong patient or graft survival after renal transplantation (9).

To address this unresolved issue, we studied the association between ACEI and/or ARB use and patient and graft survival in the Austrian Dialysis and Transplant Registry. The United Network for Organ Sharing and the US Renal Data System databases cannot be used to answer these questions because data on medication use other than immunosuppressive therapy

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are not available for study. Austria exhibits a similar prevalence rate of patients with functioning renal transplants as the United States (approximately 400 per million population). Because of the liberal organ donation law, >90% of transplants are performed with kidneys from deceased donors.

Materials and Methods

Patient Population

The population of this retrospective study was defined by merging the OEsterreichisches Dialysis and Transplant Registry (OEDTR) and EUROTRANSPLANT databases with the Vienna Kidney Biopsy Registry. The OEDTR was established by the Austrian Society of Nephrology in 1970 and has almost complete follow-up; only 17 patients have been lost since 1990. The EUROTRANSPLANT database was established in 1968 and holds complete entries of organ donor characteristics from transplants that have been performed in the EUROTRANSPLANT region. The Vienna Kidney Biopsy Registry includes all native and transplant kidney biopsies of patients who have received a renal allograft at the Medical University of Vienna since 1990.

For the evaluation of patient and graft survival, we made use of data from all patients who received their first kidney transplant at the Medical University of Vienna between January 1, 1990, and December 31, 2003. This selection led to a sample of 2031 patients and an equal number of grafts, because only the first transplant was analyzed. Before 1990, almost no patient received treatment with an ACEI, and the first substantial use of ARB started in 1996.

Variables and Definitions of Variables

All variables that were recorded in the database are listed in Appendix 1. The variables that were available from the OEDTR database at the time of transplantation include recipient demographics; underlying renal disease; course of renal replacement therapy(ies); panel reactive antibodies (highest and latest); hepatitis B virus, hepatitis C virus, and cytomegalovirus serologies; immunosuppressive regimen; and immediate posttransplantation course. Available donor characteristics in the EUROTRANSPLANT registry include cold ischemia time; HLA mismatches in A, B, and DR; age; gender; cytomegalovirus serology; cause of death; last serum creatinine; and use of vasopressors during the intensive care unit stay. Hepatitis B virus– or hepatitis C virus–positive donors were not accepted. The Vienna Kidney Biopsy Registry contains standardized descriptions of renal histopathology for each performed biopsy.

The OEDTR annual follow-up data include patient and graft status, transplant function, comorbidities (categorized into diabetes, CV disease, liver, lung, hypertension, malignancies), immunosuppressive therapy, and clinical chemistry laboratory values and biopsy results. Information on prescription drugs other than immunosuppressive regimen is not included in any of these registries but was retrieved either from the databases of the few general public Austrian Sickness Funds or by direct data entry from charts. Information on prescriptions filled can be assumed to be nearly complete, because insurance coverage through the public Sickness Fund is mandatory, and prescription drugs are available to all beneficiaries at a small dispensing fee.

Arterial hypertension was defined as mean arterial BP of >107 mmHg or at least one antihypertensive drug in >50% of the time at risk. Patients were classified as having coronary heart disease when they had unstable angina or a myocardial infarction or when coronary stenosis was documented by angiography or radioisotopic technique. Heart failure, vascular disease, and diabetes status were defined on physicians' discretion.

Delayed graft function (DGF) was defined either as dialysis dependency in the first week after engraftment or when the median calculated creatinine clearance of all seven creatinine readings in the first week was below <13 ml/min. The Modification of Diet in Renal Disease method was used to estimate creatinine clearance because it has been shown that values that are derived by this formula correlate better than other available equations with true GFR in transplant recipients (10,11).

Biopsy-confirmed acute rejection (BCAR) and chronic allograft nephropathy (CAN) were defined according to Banff 93 and 97 criteria, respectively (12,13). A total of 3546 biopsies were obtained within the study period. Banff criteria were initially not applied to 248 biopsies that were performed before January 1, 1994. These biopsies were reclassified according to the Banff 97 criteria by one of the investigators (H.R.). BCAR was defined as Banff borderline and higher grades/types of cellular rejection. Diagnosis and grading of lesions of native kidney biopsies and of the donor kidney before transplantation were performed according to the World Health Organization classification (14). Proteinuria was recorded as numerical variable in milligrams per day and derived annually from 24-h urine collections. For further analysis, proteinuria was categorized according to clinical standards into three groups: <500, 500 to 3500, and >3500 mg/d.

Immunosuppressive regimens were classified into four groups: (*1*) The standard immunosuppressive regimen was defined as triple therapy with corticosteroids, mycophenolate mofetil, and a calcineurin inhibitor (CNI); (*2*) triple therapy with corticosteroids, azathioprine, and cyclosporine; (*3*) all corticosteroid-free regimens; and (*4*) CNI-free immunosuppression or other. Induction therapy with a polyclonal antibody was performed in 378 (16.8%) patients; IL-2 antibody induction was used very infrequently (<1%) and thus was analyzed together with the polyclonals.

