# Cardiovascular and Renal Outcomes of Renin-Angiotensin System Blockade in Renal Transplant Recipients

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ABSTRACT

Background. There is considerable controversy over the benefits of renin-angiotensin system (RAS) blockade in renal transplant recipients (RTRs). The aim of the study was to research the effects of RAS blockade on allograft and patient outcome.

Methods. A retrospective analysis of the effects of RAS blockade on allograft and patient outcome in 53 pairs of RTRs receiving grafts from the same donor was performed. The 106 RTRs (53 pairs), transplanted from 2002 to 2012, were included in the study when 1 patient from the pair used an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) for a minimum period of 36 months (RAS[+]) and the second one did not use it (RAS[−]).

Results. There were no differences between RAS(+) and RAS(−) subjects in terms of age, body mass index, reason of end-stage renal disease, mismatches number, total ischemic time, episodes of cytomegalovirus infections, acute rejections, and immunosuppressive treatment. The mean time of observations was 66.28 months ± 24.39 months. RAS inhibitors were given in a mean dose of 23.1% (ACEI) and 27.08% (ARB) of the maximum recommended. The main reasons for the therapy were as follows: hypertension (39.62%), nephroprotection/proteinuria (39.62%), and polyglobulia (28.3%). The composite cardiorenal endpoint was reached by 6 (11.32%) and 7 (13.21%) patients in RAS(+) and RAS(−) group, respectively. There were no differences in changes of creatinine, potassium serum level, or estimated glomerular filtration rate between RAS(+) and RAS(−) patients in the early period after RAS blockade commencement.

Conclusion. Agents inhibiting the RAS system neither improved nor deteriorated patients and graft survival in RTRs.

RENIN-ANGIOTENSIN system (RAS) blockade reduces mortality in the general population and among non–dialysis-dependent patients with chronic kidney disease (CKD) [1,2]. The RAS blockade also decreases proteinuria and protects renal function in non-transplant patients with chronic kidney disease [3]. It remains controversial, however, whether this translates into improved patient or graft survival among renal transplant recipients (RTRs) [4]. Analyses of large databases and meta-analyses of small prospective clinical studies have provided conflicting results showing improved outcomes, detrimental effects, or null effects of post-transplantation angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy compared with other antihypertensive agents. To shed more light on this issue, we performed a retrospective analysis of the effects of RAS blockade on

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allograft and patient outcome in pairs of RTRs receiving grafts from the same donor.

## MATERIALS AND METHODS

The study objectives were as follows:

1. The assessment of the impact of RAS blockade on cardiovascular prognosis (cardiologic endpoint), kidney graft survival (nephrologic endpoint) and cardiovascular and/or graft survival (composite cardionephrologic endpoint).
2. Assessment of the RAS blockade safety in RTRs, in particular the impact of ACEI and ARB on serum creatinine, estimated glomerular filtration rate (eGFR) (CKD-EPI), and potassium serum level in the early period after RAS blockade commencement.
3. The characterization of pharmacological blockade of RAS in RTRs; in particular, reasons for therapy, dosage, and time of therapy initiation after kidney transplantation.

A retrospective analysis was conducted between March 2014 and December 2015. The data were collected from the patients' database of the Outpatient Transplantation Unit of the Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk, Gdansk, Poland. In order to minimize donor variability and bias, the study population consisted of pairs of RTRs transplanted from the same donor between 2002 and 2012 who were under the supervision of our unit. Patients were included in the study when 1 recipient from the pair used ACEI or ARB for a minimum period of 36 months (RAS+) and the other one did not use it (RAS[−]). For the objective of the study, the cardiologic endpoint was defined as acute coronary syndrome or stroke or exacerbation of cardiac failure (at least 1 class of the New York Heart Association guidelines) or diagnosis of coronary artery disease. Nephrologic endpoint was defined as decrease of eGFR below 15 mL/min/1.73 $m^2$ or a doubling of serum creatinine levels compared to baseline or initiation of dialysis therapy. To assess safety of RAS blockade in the early period of therapy, the results of serum creatinine, potassium, and eGFR (CKD-EPI) during the first visit in the department after the commencement of RAS blockade were analyzed (2–12 weeks after initiation).

