

Does size matter?

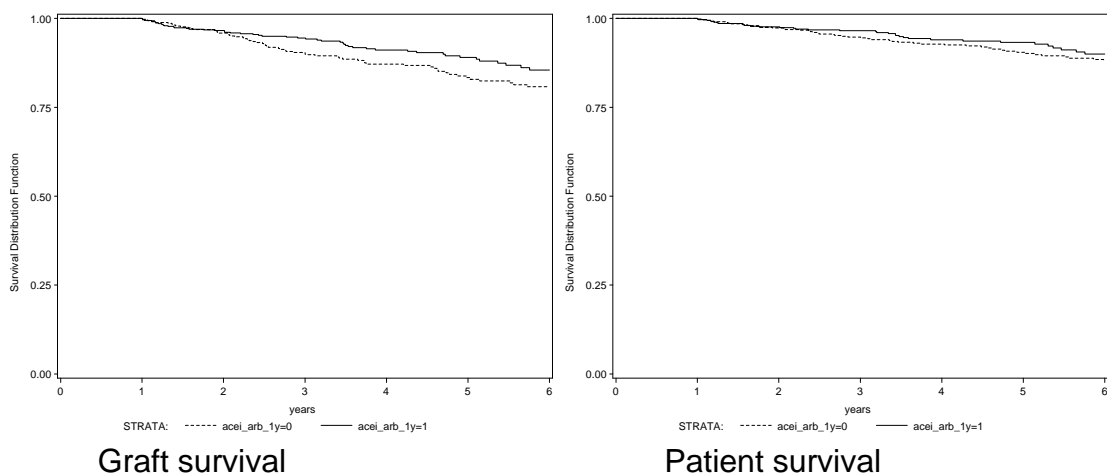
Georg Heinze and Rainer Oberbauer

Medical University of Vienna, AUSTRIA

In the November issue of this journal, Opelz and coworkers published their analysis of the association of ACEI/ARB with patient and graft survival after renal transplantation utilizing the CTS registry (Opelz G. et al. J Am Soc Nephrol 17: 3257–3262, 2006). In contrast to our study, published in JASN in March of this year, Opelz and colleagues reported that they failed to find such an association.

How can that be?

1. There are differences in the group definitions and inclusion criteria between the two studies. While we included all patients which were transplanted between 1990 and 2003 with a functioning graft three months after transplantation, Opelz et al. used only patients transplanted between 1995 and 2004 with functioning graft one year after transplantation.
2. There are differences in the way ACEI/ARB enters the analysis. While we used ACEI/ARB intake as a time-dependent variable, and *only for graphical illustration* divided our patients into those who ever received ACEI/ARB treatment after transplantation, and those who never received such treatment, Opelz et al. used ACEI/ARB in a fixed manner, comparing groups based on ACEI/ARB treatment at the time of one year after transplantation. In order to compare these results to ours, we performed a re-analysis of our database by including only patients which were transplanted from 1995 on and only those which had a functioning graft one year after transplantation. Then we used the same group definition as Opelz and colleagues and compared our new results to their and our published ones. We obtained the following survival curves (restricted to six years of follow-up, as in the publication of Opelz et al.; the solid lines refer to ACEI/ARB group, the dashed lines to noACEI/ARB group):



At six years of follow-up, the survival rates compare as follows:

Group	Graft survival		Patient survival	
	Our data	Opelz et al.	Our data	Opelz et al.
ACEI/ARB	85.5%	82.5%	90.0%	91.1%
noACEI/ARB	80.8%	83.7%	88.0%	92.0%

We computed the crude (unadjusted for confounding) hazard ratio (HR) for ACEI/ARB use with the reduced data base, for graft and patient survival. These hazard ratio estimates compare to the results based on time-varying entry of ACEI/ARB use as follows:

Mode of analysis	HR (95% confidence interval)	
	Graft survival	Patient survival
Time-varying (Heinze et al.)	0.76 (0.64-0.90)	0.70 (0.58-0.86)
Fixed at 1 year (Opelz et al.)	0.70 (0.48-1.02)	0.80 (0.52-1.24)

The inflated confidence interval obtained by using the second method can be explained by the reduced sample size (1113 instead of 2031) and the reduced follow-up time (median follow-up 4.9 years compared to 6 years). Since the differences in the HR estimates are within the margins of random variation, we can safely conclude that the way ACEI/ARB use entered our analysis is not the reason for different results obtained by Opelz et al. Thus, we must assume other causes for the discrepancy.

3. The most striking difference between the two analyses lies in the way information on ACEI/ARB treatment was obtained. In the study of Opelz et al, a questionnaire was sent out, with a return rate of 107 out of 299 participating centers. Their publication does not provide information on how completely the data was collected within those 107 centers. By contrast, we used data bases from the general public Austrian Sickness Funds and direct entry from patient charts. This is certainly the more labor-intensive strategy, but it has the advantage that our analysis finally is independent from willingness to return questionnaires, which is known to be a veritable source of bias, particularly if the return rate is as low as 36% (and even much lower when asking for ACEI/ARB intake five years after transplantation).
4. Furthermore, and equally important, we performed a very careful and laborious statistical analysis, including confounding variables also in a time-varying manner. Different strategies to identify confounding variables yielded virtually the same results. Finally, we did not explicitly recommend ACEI/ARB use, we rather encouraged the scientific community to test a potentially causal relationship between ACEI/ARB use and increased survival in a randomized controlled clinical trial.