Outcomes

Patient survival time was defined as the time from first kidney transplantation until death or study termination. Patients who survived <3 mo were treated as censored and did not contribute any information in the survival analysis.

Graft loss was defined as permanent return to dialysis or retransplantation or death. Graft loss before 90 d from transplantation was treated as censored. For the calculation of functional graft survival, patients who died with functioning grafts were censored.

Statistical Analyses

Patient characteristics were compared between groups that were defined by ACEI/ARB use (ACEI/ARB, ever used; noACEI/ARB, never used). Continuous variables are presented as mean and SD or as median and interquartile range (IQR) and compared between groups using two-sample t test. Categorical variables are presented as counts (proportions) and are compared using χ^2 tests. Cox proportional hazards regression models were used to assess the association of ACEI/ARB use and patient survival and graft survival, respectively (15). ACEI/ARB use was analyzed as a time-dependent variable (16). Survival curves were graphically compared between the patient groups defined above using the method of Kaplan and Meier (17). The P values shown in the Kaplan-Meier plots refer to log rank.

Potential confounders that were considered in the analysis of patient survival were year of first renal replacement therapy, cumulative time on dialysis, cumulative transplantation number, recipient age, body weight, and GFR. Furthermore, diabetes status, vascular disease, heart disease, hemoglobin, cholesterol, and number of antihypertensive drugs entered the analysis as time-dependent variables. We did not include erythropoietin and statin therapy in our analysis because this

would have led to colinearity with hemoglobin and cholesterol. In the analysis of graft survival, we considered as potential confounders DGF; panel reactive antibodies at time of transplantation; HLA mismatch; donor age; BCAR; CAN; and the time-dependent variables diabetes status, vascular disease, heart disease, proteinuria, hemoglobin, cholesterol, number of antihypertensive drugs, oral antidiabetic medication, insulin, and immunosuppressive regimen. Because a Cox model involving longitudinal measurements of continuous covariates requires precise measurements of those covariates at each event time, we aggregated proteinuria, hemoglobin, and cholesterol before entering further analysis by computing the patient-specific medians per calendar year.

We chose four different approaches to adjust the association between ACEI/ARB use and patient and graft survival for potential confounders. First, we addressed confounding of ACEI/ARB use by clinical indication by means of propensity score analysis. Propensity scores were computed using logistic regression of ACEI/ARB use on all potential confounders (18). Because ACEI/ARB use and most confounders are time-dependent variables, we used all longitudinal observations of each patient, weighting observations proportionally to the period for which ACEI/ARB use and covariates remained unchanged. The estimated propensity scores then were categorized into quintiles, which were used to stratify Cox regression analysis. Second, the propensity score was entered into the Cox model as a time-dependent continuous covariate. Third, we built an "experience-based" multivariable model that included variables that we considered clinically relevant. Fourth, we defined a variable as a confounder when its inclusion in the univariate model involving only ACEI/ARB use changed the hazard ratio (HR) of ACEI/ARB by >10% (19).

We checked for interactions between the effect of ACEI/ARB use and of proteinuria and CAN on graft survival and for interactions between the effects of ACEI/ARB use and of time of first renal replacement therapy, diabetes status, CV comorbidity, and number of transplants on patient survival. For continuous independent variables, the linearity of their relationship with the log hazard was assessed by graphical inspection of martingale residuals. The assumption of proportional hazards for the covariates was tested formally by calculating the slope of the scaled Schoenfeld residuals on time. Statistical analysis was conducted using the SAS for Windows software, version 9.1.3 (SAS Institute, Inc., Cary, NC).

Results

The characteristics of the study population are listed in Table 1. A total of 2031 patients received 2031 first renal transplants and 197 retransplants within the study period of 14 yr. Analyzing ACEI/ARB according to the duration of actual use resulted in a U-shaped distribution histogram. Because 781 (38.5% of total) patients never received ACEI/ARB therapy and 638 (31.4%) patients used ACEI/ARB during the entire follow-up, only 612 (30.1%) received this therapy during various times of follow-up. Thus, we decided to dichotomize ACEI/ARB use for Table 1 and for the graphical display of Kaplan-Meier survival analysis into those who never used ACEI/ARB and in those who ever received ACEI/ARB. *P* values are independent of this dichotomization because ACEI/ARB use entered all survival analyses as time-dependent variable. The median duration of ACEI/ARB intake was 3.5 yr.

The prevalence of ACEI use at the beginning of the study in 1990 was 9% and increased continuously to roughly 47% in 2003. Accordingly, substantial ARB use started in 1997 and reached approximately 18% of all patients who received a graft in late 2003. Variables that significantly predicted the use of ACEI/ARB in the propensity score model are provided in Table 2. A standard immunosuppressive regimen was used in 18.7% of functional graft life; steroid-free immunosuppression in 18.5%, triple therapy with corticosteroids, azathioprine, and cyclosporine in 25.8%; and others in 37.0%. The "others" group consisted of other CNI-based or CNI-free protocols with or without mammalian target of rapamycin (mTOR) antagonists. mTOR antagonists were used in 0.9% of total graft survival times.

