

## Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in renal transplantation between 1990 and 2002 in Spain

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### Abstract

**Background.** Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II type 1 receptor blockers (ARB) decrease cardiovascular mortality and slow the progression of renal disease in non-transplant patients, but their impact on kidney transplant outcome has not been well established.

**Methods.** Patients receiving a renal allograft in Spain in 1990, 1994, 1998 and 2002 were considered for the present study. Only adult ( $\geq 18$  years) recipients of a single kidney transplant functioning at the end of the first year were considered. A total of 4842 patients with clinical data about ACEI/ARB therapy were included.

**Results.** During the initial 2 years after transplant, ACEI/ARB were less frequently used in the 1990 and 1994 cohorts than in 1998 and 2002 (15.1%, 24.6%, 33.5% and 45.1%, respectively;  $P < 0.001$ ). During the first year, a total of 1063 patients (22.8%) received ACEI/ARB treatment, and graft survival (50.0% for treated patients and 51.4% for untreated,  $P = \text{ns}$ ), death-censored graft survival (60.6% versus 63.5%,  $P = \text{ns}$ ) and patient survival (68.8% versus 66.6%,  $P = \text{ns}$ ) were not different. During the initial 2 years, 1472 patients (31.4%) received treatment with ACEI/ARB, and graft survival tended to be higher in treated patients (54.4% and 50.9%,  $P = 0.063$ ). Since there was an interaction between ACEI/ARB treatment and year of transplant, graft survival was analysed in each cohort. Cox regression analysis including the propensity score for ACEI/ARB treatment showed an association between ACEI/ARB treatment and graft survival in the 2002 cohort (relative risk 0.36 and 95% confidence interval 0.17–0.75,  $P = 0.007$ ). Death-censored graft survival (63.8% versus 63.1%,  $P = \text{ns}$ ) and patient survival (68.1% and 66.5%,  $P = \text{ns}$ ) were not significantly different.

**Conclusions.** The use of ACEI/ARB during the initial 2 years after transplantation was associated with a better graft survival, but this effect was only observed in the 2002 cohort.

**Keywords:** angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; graft survival; renal transplantation

### Introduction

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II type 1 receptor blockers (ARB) decrease cardiovascular mortality, reduce proteinuria and delay progression to end-stage renal failure in native kidneys [1–3]. Trials using ACEI or ARB in renal transplant recipients to study their potential benefit on graft function are limited, and until now there has been only one systematic review [4]. Taking into consideration the better understanding of the mechanisms leading to chronic renal allograft dysfunction and the better understanding of the systemic and intrarenal effects of ACEI/ARB [5], it has been suggested that these medications may also prolong renal allograft survival [6–9]. However, these advantages should be balanced with an increased prevalence of side effects such as anaemia, decreased glomerular filtration rate and hyperkalaemia [4, 10] that may limit the effectiveness of these drugs in the kidney transplant population.

In the present study, we evaluate the association between ACEI/ARB treatment and graft and patient outcome in patients transplanted in 1990, 1994, 1998 and 2002 in Spain.

**Table 1.** Treatment with ACEI/ARB by year of transplantation

ACEI/ARB	1990 N (%)	1994 N (%)	1998 N (%)	2002 N (%)	Overall N (%)	P-value <sup>c</sup>
At 3 months	49 (6.1)	64 (5.9)	114 (7.6)	240 (18.8)	467 (10.0)	<0.001
At 1 year	78 (9.7)	148 (13.7)	324 (21.5)	447 (34.9)	997 (21.4)	<0.001
At 2 year	101 (12.9)	225 (21.7)	451 (31.0)	529 (43.3)	1306 (29.0)	<0.001
During first year <sup>a</sup>	86 (10.7)	164 (15.2)	341 (22.7)	472 (36.9)	1063 (22.8)	<0.001
During second year <sup>b</sup>	122 (15.1)	266 (24.6)	505 (33.5)	579 (45.1)	1472 (31.4)	<0.001

<sup>a</sup>ACEI/ARB in visit at 3 months and/or 1 year.

<sup>b</sup>ACEI/ARB in visit at 3 months and/or 1 and/or 2 years.

<sup>c</sup>Chi-square test.

