No Improvement of Patient or Graft Survival in Transplant Recipients Treated with Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Type 1 Receptor Blockers: A Collaborative Transplant Study Report

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It was reported recently that treatment of kidney transplant recipients with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II type 1 receptor blockers (ARB) is associated with strikingly improved long-term graft and patient survival. This finding has important implications for future posttransplantation therapy recommendations. In an analysis of 17,209 kidney and 1744 heart transplant recipients, an association of treatment with ACEI/ARB with improved transplant outcome could not be confirmed. It is concluded that recommendations for a widespread use of ACEI/ARB treatment in transplant recipients are unwarranted.

J Am Soc Nephrol 17: 3257–3262, 2006. doi: 10.1681/ASN.2006050543

Research in clinical kidney transplantation is increasingly focusing on long-term outcome. A recent publication by Heinze *et al.* (1), based on an analysis of 2031 patients, received much attention because it showed that treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II type 1 receptor blockers (ARB) resulted in strikingly better long-term graft and patient survival as compared with patients who did not receive such treatment. Patient survival was approximately 20% and graft survival was approximately 30% better at 5 yr in patients who received ACEI or ARB treatment, a result that is nothing less than spectacular. A lower rate of cardiovascular death was identified as the main treatment benefit. Consequently, the authors recommended more frequent use of these medications in kidney transplant recipients. If confirmed, then treatment with ACEI or ARB would represent the most powerful hitherto documented means by which long-term graft and patient survival can be improved. Because of the far-reaching implications of this important finding, potentially beyond the field of renal transplantation, we conducted an analysis of ACEI/ARB in kidney and heart transplant recipients who were reported to the Collaborative Transplant Study (CTS) (2).

Materials and Methods

All recipients of a first kidney transplant that was performed from 1995 through 2004, who had a functioning graft 1 yr after transplantation, and for whom information was available on treatment or the absence of treatment with an ACEI or ARB were included in this analysis. Information on treatment with ACEI or ARB was requested on the CTS (2) questionnaires from 1995 onward at yearly intervals after transplantation and typically was provided by centers that use ACEI/ARB in some of their patients. A total of 107 of 299 kidney transplant centers that participated in CTS provided data on ACEI/ARB use, which is part of the nonmandatory "extended follow-up" CTS study questionnaire (2). Of centers that provided information on extended follow-up, the part of the questionnaire on ACEI/ARB use was completed for 85.1% of patients followed. A parallel analysis was performed in recipients of cardiac transplants who were reported to the CTS registry by 36 centers.

Graft and patient as well as death-censored graft survival rates commencing 1 yr after transplantation (the first data point at which treatment with ACEI/ARB was recorded) were computed according to the Kaplan-Meier method (3), and the log rank test was used to estimate statistical significance. Multivariate Cox regression analysis (4) was performed using the covariables year of transplantation, donor relationship (deceased, HLA-identical sibling, HLA haplotype-matched related, other living donor), recipient geographic origin (continent), original disease that led to ESRD, duration of pretransplantation dialysis, recipient and donor gender, race and age, number of HLA mismatches, preformed panel-reactive lymphocytotoxic antibodies, cold ischemia time in hours, and indication of increased pretransplantation cardiovascular risk, as well as the following variables that were recorded at 1 yr after transplant: Systolic BP, treatment for hypertension other than diuretics, immunosuppression with calcineurin inhibitor or not, treatment for rejection during first posttransplantation year, and serum creatinine. Confounder variables were categorized suitably for Cox regression analysis, and interaction terms were considered appropriately. $P < 0.05$ was taken to indicate statistical significance.

Results

In total, 17,209 kidney transplant recipients were included in this analysis. Approximately one third (33.5%) of the patients were on treatment with an ACEI or ARB 1 yr after transplantation. The fraction of recipients who were receiving ACEI/ARB increased from 17% in 1996 to 28% in 2000 and further to

Received May 31, 2006. Accepted August 27, 2006.

Published online ahead of print. Publication date available at www.jasn.org.