The ACEI/ARB group consisted of significantly older recipients of older donor organs than the noACEI/ARB group. Patients with type 2 diabetes or CV disease were more likely to receive ACEI/ARB treatment, possibly introducing confounding by indication. Furthermore, the incidence of arterial hypertension and the number of antihypertensive drugs used were higher in the ACEI/ARB group compared with the noACEI/ARB group. Systolic and diastolic BP, however, were equally controlled and not different in both groups.

Patient Survival

Median survival time was longer than the study period of 14 yr (25th percentile 7.9 yr). Of 1892 patients who were still under observation after 90 d from transplantation, a total of 414 patients died after 90 d from transplantation and within the 14 yr of study, 185 in the ACEI/ARB and 229 in the noACEI/ARB group. Ten-year survival rates were 74% in ACEI/ARB users but only 53% in noACEI/ARB recipients (Figure 1). The main causes of death were CV events (37.7% of all deaths) followed by infection (30.1% of all deaths) and malignancies (9.8% of all deaths).

The HR comparing ACEI/ARB users with nonusers were almost identical in all four different strategies of analysis performed. When using quintiles of propensity scores as strata in the Cox proportional hazard model, the HR for death was 0.62 (95% confidence interval [CI] 0.48 to 0.79). When the propensity score was included as a continuous variable into the Cox model, the HR remained unchanged at 0.63 (95% CI 0.49 to 0.81). The overall fit of the propensity score model was good, as evidenced by the C-index of 0.84. The experience-based multivariable model, which included only the clinically most relevant variables, revealed an HR of 0.57 (95% CI 0.40 to 0.81) for death (Table 3). The HR of death that was caused by CV events was 0.67 (95% CI 0.48 to 0.93). Strong predictors of death were recipient age, cumulative time on dialysis, and type 2 diabetes. Conversely, the number of consecutive transplants was not associated with an increased risk for death.

The variables that indicated cerebrovascular and peripheral vascular disease, heart diseases, cholesterol, hemoglobin, and number of antihypertensive drugs were identified as confounders and therefore included in a multivariable Cox model (Table 3). The HR of ACEI/ARB even decreased slightly to 0.58 (95% CI 0.38 to 0.88) in this model, suggesting a more pronounced protective effect. Most of the confounding variables that represented comorbidities were associated with a higher risk for mortality. Serum cholesterol was inversely associated with

Table 1. Characteristics of all patients and categorization into ACEI/ARB use[a]

Characteristics	*n*	All	ACEI/ARB	noACEI/ARB	*P* Value
No. of patients in analysis	2031	2031	1250 (61.5%)	781 (38.5%)	
Cumulative transplant numbers 1/2/3/4	2031	2031 (91.2%)	1250 (90.6%)	781 (92.1%)	0.20
		175 (7.9%)	119 (8.6%)	56 (6.6%)	
		19 (0.9%)	10 (0.7%)	9 (1.1%)	
		3 (0.1%)	1 (0.1%)	2 (0.2%)	
Patient years at risk[b]	2031	11048	7366	3682	
Median (1st, 3rd quartiles) years of follow-up	2031	6.0 (2.6, 10.0)	6.0 (3.0, 9.9)	6.2 (1.6, 10.1)	
No. died/censored within 90 d after transplantation	2031	77/62	16/28	61/34	
No. died after 90 d	1892	414 (21.8%)	185 (15.3%)	229 (33.3%)	<0.001[c]
No. of grafts[d]	2031	2031	1190	841	
Total graft years at risk	2031	9618	6254	3364	
Median (1st, 3rd quartiles) graft years at risk	2031	5.2 (2.1, 9.3)	5.4 (2.7, 9.4)	5.6 (1.0, 9.7)	
No. of graft failures/censored within 90 d	2031	164/61	46/27	118/34	
No. of graft failures after 90 d	1806	543 (30.1%)	253 (22.6%)	290 (42.1%)	0.002[c]
Median (1st, 3rd quartiles) years of ACEI/ARB intake	2031	—	3.5 (1.6, 6.0)	—	
Mean (SD) donor age (yr)	1964	43.2 (16.1)	43.9 (15.9)	42.1 (16.3)	0.011
Donor female gender (%)	1970	799 (40.6%)	473 (41.1%)	326 (39.9%)	0.59
Mean (SD) recipient age at transplantation (yr)	2031	48.4 (15.4)	49.1 (14.2)	47.3 (17.0)	0.012
Recipient female gender (%)	2031	805 (39.6%)	450 (37.8%)	355 (42.2%)	0.046
Mean (SD) recipient body weight (kg)	1531	73.1 (16.9)	75.0 (15.3)	67.6 (19.2)	<0.001
Median (1st, 3rd quartiles) panel reactive antibodies at transplantation (%)	2031	0 (0, 4)	0 (0, 4)	0 (0, 4)	0.33
Mean (SD) sum of HLA mismatches	2031	2.46 (1.31)	2.47 (1.33)	2.45 (1.28)	0.73
Type 1 diabetes (%)	2018	27 (1.3%)	14 (1.1%)	13 (1.7%)	0.29
Type 2 diabetes (%)	2018	437 (21.7%)	303 (24.4%)	134 (17.3%)	<0.001
Arterial hypertension (%)[e]	2031	1701 (83.8%)	1175 (94.0%)	526 (67.4%)	<0.001
DGF (%)	1898	436 (23.0%)	259 (23.0%)	177 (22.9%)	0.97
Grafts with at least one BCAR (%)	2031	648 (31.9%)	425 (35.7%)	223 (26.5%)	<0.001
CNI-based immunosuppression (%)	2031	1755 (86.4%)	1098 (87.8%)	657 (84.1%)	0.017
No. of antihypertensive drugs (median [quartiles])[f]	2031	2.0 (1, 3)	2.8 (1.9, 3.7)	1 (0, 2)	<0.001
Mean (SD) systolic BP (mmHg)[f]	1476	138.3 (21.9)	137.8 (14.0)	139.3 (32.9)	0.35
Mean (SD) diastolic BP (mmHg)[f]	1476	80.8 (12.6)	80.8 (13.7)	80.7 (9.7)	0.85
Patient years with heart disease	2018	2059	1561	498	
Patient years with vascular disease	2018	1279	1001	278	