**Table 2.** Baseline characteristics into ACEI/ARB use during the first year

Characteristics	No ACEI/ARB N (%)	ACEI/ARB N (%)	P-value
Donor age (year)	41.6 (16.8)	43.1 (17.0)	0.023
Donor female gender	1287 (35.7)	364 (34.3)	0.387
Patient age (year), mean (SD)	46.2 (13.3)	47.6 (12.8)	0.010
Patient female gender	1389 (38.5)	334 (31.5)	<0.001
Diabetes at transplantation	156 (4.6)	97 (9.3%)	<0.001
Hepatitis C virus positive	502 (15.1)	104 (10.3)	<0.001
Weight (kg), mean (SD)	65.8 (12)	68.5 (12.4)	<0.001
HLA mismatches			
0	1249 (35.7)	307 (29.5)	<0.001
1	1977 (56.6)	593 (57.1)	<0.001
2	270 (7.7)	139 (13.4)	0.001
Immunosuppression			
Cyclosporine without mycophenolate mofetil	1834 (51.1)	342 (32.2)	<0.001
Cyclosporine with mycophenolate mofetil	813 (22.6)	266 (25)	<0.001
Tacrolimus based	639 (17.8)	332 (31.2)	<0.001
Other treatments	304 (8.5)	123 (11.6)	<0.001
Delayed graft function	1027 (30.2)	318 (32.1)	0.254
Acute rejection	1053 (29.2)	264 (24.8)	0.005
New onset diabetes after transplantation	193 (5.6)	57 (5.4)	<0.001
Impaired glucose tolerance after transplant	624 (18)	219 (20.9)	
Creatinine 1 year (mg/dl), mean (SD)	1.6 (0.7)	1.7 (0.7)	0.014
Proteinuria 1 year (g/day), mean (SD)	0.3 (0.8)	0.4 (1.0)	<0.001
Cholesterol 1 year (mg/dl), mean (SD)	220.9 (45.9)	213.7 (45.8)	0.296
Triglycerides 1 year (mg/dl), mean (SD)	148.4 (71.5)	152.7 (74.6)	<0.001

## Materials and methods

### Study design

Patients receiving a renal allograft in Spain in 1990, 1994, 1998 and 2002 were considered for the present study. All Spanish adult transplant centres were invited to participate, and only adult patients ( $\geq 18$  years) receiving a single kidney transplant that was functioning at the end of the first year were considered. Patients receiving multi-organ or double transplants were excluded. Last follow-up was on 31 December 2005.

### Clinical variables

The following variables were evaluated at the time of surgery: source of the organ (living or deceased donor), donation before or after cardiac death, cause of donor death (trauma, stroke or others), age and gender of the donor and the recipient, height and weight of the recipient, presence of hepatitis B surface antigen and hepatitis C virus antibodies in the donor and the recipient, aetiology of end-stage renal disease, time on dialysis, last panel reactive antibodies (PRA), number of human leukocyte antigen (HLA) mismatches and cold ischaemia and re-anastomosis times.

After surgery, the presence of delayed graft function and acute rejection were recorded. Immunosuppressive treatment at 1 year was described on an intention-to-treat basis and classified into four major groups: (i) cyclosporine-based not associated with mycophenolate mofetil, (ii) cyclosporine-based associated with mycophenolate mofetil, (iii) tacrolimus-based treatment and (iv) other treatments.

At 3 months and yearly thereafter, serum creatinine, 24 h proteinuria, serum fasting glucose and serum cholesterol and triglycerides were recorded. Treatment with antihypertensive drugs including ACEI or ARB was also recorded.

### Definition of variables

Total number of HLA mismatches was calculated as the addition of the number of mismatches in the A, B and DR loci. Delayed graft function was defined as haemodialysis requirements during the first week after surgery once accelerated or hyperacute rejection, vascular complications and urinary tract obstruction were ruled out. The diagnosis of acute rejection was defined at each centre based on clinical and/or histological data.

This study was approved by the Ethics Committee of the Hospital Universitario de Bellvitge. Medical records review was performed according to Spanish law with reference to clinical data confidentiality protection. A blinded code was assigned to each participating hospital in order to take the centre effect into consideration.

### Statistics

Descriptive results are expressed as frequencies and percentages for categorical variables; median, 25th and 75th percentiles for skewed continuous variables and mean  $\pm$  standard deviation for normally distributed continuous variables. These variables were compared in ACEI/ARB users