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ISSN: 1046-6673/1711-3257

46% in patients who received a transplant in 2004. Using treatment with ACEI or ARB 1 yr after transplantation as an indicator, we found no evidence for improved graft or patient survival during the subsequent 5 yr in patients who received treatment (Figure 1). The graft survival rates at 6 yr for patients with or without ACEI/ARB treatment were 82.5% (SE 0.8%) and 83.7% (SE 0.5%; $P = 0.40$), and the corresponding patient survival rates were 91.1% (SE 0.6%) and 92.0% (SE 0.4%), respectively ($P = 0.32$). Neither was there a difference in death-censored graft survival: 89.4% (SE 0.7%) *versus* 89.5% (SE 0.4%), respectively ($P = 0.72$). Multivariate Cox regression analysis considering multiple confounders confirmed this result; associated risk ratios (RR) for important potential confounders are listed in Table 1. The Cox regression result suggests that confounding background factors were not responsible for our inability to detect an advantage of ACEI/ARB treatment (graft survival: risk ratio RR 1.05 [95% confidence interval (CI) 0.94 to 1.17; $P = 0.42$]; patient survival: RR 1.01 [95% CI 0.86 to 1.18; $P = 0.90$]). Neither was a beneficial effect of treatment demonstrable when recipients of grafts from deceased donors or living donors were analyzed separately (Figure 2). The rate of cardiovascular death in patients with or without ACEI/ARB treatment was virtually identical, showing a negligible difference of 0.4% ($P = 0.66$).

Because this finding was in stark contrast to the publication of Heinze *et al*. (1), we performed additional analyses to test the robustness of our data. We limited the analysis to recipients of deceased-donor transplants and examined first whether the 1-yr indicator point might have been insufficient for identifying patient subgroups with sufficient ACEI/ARB exposure. Therefore, we analyzed patients who were known to have received ACEI/ARB at 1, 2, and 3 yr and compared them with patients who did not receive treatment at 1, 2, and 3 yr. Analysis of graft survival for the subsequent 3 yr showed no difference between the two groups (Figure 3). Neither was there a difference in patient or functional survival. We were able to observe 1519 patients after 5 yr of follow-up, 491 of whom were recorded to have been treated at each yearly interval from 1 to 5 yr with ACEI/ARB and 1028 of whom were never treated. Subsequent follow-up was too short for meaningful survival computations. However, the two groups of patients had a virtually identical distribution of serum creatinine values at 5 yr: 53.0% of patients on continuous ACEI/ARB treatment had a creatinine of <130 μmol/L, 44.4% had 130 to 259 μmol/L, 2.0% had 260 to 400 μmol/L, and 0.6% had >400 μmol/L. The corresponding values for patients who never received ACEI/ARB were 51.8% with <130 μmol/L, 44.0% with 130 to 259 μmol/L, 3.3% with 260 to 400 μmol/L, and 0.9% with >400 μmol/L (Mantel-Haenszel test: $P = 0.37$). In the absence of detailed data on posttransplantation cardiovascular comorbidity, we focused on subgroups of patients who could be presumed to be at increased cardiovascular risk: Patients with diabetic or hypertensive nephropathy, patients who were categorized by the transplant centers before transplantation to be at increased cardiovascular risk, patients who were older than 60 yr, patients with a 1-yr systolic BP of ≥140 mmHg, patients with a total serum cholesterol at 1 yr of ≥200 mg/dl, and patients with a 1-yr serum creatinine of ≥130 μmol/L. In none of these patient subsets could a significant advantage of treatment with ACEI/ARB be demonstrated (Table 2). The result comparing graft outcome in patients with or without ACEI/ARB treatment in relation to systolic BP suggests that treatment with ACEI/ARB does not exert a BP-independent beneficial effect. Figure 4 illustrates that the widely known deleterious effect of posttransplantation hypertension on kidney graft survival (5) was determined by the extent to which BP was con-