[a]ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II type 1 receptor blockers; BCAR, biopsy confirmed acute rejection; CNI, calcineurin inhibitor; DGF, delayed graft function.
[b]Inclusion criterion for patient survival: Date of first transplant from 1990 onward.
[c]Log-rank test.
[d]Numbers are different from the first two lines in the table because 60 patients did not receive ACEI/ARB during their first transplant but thereafter (used for analysis of patient survival).
[e]Defined as mean arterial pressure >107 mmHg or at least one antihypertensive drug in >50% of the time at risk.
[f]Averaged per patient.

mortality. This risk factor paradox has been described before in patients who had renal failure and were treated by hemodialysis (4).

Interaction analysis did not reveal any statistically significant effect of the variables, time of first renal replacement therapy, diabetes status, and number of transplants on the HR of ACEI/ARB. The assumption of proportional hazards for the covariates was not violated in any of the Cox models as evidenced by the nonsignificant slope in a generalized linear regression of the scaled Schoenfeld residuals on time. When the analysis was limited to those with a functioning graft at 1 yr ($n = 1717$), the results for patient and graft survival were maternally unchanged (data not shown).

Graft Survival

The 2031 first-time transplants that were entered in the analysis of graft survival comprised a total of 9618 graft years at risk with a median time at risk of 5.2 yr (IQR 2.1 to 9.3). Median graft survival was 6.4 yr (IQR 3.1 to 10.0). Functional graft survival (censored for death) is graphically compared between

Table 2. Covariables that significantly predicted the use of ACEI/ARB in the multivariable logistic regression analysis (propensity score model)[a]

Variable	Risk Ratio	95% CI	*P* Value
No. of antihypertensive drugs	2.86	2.62 to 3.12	<0.001
Year of first renal replacement therapy	1.06	1.02 to 1.10	0.002
Transplant numbers	0.61	0.42 to 0.89	0.011
Insulin use	1.93	1.09 to 3.41	0.024
GFR ≤ 15 *versus* GFR > 30 ml/min	0.65	0.45 to 0.94	0.021
Donor age	0.99	0.98 to 1.00	0.034
Proteinuria > 3500 *versus* < 500 mg/d	1.49	1.01 to 2.21	0.046

[a]CI, confidence interval.

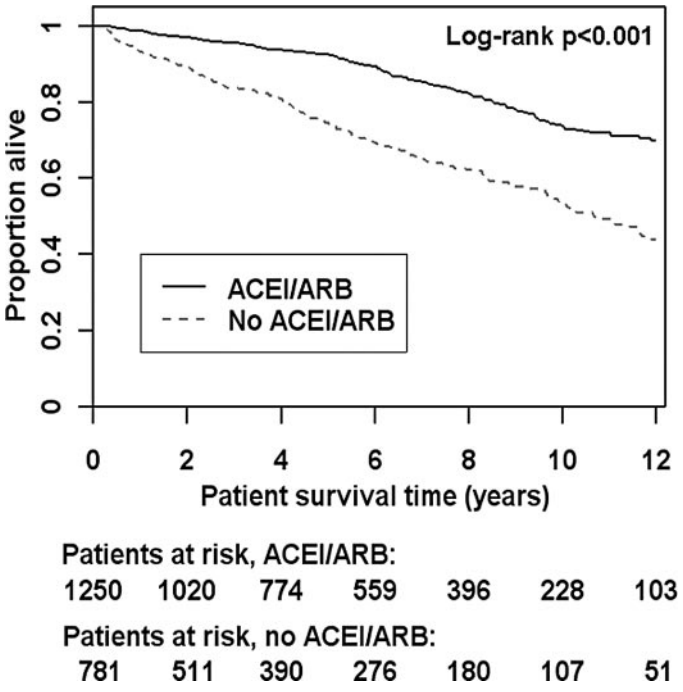

Figure 1. Kaplan-Meier estimates of patient survival. Angiotensin-converting enzyme inhibitors/angiotensin II type 1 receptor blockers (ACEI/ARB) users lived significantly longer compared with noACEI/ARB patients (log rank: $P < 0.001$).