**Table 3.** Baseline characteristics into ACEI/ARB use during 2<sup>st</sup> year

Characteristics	no ACEI/ARB N (%)	ACEI/ARB N (%)	P-value
Donor age (year), mean (SD)	41.3 (16.9)	43.4 (16.8)	<0.001
Donor female gender	1146 (35.7)	508 (34.5)	0.430
Patient age (year), mean (SD)	46.1 (13.4)	47.4 (12.7)	0.006
Patient female gender	1281 (39.9)	444 (30.2)	<0.001
Diabetes at transplantation	135 (4.4)	119 (8.3)	<0.001
Hepatitis C virus	459 (15.6)	149 (10.6)	<0.001
Weight (kg), mean (SD)	65.4 (12.0)	68.5 (12.4)	<0.001
HLA mismatches			
0	1123 (36.2)	440 (30.5)	<0.001
1	1746 (56.2)	829 (57.4)	<0.001
2	236 (7.6)	174 (12.1)	<0.001
Immunosuppression			
CSA without MMF	1671 (52.3)	513 (34.9)	<0.001
CSA with MMF	701 (21.9)	380 (25.8)	<0.001
Tacrolimus based	554 (17.3)	420 (28.6)	<0.001
Other treatments	270 (8.4)	158 (10.7)	<0.001
Delayed graft function	916 (30.2)	437 (31.8)	0.264
Acute rejection	940 (29.3)	380 (25.8)	0.014
New onset diabetes after transplantation	161 (5.3)	89 (6.1)	<0.001
Impaired glucose tolerance after transplant	549 (17.9)	294 (20.2)	<0.001
Creatinine 1 year (mg/dl), mean (SD)	1.6 (0.7)	1.7 (0.7)	0.004
Proteinuria 1 year (g/day), mean (SD)	0.3 (0.8)	0.4 (0.9)	<0.001
Cholesterol 1 year (mg/dl), mean (SD)	221.4 (46.0)	214.7 (45.6)	0.959
Triglycerides 1 year (mg/dl), mean (SD)	149.1 (72.2)	150.0 (72.6)	0.001

and non users by means of chi-square test for categorical data, Wilcoxon *t*-test for ordinal or not normally distributed continuous data and Student's *t*-test for continuous normally distributed data.

Kaplan–Meier analysis was used to estimate overall graft survival, death-censored graft survival and patient survival. Log rank test was employed to compare differences between groups.

Use of ACEI/ARB was analysed considering two different settings in order to take into account the timing of the introduction of treatment: introduction during the first year after transplantation and introduction during the initial 2 years after transplantation. Since the mean follow-up in the 2002 cohort was 3 years, no attempts were made to evaluate introduction of this treatment after 3 years or later.

Cox regression analysis adjusting for year of transplantation was employed to analyse the association between ACEI/ARB use and graft survival, death-censored graft survival and patient survival. Since this analysis showed an interaction between year of transplant and ACEI/ARB treatment, the effect of this treatment was analysed in each cohort of patients separately. Multivariate backward Cox regression analysis was performed to further evaluate the independent association of ACEI/ARB and survival.

In order to take into consideration confounding by indication, a propensity score was calculated and introduced in all multivariate analysis. The propensity score was calculated by a logistic regression considering all clinical variables that were significantly different between patients treated or not with ACEI/ARB. This analysis provides a probability score of being treated with ACEI/ARB for each patient, and this score (ranging from 0 to 1) was divided in quartiles and considered in the multivariate Cox regression analysis.

## Results

### Patients

A total of 4842 patients were considered in the present study and distributed in the 1990, 1994, 1998 and 2002 cohorts as 851, 1124, 1512 and 1355 patients, respectively.

In the 1990 and 1994 cohorts, ACEI/ARB were less frequently used than in 1998 and 2002 (Table 1). Characteristics of patients according to ACEI/ARB use during the first and second years are summarized in Tables 2 and 3.

### Survival and ACEI/ARB treatment during the first year after transplant

The proportion of recipients receiving ACEI/ARB treatment during the first year after transplantation increased from 10.7% in the 1990 cohort to 39.9% in the 2002 cohort. During the first year of follow-up, a total of 1063 patients (22.8%) were treated with ACEI/ARB, and graft survival was 51.4% for patients not receiving ACEI/ARB and 50.5% for treated patients (*P* = ns). Cox regression analysis adjusting for the year of transplant confirmed that there was no association between ACEI/ARB use and graft survival. However, there was a significant interaction between year of transplant and ACEI/ARB treatment (*P* = 0.046). For this reason, the effect of ACEI/ARB treatment on graft survival was analysed in each cohort. A significant difference was only observed in the 1994 cohort in the univariate analysis (relative risk (RR): 0.74 and 95% confidence interval (CI): 0.56–0.97; *P* = 0.03), but multivariate Cox regression analysis including the propensity score for ACEI/ARB treatment did not confirm the association between ACEI/ARB treatment and graft survival in the 1994 cohort.

Death-censored graft survival was 63.5% for untreated patients and 60.6% for treated patients (*P* = ns). Similarly, patient survival was 66.6% and 68.8%, respectively (*P* = ns).