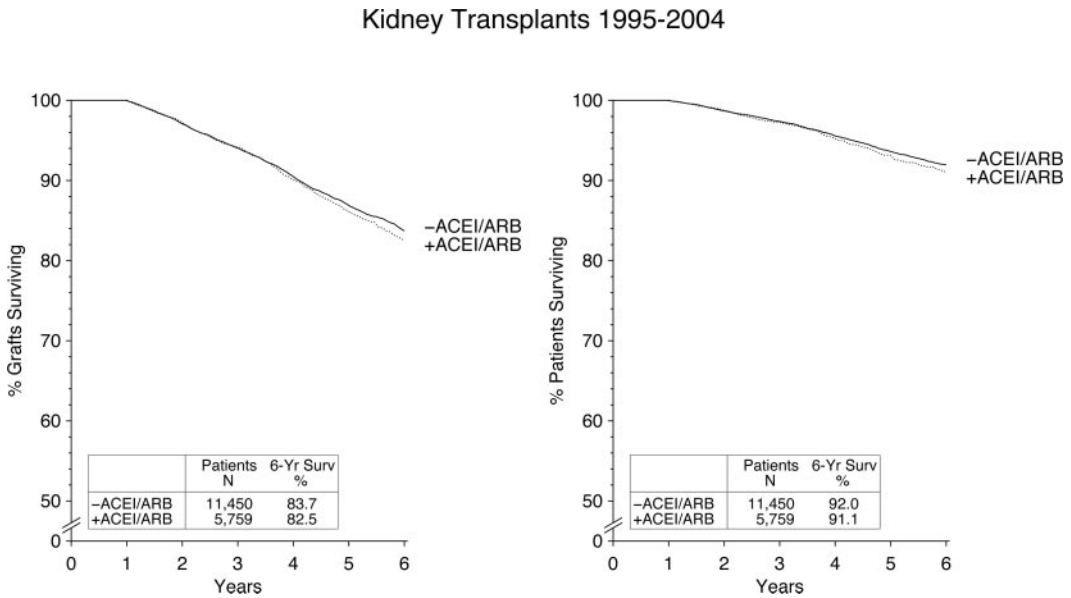

Figure 1. Graft (left) and patient (right) survival rates of kidney transplant recipients either on treatment with angiotensin-converting enzyme inhibitors/angiotensin II type 1 receptor blockers (ACEI/ARB) 1 yr after transplantation (+ACEI/ARB) or not treated with ACEI/ARB (−ACEI/ARB). Numbers of patients studied and percentage of survival are indicated at bottom. There was no significant difference in survival between patients who did or did not receive ACEI/ARB treatment.

Table 1. Risk ratios for confounders in Cox regression analysis for graft survival from 2 to 6 yr: First kidney transplants performed 1995 through 2004[a]

Variable	RR	95% CI	*P*
Donor relationship (*versus* deceased donor)			
1-haplotype related	0.80	0.68 to 0.95	0.013
HLA identical sibling	0.43	0.29 to 0.66	<0.001
other living	0.66	0.55 to 0.80	<0.001
Donor age (*versus* <60 yr)			
60 to 69 yr	1.13	0.97 to 1.33	0.12
≥70 yr	1.60	1.25 to 2.05	<0.001
Recipient age (*versus* 19 to 59 yr)			
≤18 yr	1.20	0.98 to 1.47	0.074
60 to 69 yr	1.45	1.24 to 1.68	<0.001
≥70 yr	1.92	1.33 to 2.76	<0.001
Original disease diabetic nephropathy	1.31	1.08 to 1.59	0.006
Cardiovascular risk[b]	1.44	1.19 to 1.74	<0.001
Transplant year (per calendar year)	0.92	0.89 to 0.95	<0.001
Follow-up at 1 yr			
systolic BP (*versus* <140 mmHg)			
140 to 159 mmHg	1.18	1.05 to 1.32	0.005
≥160 mmHg	1.52	1.32 to 1.75	<0.001
serum creatinine (*versus* <130 μmol/L)			
130 to 259 μmol/L	1.74	1.51 to 2.02	<0.001
≥260 μmol/L	8.66	7.09 to 10.6	<0.001
rejection treatment during first year	1.23	1.10 to 1.38	<0.001
no calcineurin inhibitor at 1 yr	1.73	1.39 to 2.16	<0.001

[a]CI, confidence interval; RR, risk ratio.
[b]Patients who were categorized by transplant center before transplantation to be at increased cardiovascular risk.