ACEI/ARB and noACEI/ARB users in Figure 2. ACEI/ARB users experienced fewer graft losses than noACEI/ARB users, mainly at the beginning of follow-up. Ten-year functional graft survival rates were 76% in ACEI/ARB users and 71% in noACEI/ARB users. When death was counted as an event, actual graft survival was significantly longer in patients with ACEI/ARB therapy (Figure 3). Of 1806 graft periods that exceeded 90 d of observation, 253 failed in 1117 ACEI/ARB-treated patients and 290 in 689 noACEI/ARB patients. The 10-year graft survival rates were 59% among ACEI/ARB users and 41% among noACEI/ARB recipients.

The HR for functional graft survival (death censored) was 0.56 (95% CI 0.40 to 0.78) in the Cox model with covariables selected on the basis of clinical experience, 0.49 (95% CI 0.33 to 0.73) in the confounder model, 0.58 (95% CI 0.47 to 0.72) in the stratified propensity score model, and 0.57 (95% CI 0.46 to 0.71) in the model with continuous entry of propensity scores.

In the analysis of actual graft survival (counting death as event) using a Cox model stratified for quintiles of propensity scores, the HR for graft loss was 0.58 (95% CI 0.47 to 0.72) in the ACEI/ARB compared with never users. The HR was identical when the propensity score was included as a numerical variable into the model (HR 0.57; 95% CI 0.46 to 0.71). The fit of the propensity score model was adequate as confirmed by the C-index of 0.85. Similar as in the patient survival analysis, parameter estimates of effect and HR of ACEI/ARB use remained almost identical regardless of the type of analysis.

The multivariable model that consisted of variables that were based on clinical transplant expertise revealed an HR of 0.55 (95% CI 0.43 to 0.70) for ACEI/ARB and actual graft failure (Table 4). The number of antihypertensive drugs, a proxy for the severity of arterial hypertension, was highly associated with graft malfunction as were CAN and proteinuria. Donor age, diabetes status, and "other immunosuppression" could be confirmed to be independent predictors of graft failure only when BCAR, CAN, and the time-dependent variable proteinuria were removed from the model (data not shown). The use of polyclonal induction therapy was not significantly associated with graft survival in a multivariable model that was adjusted for immunologic risk for graft failure. The multivariable model that was built with the identified confounders, number of antihypertensive drugs, heart and vascular disease, serum cholesterol, and hemoglobin again showed similar results (Table 4). The HR for actual graft failure was 0.51 (95% CI 0.37 to 0.72) in ACEI/ARB users compared with nonusers. The number of antihypertensive drugs and lower level of hemoglobin were highly associated with adverse outcome. Analysis of interactions between ACEI/ARB effect and the clinically plausible other variables such as DGF, CAN, and proteinuria failed to show any significance when the entire graft lifetime was considered. In the subgroup of 257 patients with biopsy-confirmed CAN, 104 grafts subsequently lost their function within the follow-up period. Biopsies that revealed CAN were performed at a median of 3.1 yr after transplantation. The

Table 3. Associations of ACEI/ARB use and patient death[a]

Variable	HR	95% CI	*P* Value
Multivariable model based on clinical expertise			
ACEI/ARB	0.57	0.40 to 0.81	0.002
no. of antihypertensive drugs	1.10	1.00 to 1.24	0.10
cumulative time on dialysis (per year)	1.13	1.04 to 1.24	0.006
recipient age at transplantation (per decade)	1.75	1.54 to 1.99	<0.001
year of first renal replacement therapy	1.05	1.00 to 1.11	0.075
transplant numbers	0.82	0.55 to 1.22	0.32
type 1 diabetes	1.46	0.36 to 5.97	0.61
type 2 diabetes	1.50	1.07 to 2.11	<0.018
$15 < GFR \leq 30$ *versus* $GFR > 30$ ml/min	2.92	2.08 to 4.10	<0.001
$GFR \leq 15$ *versus* $GFR > 30$ ml/min	6.00	4.15 to 8.68	<0.001
Multivariable model adjusted for variables identified as confounders			
ACEI/ARB	0.58	0.38 to 0.88	0.011
no. of antihypertensive drugs	1.09	0.95 to 1.25	0.23
cerebrovascular disease	2.05	1.36 to 3.08	<0.001
peripheral vascular disease	2.06	1.40 to 3.04	<0.001
coronary heart disease	2.70	1.77 to 4.10	<0.001
heart failure	1.63	0.94 to 2.83	0.082
cholesterol (per 10 mg/dl)	0.93	0.90 to 0.96	<0.001
hemoglobin (per g/dl)	0.82	0.76 to 0.89	<0.001

[a]Variables were included on the basis of clinical experience or when identified as confounders. Predicting variables with the exception of recipient age and year of first renal replacement therapy were used as time-dependent covariates in the Cox regression analysis. HR, hazard ratio.