Data were evaluated using a Statistica (version 12.0, Stat Soft Inc., Palo Alto, Calif, United States) software package. The variables are expressed as mean value ± standard deviation (SD), numbers, or frequencies (percentages). A $\chi^2$ test was performed in order to measure the differences between selected categories. The quantitative variables were assessed by Student's $t$ test. A $P < .05$ was considered statistically significant.

## RESULTS

### Patients

The characteristics of patients are presented in Tables 1 through 5. There were no differences between RAS(+) and RAS(−) subjects in terms of sex, age, body mass index, serum creatinine level and eGFR level, the reason of end-stage renal disease, methods and time of dialysis before transplantation, or frequency of pre-emptive transplantations (Tables 1, 2, and 4). RAS(+) and RAS(−) patients did not differ in terms of mismatches number, duration of cold and total ischemia, episodes of cytomegalovirus infections, acute rejections, and immunosuppressive treatment (Table 5). RAS(+) patients had significantly greater hemoglobin levels, and more of them presented with diabetes (Tables 1 and 3).

**Table 1. General Characteristics of Patients at the Beginning of Observation, N = 53 Pairs**

| Parameter | Patients RAS(+) | Patients RAS(−) | P |
|---|---|---|---|
| Sex (number of patients) | | | |
| F | 17 | 24 | NS |
| M | 36 | 29 | NS |
| Age (years) | 44.79 ± 12.41 | 44.13 ± 13.84 | NS |
| BMI (kg/$m^2$) | 24.12 ± 4.05 | 23.83 ± 3.96 | NS |
| Serum creatinine (mg/dL) | 1.45 ± 0.35 | 1.45 ± 0.48 | NS |
| eGFR (mL/min/1.73 $m^2$) | 56.72 ± 16.06 | 56.97 ± 19.01 | NS |
| Hb (g/dL) | 14.18 ± 2.11 | 12.91 ± 1.57 | .0007 |
| $K^+$ (mEq/L) | 4.21 ± 0.38 | 4.28 ± 0.46 | NS |
| Observation time (months) | | | |
| Minimal | 36 | | |
| Maximal | 118 | | |
| Mean | 66.28 ± 24.39 | | |

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; F, female; Hb, hemoglobin; K, potassium; M, male; NS, not significant; RAS, renin-angiotensin system.

The mean time of observations was 66.28 ± 24.39 months. Out of the 53 pairs of patients included in the study, 20 pairs (37.74%) were still active at the end of observation. The observation of 14 pairs (26.41%) was terminated between 36 and 118 months of observation due to death or end-stage renal disease; the observation of 19 pairs (35.85%) was discontinued due to the introduction of RAS blockade to the therapy in RAS(−) patients or the termination of RAS blockade in RAS(+) patients.

### Pharmacological Blockade of RAS

In the RAS(+) group, 47 of the 53 patients were treated with ACEI, and 6 of the 53 patients received ARB. In the RAS(+) group the mean period after kidney transplantation after which RAS blockade was initiated was 20.89 ± 20.96 months. RAS inhibitors were given in a mean dose of 23.1% (ACEI) and 27.08% (ARB) of the maximum recommended antihypertensive dosage according to the manufacturers. The main reasons for therapy were as follows: hypertension (39.62%), nephroprotection/proteinuria (39.62%), and polyglobulia (28.3%). For 7 patients RAS blockade was terminated between 36 and 118 months of therapy because of: deterioration of graft function <15 mL/min/1.73 $m^2$ (1 patient), hypotension (1 patient), anemia

**Table 2. The Causes of End-Stage Renal Disease**

| Diagnosis | RAS(+), n (%) | RAS(−), n (%) | P |
|---|---|---|---|
| Chronic glomerulonephritis | 21 (39.62%) | 21 (39.62%) | NS |
| Diabetic nephropathy | 8 (15.09%) | 7 (13.21%) | NS |
| Hypertensive nephropathy | 6 (11.32%) | 4 (7.55%) | NS |
| Tubulointerstitial nephritis | 3 (5.66%) | 2 (3.77%) | NS |
| ADPKD | 4 (7.55%) | 6 (11.32%) | NS |
| Unknown | 4 (7.55%) | 6 (11.32%) | NS |
| Others | 7 (13.21%) | 7 (13.21%) | NS |

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; NS, not significant; RAS, renin-angiotensin system.