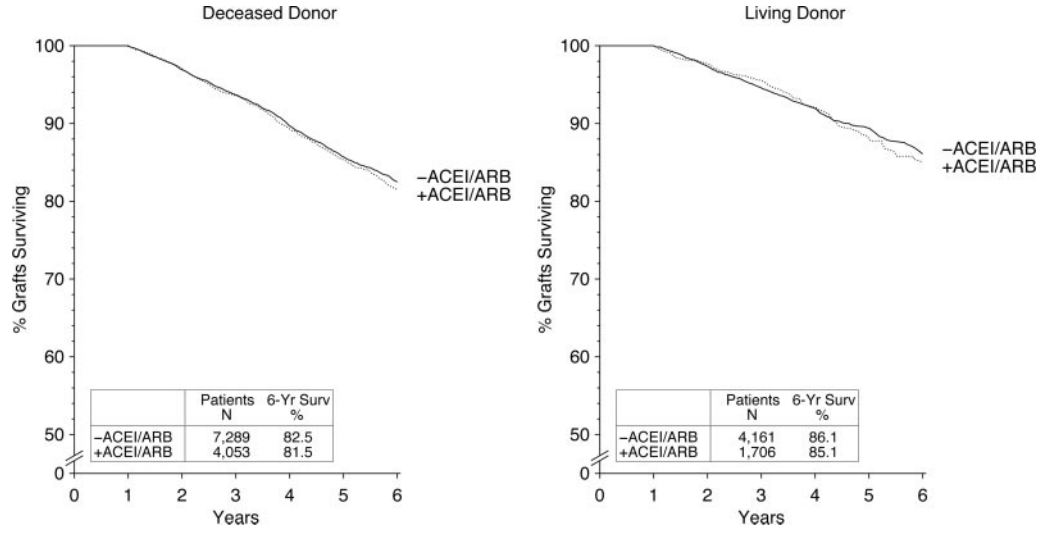

Figure 2. Comparison of graft survival in recipients of kidney transplants from deceased donors (left) or living donors (right). Treatment with ACEI/ARB showed no significant influence on graft survival.

trolled, irrespective of whether patients were treated with ACEI/ARB. We next examined whether treatment with ACEI/ARB might affect the survival rate of heart transplant recipients. As shown in Figure 5, no significant treatment benefit was found (RR 0.88; 95% CI 0.63 to 1.23; $P = 0.46$).

Discussion

On the basis of favorable results that were obtained in studies of nontransplantation patients who were at high cardiovascular risk (6–8), it was a reasonable hypothesis to propose a benefi-

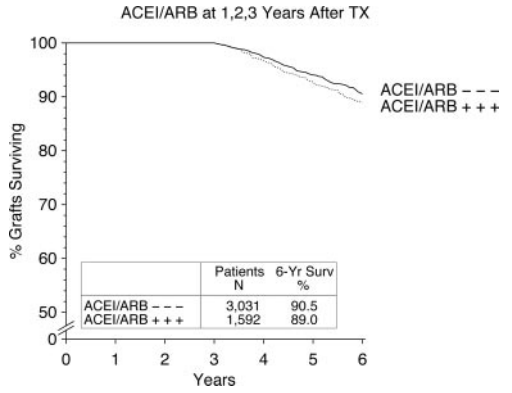

Figure 3. Analysis of patients who were treated with ACEI/ARB 1, 2, and 3 yr after transplantation with patients who were not receiving treatment at 1, 2, and 3 yr. Graft survival during the subsequent 3 yr was not significantly different ($P = 0.14$).