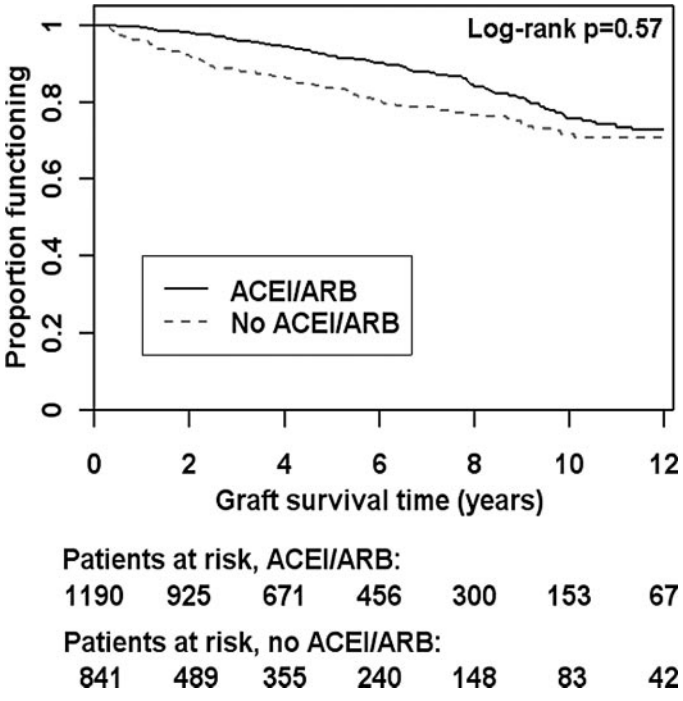

Figure 2. Kaplan-Meier estimates of functional (death censored) graft survival (log rank: $P = 0.57$).

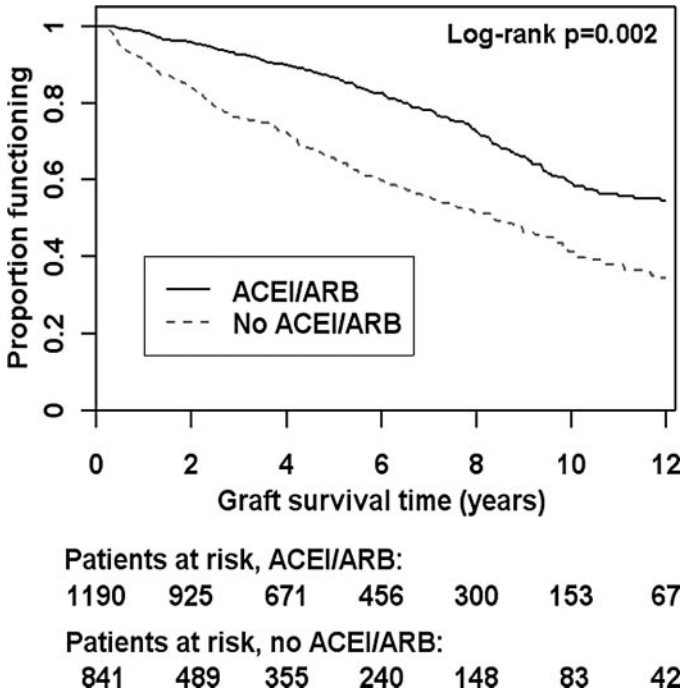

Figure 3. Kaplan-Meier estimates of actual graft survival counting death as event. ACEI/ARB therapy was associated with longer graft survival (log-rank: $P = 0.002$).

Table 4. Associations of ACEI/ARB use and graft failure[a]

Variable	HR	95% CI	*P* Value
Multivariable model based on clinical expertise			
ACEI/ARB	0.55	0.43 to 0.70	<0.001
no. of antihypertensive drugs	1.24	1.14 to 1.35	<0.001
donor age (per decade)	1.07	1.00 to 1.14	0.054
type 1 diabetes	3.37	1.71 to 6.61	<0.001
type 2 diabetes	1.24	0.95 to 1.62	0.11
IS (S + AZA + CSA) *versus* SIS[b]	0.84	0.59 to 1.18	0.30
IS (steroid-free) *versus* SIS	0.69	0.46 to 1.03	0.07
other IS *versus* SIS	1.19	0.88 to 1.59	0.26
BCAR	1.13	0.90 to 1.42	0.31
proteinuria between 500 and 3500 *versus* <500 mg/d	1.68	1.32 to 2.13	<0.001
proteinuria > 3500 *versus* <500 mg/d	1.92	1.42 to 2.60	<0.001
CAN	1.38	1.08 to 1.77	0.011
Multivariable model adjusted for variables identified as confounders			
ACEI/ARB	0.51	0.37 to 0.72	<0.001
no. of antihypertensive drugs	1.25	1.11 to 1.39	<0.001
cerebrovascular disease	1.56	1.05 to 2.30	0.026
peripheral vascular disease	1.81	1.27 to 2.59	0.001
coronary heart disease	1.15	0.80 to 1.64	0.44
heart failure	1.41	0.92 to 2.18	0.12
cholesterol (per 10 mg/dl)	1.00	0.98 to 1.02	0.98
hemoglobin (per 1g/dl)	0.71	0.67 to 0.75	<0.001