### Survival and ACEI/ARB during the initial 2 years after transplant

The proportion of recipients receiving ACEI/ARB treatment during the initial 2 years after transplantation increased from 15.1% in the 1990 cohort to 45.1% in the 2002 cohort. During the initial 2 years after transplantation, 1472 patients (31.4%) received treatment with ACEI/ARB,

**Table 4.** Multivariate Cox regression analysis of graft survival in the 2002 cohort including the propensity score for ACEI/ARB treatment.

Variable	RR	IC 95%	P-value
Hepatitis C virus positive	2.50	1.21–5.57	0.0252
Surgical complications	2.32	1.11–4.87	0.0247
Delayed graft function	1.92	1.02–3.60	0.0412
ACEI/ARB during second year	0.36	0.17–0.75	0.0069
Creatinine at 3 months	2.33	1.47–3.68	0.0003
Creatinine increase from 3 months to 1 year	4.17	2.80–6.20	<0.0001

and graft survival was 50.9% for patients not treated with ACEI/ARB and 54.4% for patients treated with ACEI/ARB ( $P = 0.063$ ). Cox regression analysis adjusting for the year of transplant showed that there was no association between ACEI/ARB use and graft survival. However, there was a significant interaction between year of transplant and ACEI/ARB treatment ( $P = 0.037$ ). For this reason, the effect of ACEI/ARB on graft survival was further analysed in each cohort of patients. A lower risk of graft failure was observed in patients transplanted in 2002 (relative risk: 0.46 and 95% CI of 0.23–0.88;  $P = 0.020$ ). Multivariate Cox regression analysis including the propensity score for ACEI/ARB treatment confirmed the association between ACEI/ARB treatment and graft survival in the 2002 cohort (Table 4).

Death-censored graft survival was 63.1% for untreated patients and 63.8% for treated patients ( $P = ns$ ). Similarly, patient survival was 66.5% and 68.1%, respectively ( $P = ns$ ).

## Discussion

A significant proportion of kidney transplant recipients have a reduced glomerular filtration rate and, accordingly, an increased cardiovascular risk and increased probability for renal function deterioration [11]. Different strategies have been employed to slow the decline of renal function including the adjustment of immunosuppression, treatment of hypertension or treatment of lipid abnormalities [12,13]. The proven efficacy of treatment with ACEI/ARB on the progression of native renal disease suggested that a similar benefit may be observed in transplanted patients. Possible renoprotective mechanisms of these medications include a decrease in the systemic and intraglomerular blood pressure, prevention of renal scarring, inhibition of AT II-mediated glomerulosclerosis and reduction of proteinuria [5,14,15]. These expectations were sustained by a recent report [7] showing that treatment with ACEI/ARB in 2,031 renal transplants performed between 1990 and 2003 in an Austrian centre was associated with a significant improvement of long-term graft and patient survival. However, the retrospective study conducted by Opelz *et al.* [9] including 17 207 kidney recipients and 1744 heart transplants failed to demonstrate an association between ACEI/ARB treatment and transplant outcome. Recently, Amara *et al.* [17] showed that the rate of decline of renal

function in patients with chronic allograft nephropathy and severe renal impairment was not adversely affected by 1-year lisinopril treatment, but there was no amelioration of renal function deterioration rate.

In our study, we analysed patients treated with ACEI/ARB during the first year or the first 2 years of follow-up in comparison to patients not receiving renin-angiotensin blockade. Analysis of patient and graft survival in patients treated with ACEI/ARB during the first year did not show any difference between groups. The proportion of recipients receiving ACEI/ARB during the first year after transplantation increased from 10.7% in the 1990 cohort to 39.9% in the 2002 cohort, showing an important time-dependent modification of the indication criteria for ACEI/ARB in transplanted patients.

The evaluation of patients treated with ACEI/ARB during the initial two years yielded similar results. There were no differences in graft survival between treated or not treated patients in the analysis of all cohorts, but since there was an interaction between treatment and year of transplant, we further analysed each cohort separately. This analysis showed a reduced risk of graft failure for treated patients transplanted in 2002. Multivariate Cox regression analysis including a propensity score confirmed this finding. However, it is important to notice that there are limitations in this observational, retrospective study. The association between ACEI/ARB and outcome may be spurious, since multiple comparisons were done and the association between treatment and outcome was relatively weak. The advantage that in the 2002 cohort treated and untreated patients were distributed in a similar proportion may be overcome by the shorter follow-up of these patients. Thus, the potential benefit of ACEI/ARB on outcome is a question that remains open and that can only be answered by means of prospective randomized clinical trials.

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