cial effect of treatment with ACEI/ARB in kidney transplant recipients. ACEI/ARB treatment reduces myocardial infarction, stroke, and cardiovascular death in nontransplant populations (6–8). Cardiovascular death is a main cause of death in kidney recipients (9). We are unaware of large, prospective studies aimed at the evaluation of ACEI/ARB treatment in transplant recipients. However, off-label treatment of transplant patients was initiated in the mid-1990s in the hope that the rate of cardiovascular death might be lowered. Furthermore, the proven efficacy of treatment with ACEI/ARB on progression of native renal disease (10,11) led to speculation that long-term graft function also might benefit. These expectations were substantiated by the recent report of Heinze *et al.* (1), which showed that treatment with ACEI/ARB indeed was associated with a striking improvement of posttransplantation graft and patient survival. The graft survival rate was approximately 30% higher at 5 yr in patients who were receiving treatment compared with patients who were not receiving treatment, and the corresponding difference in patient survival was equally impressive: Approximately 20% at 5 yr (1). However, in our analysis of 17,209 kidney recipients who were reported to the CTS, we were unable to confirm a positive effect of treatment with ACEI/ARB.

The contrasting results that were obtained in the two studies ask for critical examination. Whereas Heinze *et al.* excluded the first 90 d after transplantation from analysis, we excluded the first posttransplantation year. The difference in method should not affect the ability to detect a qualitative difference in long-term outcome between groups of patients with or without ACEI/ARB treatment. Heinze *et al.* reported a 5-yr patient survival rate in patients who did not receive ACEI/ARB of approximately 70% (1). This result is highly unusual. Even in the era from 1985 through 1990, before ACEI/ARB was used in any kidney transplant recipients, the CTS data show an overall patient survival rate for recipients of diseased donor kidneys of 83% at 5 yr. Heinze *et al.* excluded mortality during the first 90 d and included an unspecified fraction of living donors, which makes the low patient survival rate that was obtained in their analysis even more unusual. The authors stated that they separated their patients into those who never used ACEI/ARB and those who ever used ACEI/ARB (1). Although the exact method of how this was done was not described, the procedure conceivably led to an artificially inflated success rate for patients who were receiving ACEI/ARB. For example, a patient who did not receive treatment during the first 3 yr but was put on ACEI/ARB from 3 yr onward could not possibly have failed before year 3. By this definition, patients who never received ACEI/ARB had a possibility of failure at any time after transplantation, whereas patients in whom treatment was initiated several years after transplantation had a possibility of failure only subsequent to the first treatment with ACEI/ARB. We believe that categorization of patients according to treatment at a given point in time (*e.g.*, 1 yr after transplantation) and analysis according to the "intention to treat" principle is appropriate for studying treatment effects of ACEI/ARB on long-term outcome. A possible shortcoming of this approach is that

Table 2. RR of treatment with ACEI/ARB *versus* no treatment[a]

Patient Subpopulation	No. of Patients	Graft Survival			Patient Survival		
		RR	*P*	95% CI	RR	*P*	95% CI
Diabetic nephropathy	1153	0.82	0.30	0.56 to 1.20	0.68	0.09	0.43 to 1.06
Hypertensive nephropathy	1128	1.12	0.59	0.75 to 1.67	1.40	0.20	0.84 to 2.35
Pretransplantation cardiovascular risk	1030	0.95	0.81	0.65 to 1.40	1.05	0.81	0.69 to 1.61
Recipient age <60 yr	14,603	1.04	0.54	0.92 to 1.17	0.96	0.68	0.80 to 1.16
Recipient age ≥60 yr	2429	1.05	0.71	0.82 to 1.34	1.15	0.34	0.86 to 1.54
1-yr systolic BP <140 mmHg	9808	0.98	0.80	0.82 to 1.16	0.86	0.24	0.67 to 1.10
1-yr systolic BP ≥140 mmHg	6869	1.08	0.31	0.93 to 1.25	1.13	0.25	0.92 to 1.41
1-yr serum cholesterol <200 mg/dl	6197	0.97	0.75	0.78 to 1.20	0.92	0.58	0.68 to 1.24
1-yr serum cholesterol ≥200 mg/dl	7593	1.02	0.81	0.87 to 1.19	1.04	0.74	0.83 to 1.30
1-yr serum creatinine <130 μmol/L	9574	1.06	0.55	0.87 to 1.29	0.99	0.95	0.77 to 1.27
1-yr serum creatinine ≥130 μmol/L	7461	1.03	0.62	0.91 to 1.18	1.03	0.79	0.84 to 1.26

[a]Recipients of first kidney transplants from deceased donors were analyzed from 2 to 6 yr of follow-up. ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II type 1 receptor blockers.