[a]Variables were included on the basis of clinical experience or when identified as confounders. All predicting variables with the exception of donor age, BCAR, and CAN were used as time-dependent covariates in the Cox regression analysis. CAN, chronic allograft nephropathy; AZA, azathioprine; CsA, cyclosporin A; MMF, mycophenolate mofetil.

[b]Standard immunosuppression (SIS) is S + MMF + CSA; other IS include CNI-based as well as CNI-free regimen with or without mammalian target of rapamycin (mTOR) antagonists.

Table 5. Summary of analyses

Model (No. of Patients in Analysis)	HR	95% CI	*P* Value
Patient death			
propensity score, stratified by quintiles (n = 2031; 414 events)	0.63	0.49 to 0.81	<0.001
propensity score, as numerical covariable (n = 2031; 414 events)	0.62	0.48 to 0.79	<0.001
clinical expertise model (n = 1631; n = 187 events)	0.57	0.40 to 0.81	0.002
confounder model (n = 915; 139 events)	0.58	0.38 to 0.88	0.011
Actual graft failure			
propensity score, stratified by quintiles (n = 2031; 543 events)	0.58	0.47 to 0.72	<0.001
propensity score, as numerical covariable (n = 2031; 543 events)	0.57	0.46 to 0.71	<0.001
clinical expertise model (n = 1311; 306 events)	0.55	0.43 to 0.70	<0.001
confounder model (n = 882; 204 events)	0.51	0.37 to 0.72	<0.001
Functional graft failure			
propensity score, stratified by quintiles (n = 2031; 246 events)	0.58	0.47 to 0.72	<0.001
propensity score, as numerical covariable (n = 2031; 246 events)	0.57	0.46 to 0.71	<0.001
clinical expertise model (n = 1384; 198 events)	0.56	0.40 to 0.78	<0.001
confounder model (n = 938; 142 events)	0.49	0.33 to 0.73	<0.001

ACEI/ARB-treated patients exhibited a longer remaining median graft survival compared with patients without ACEI/ARB treatment (4.6 *versus* 2.7 yr; $P = 0.002$).

The effect of ACEI/ARB on actual graft survival was relatively constant over time as evidenced by the analysis of Schoenfeld residuals, which did not show any interaction with time after transplantation ($P = 0.68$). Table 5 provides a results summary of patients and graft survival derived by the four Cox regression models.

Discussion

In this article, we showed that use of ACEI/ARB medication in renal transplant recipients is associated with improved patient and graft survival. The results were robust regardless of the analytical strategy chosen: HR and 95% CI were almost identical in all four sets of regression models. However, there are some limitations of our study. First, no causal inference can be drawn from this nonrandomized trial. Second, the pathophysiology behind the beneficial effect of ACEI/ARB on patient and graft survival cannot be elucidated from this cohort study. It may be hypothesized that similar to other clinical conditions that are associated with activation of the renin-angiotensin system and high vascular risk, the improvement of endothelial dysfunction by increased nitric oxide bioavailability and amelioration of neurohumoral activation may contribute partly to the observed effect (20). Furthermore, this class of agents exhibits beneficial effects on arterial stiffness independent of their antihypertensive potency (21). These may be explanations for why patients with ACEI/ARB therapy exhibited a reduced risk for CV death in our study. Inhibition of the renin-angiotensin system by ACEI or ARB has also been shown to reduce the risk for major atherosclerotic events such as myocardial infarction or stroke or CV death in nontransplant patients with vascular disease, especially in patients with diabetes and arterial hypertension (3,22–25). The analysis of patients with CV death and diabetes in our study did not suggest the presence of effect modification by ACEI/ARB, which may be attributable to limited power for performing this subgroup analysis.

Part of the effect of ACEI/ARB therapy on graft survival may be due to blockade of recently discovered AT1 receptor antibodies that are associated with therapy refractory vascular rejection in renal transplant recipients (26). Furthermore, AT1 receptors mediate inflammation and are involved in the profibrotic action exhibited by potent cytokines. Angiotensin II is also synthesized by the proximal renal tubule cells and exhibits powerful hemodynamic and nonhemodynamic effects, all implicated in the progression of chronic kidney disease (27).

In renal transplant recipients, only one randomized, controlled, multicenter trial was designed to investigate the effect of ARB on patient and graft survival. This international trial with the acronym SECRET (Study on Evaluation of Candesartan after REnal Transplantation) was started in 2000 but stopped after all patients had been enrolled and followed up for a median of 23 mo, because the observed event rate was substantially lower than originally expected.