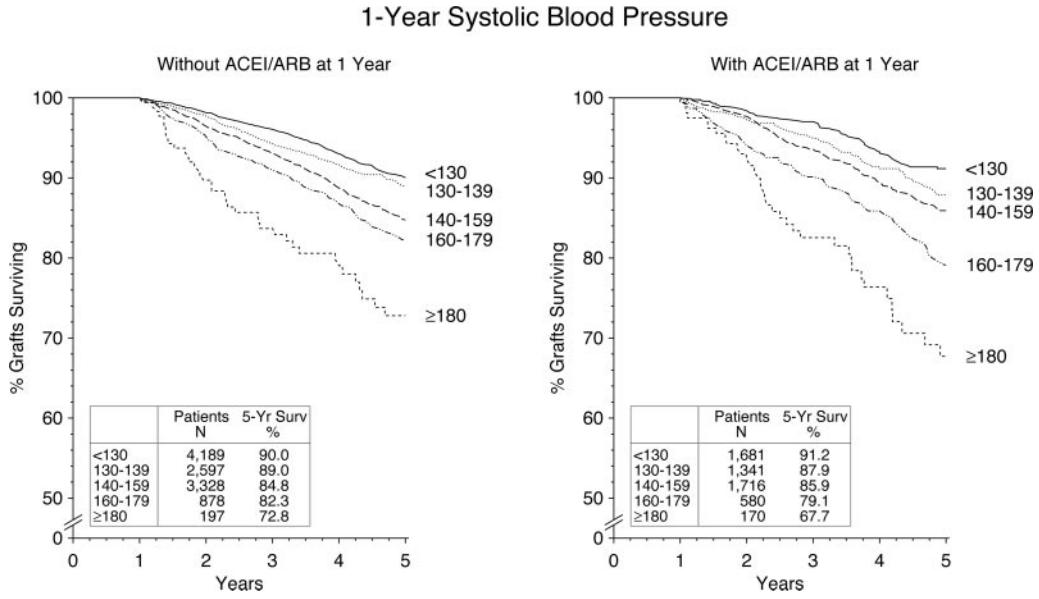

Figure 4. Graft survival rates in patients with or without ACEI/ARB treatment according to systolic BP 1 yr after transplantation. A deleterious effect of hypertension on graft survival was noted regardless of whether patients were treated with ACEI/ARB (regression $P < 0.001$ in both patient groups shown). Outcome was related to the degree of BP control and not to treatment with ACEI/ARB. In none of the BP subgroups was the difference in graft survival between patients with or without ACEI/ARB statistically significant.

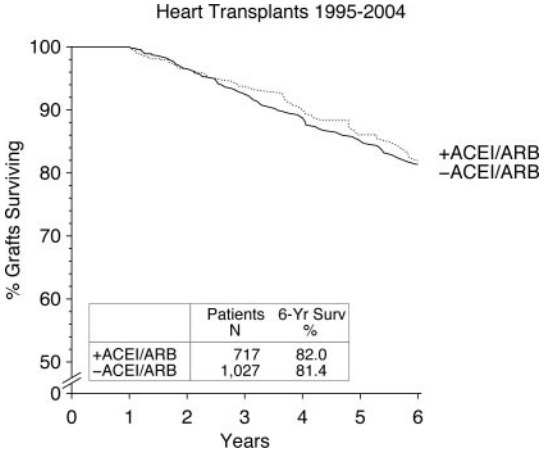

Figure 5. Survival of heart transplants in patients with or without ACEI/ARB treatment 1 yr after transplantation. No significant difference in long-term survival was observed.

we cannot exclude the possibility that a patient may have been receiving ACEI/ARB at 1 yr and removed from treatment a few months later. Heinze *et al.* counted such patients in the "treated" group, and this uncertainty therefore is irrelevant for explaining the difference between the results that were obtained in the two studies. Our subanalysis comparing patients who were receiving ACEI/ARB treatment at 1, 2, and 3 yr with patients who did not receive ACEI/ARB at 1, 2, and 3 yr likely compared a group in which most patients were on continuous treatment with another group in which most patients were not treated at all; this subanalysis also failed to show a treatment benefit (Figure 3). The results that were obtained in various patient risk categories shown in Table 2, as well as the result that was obtained in heart transplant recipients (Figure 5), led us to conclude that treatment with ACEI/ARB is not associated with noticeably improved graft or patient survival in transplant recipients.

A limitation of our study is that information on posttransplantation cardiovascular risk factors was not available, because one would expect any treatment benefits of ACEI/ARB to be pronounced in patients who are at increased cardiovascular risk. As an approximation, we analyzed subgroups of patients who can be assumed to have been at increased cardiovascular risk: Patients with diabetic or hypertensive nephropathy, patients who were categorized before transplantation by the transplant centers to be at increased cardiovascular risk, patients who were older than 60 yr at the time of transplantation, patients with posttransplantation hypercholesteremia, and patients with posttransplantation hypertension. In addition, we examined 1744 heart transplant recipients. In none of these patient subgroups was a beneficial effect of ACEI/ARB treatment on graft or patient survival demonstrable.

One must consider the possibility that patients who were treated with ACEI/ARB may have been deemed high risk on the basis of various clinical parameters and that the equivalent graft and patient survival rates that were observed in patients with or without treatment therefore may reflect a positive effect of ACEI/ARB in high-risk patients. In the absence of prospective trial data, however, such argumentation would be speculative. The strikingly higher graft and patient survival rates that were reported by Heinze *et al.* (1) were not confirmed in our analysis. On the basis of the currently available evidence, we believe that recommenda-

tions for the liberal treatment of transplant recipients with ACEI/ARB are premature.

Acknowledgments

The generous support of staff members at the following 107 kidney and 36 heart transplant centers who provided data for this study is gratefully acknowledged: Kidney transplant centers: Aachen, Adelaide, Ankara, Antalya, Belfast, Belo Horizonte (2 centers), Berlin, Bern, Botucatu, Brisbane, Bristol, Budapest, Cape Town (2 centers), Caracas, Christchurch, Cincinnati, Cologne, Cordoba, Duesseldorf, Durban, Edmonton, Erlangen-Nuernberg, Florence, Frankfurt, Freiburg, Fulda, Geneva, Giessen, Glasgow, Goettingen, Grand Rapids, Guadalajara, Halle, Hamilton, Hann-Muenden, Hawthorne, Heidelberg, Homburg, Hong Kong (2 centers), Innsbruck, Izmir, Jena, Kaiserslautern, Katowice, Kaunas, Kermanshah, Leicester, Leuven, Liege, Lima, Linz, Ljubljana, Luebeck, Maceio, Manila, Mannheim, Maracaibo, Marburg, Martin, Medellin, Mexico City, Milan, Muenster, Nancy, Newcastle, Novara, Oviedo, Pamplona, Panama, Pato Branco, Pecs, Perth, Poitiers, Prague, Quebec, Regensburg, Reims, Rio de Janeiro, Rostock, Santander, Sao Paulo (2 centers), Seoul, Shreveport, St. Gallen, Strasbourg, Sydney (2 centers), Szeged, Tehran, Tel Aviv, Toulouse, Tuebingen, Turin, Ulm, Uppsala, Valdivia, Valencia (2 centers), Vilnius, Winnipeg, Wuerzburg, Zagreb, and Zurich. Heart transplant centers: Aachen, Auckland, Brisbane, Charleston, Columbus, Dallas, Duesseldorf, Edmonton, Essen, Giessen, Graz, Hamburg, Heidelberg, Helsinki, Hershey, Jena, Kansas City, Lausanne, Leuven, Liege, Loma Linda, Loyola, Manchester, Medellin, Miami, Milwaukee, Montreal, Nancy, Papworth-Cambridge, Paris, Quebec, Sheffield, Tucson, Turin, Vancouver, and Zurich.

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