A recent retrospective study by Tutone *et al.* (28) investigated the association of BP and patient and graft survival in 622 kidney transplant recipients. The authors also reported ACEI use to be associated with prolonged patient and graft survival, but this statement is not supported by their statistical evaluation. The authors' statement is based on the fact that although no difference was found in patient and graft survival between ACEI users and nonusers, patients who received ACEI were older and exhibited higher BP. It is of note that only 11% of the study population was receiving ACEI, and no statistical adjustment for comorbidities other than diabetes status was performed. Furthermore, medications other than antihypertensive therapy were not reported, and transplant kidney biopsy findings such as acute rejection and CAN were not included in the analysis.

Other authors found ACEI/ARB therapy effective in preventing deterioration of renal function in advanced transplant failure. The main cause of late graft loss is CAN. The pathophysiology of this entity is not well characterized, but it is assumed that many alloantigen-dependent and alloantigen-independent mechanisms contribute to it. The diagnosis of CAN is made on transplant biopsies and classified histologically. The functional consequence of CAN is usually deteriorating renal transplant function. Artz *et al.* (29) recently published a small cohort study on the effect of ACEI/ARB in patients with established CAN. The grafts of the 23 patients who were treated with ACEI/ARB survived significantly longer than those of recipients without this medication. The median graft survival in the ACEI/ARB group was roughly 6.5 yr but only 2 yr in patients without that medication. Accordingly, grafts with biopsy-confirmed CAN remained functional only for 2.7 yr in the noACEI/ARB group but functioned for 4.6 yr in the ACEI/ARB group in our analysis.

Proteinuria that results from transplant glomerulopathy, one of the hallmarks of CAN, is another functional consequence of CAN. In our analysis, proteinuria was highly associated with graft failure. Several small and mostly uncontrolled studies showed that ACEI/ARB exhibit antiproteinuric activity (30–32). It is unclear, however, whether the antiproteinuric effect is indeed independent of the antihypertensive effect (33,34). We did not observe an interaction of proteinuria and ACEI/ARB use, suggesting that the effect of ACEI/ARB on graft survival is equal in patients without and with proteinuria. It was shown previously that residual proteinuria in ACEI/ARB-treated patients is an equal risk factor for progression of renal disease as comparable grade proteinuria in untreated patients (35).

Conclusion

Our data suggest that ACEI/ARB therapy may be an important part of the polypharmacologic intervention aimed at reducing the high mortality among renal transplant recipients and at improving transplant survival. However, the causal relationship of the reported findings needs to be tested in a randomized, controlled trial.

Appendix 1. List of all variables in the database used for analysis

Variable Category	Variables
Patient demographics	Gender
	Date of birth
	Code of the referral dialysis center
	Diagnosis of native renal disease
	Date of first renal replacement therapy
	Date last seen
	Date of death
	Cause of death
Renal histology	Biopsy reading of native kidney disease
	Donor kidney biopsy (obtained before engraftment)
	Follow-up biopsies
Transplantation	Date of transplantation(s)
	Date of graft failure(s)
	Donor source (cadaveric, living related/unrelated) and EUROTRANSPLANT country
	Donor age
	Donor gender
	HLA mismatches in A, B, DR
	Cold ischemic time
	Panel reactive antibodies max, latest
	CMV serology donor and recipient
	DGF/dialysis
	BCAR/CAN
	Treatment of rejection (steroid pulse/polyclonals)
Medication (annually)	Immunosuppressive induction therapy
	Maintenance immunosuppression
	Antihypertensive drugs and category (calcium channel blocker, β/α blocker, ACEI/ARB, diuretics, vasodilators, else)
	Statins
	Erythropoietin(s)
	Oral antidiabetics
	Insulin
Comorbidities (annually)	Diabetes (0 to 2)
	0...type 1, 1...type 2, 2...else
	Malignancy (0–3)
	0...no, 1...solid TU (and location), 2...PTLD, 3...else
	Liver (0 to 3)
	0...no, 1...alcohol, 2 viral, 3...else
	Lung (0,1)
	0...no, 1...COPD
	Heart (0 to 3)
	0 ... no, 1...CHD, 2...CMP, 3...else
	Vascular (0 to 3)
	0...no, 1...cerebral, 2...peripheral, 3...else
	BP (systolic/diastolic)
	HBV/HCV/CMV serology
	Body weight
Laboratory (annually)	Creatinine, BUN, sodium, potassium, phosphate, glucose, HbA_{1c}, ASAT, ALAT, total protein, albumin, CRP, cholesterol, iPTH, hemoglobin, hematocrit, proteinuria, microalbuminuria

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This study establishes a benefit for ACE inhibitors and/or angiotensin receptor blockers in prolonging both patient and graft survival after renal transplantation. It is related to a paper by Müller and Luft in this month's *CJASN*, which postulates a similar or greater effect on target organ damage of an agent that directly inhibits renin (pages 221–228).