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RESEARCH ARTICLE

PROTEINURIA, ACE INHIBITOR OR ANGIOTENSIN II RECEPTOR BLOCKER AND SURVIVAL IN KIDNEY TRANSPLANT RECIPIENTS IN BULGARIA

***Vera Stamenova, Maya Petrova, Tanya Metodieva, Borelli Zlatkov, Jean Filipov, Martin Lubih and Emil Paskalev**

Medical University Sofia, Nephrology and Transplantation Center, UMHAT "Alexandrovska", Sofia, Bulgaria

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ABSTRACT

Background: After kidney transplantation proteinuria not only indicates graft pathology, but contributes to disease progression, graft loss and worse patient outcomes. Treatment of the underlying cause may not always result in normalizing protein excretion rates. Angiotensin converting enzyme inhibitors (ACEinh) or angiotensin receptor blockers (ARBs) treatment in kidney transplant recipients is a field of debate and ongoing research focusing on patient survival and delaying the need for dialysis after kidney transplantation.

Methods: We performed a retrospective single center study on 277 patients who received a kidney transplant between 01.01.2005 and 31.12.2010. We ran a Log Rank test and univariate and multivariate Cox regression analysis to study the effect of proteinuria and ACEinh/ARB treatment on survival. In patients with biopsy proven graft pathology (N 91) we compared survival rates of patients with and without ACEinh/ARB treatment.

Results: Proteinuria at 3 months post transplantation significantly lowered patient ($p=0.021$) and graft survival (overall and censored for death –$p<0.001$ and $p=0.004$). Proteinuria was an independent factor for worse outcomes for the overall graft survival (HR 1.718, 95% CI 1.072 to 2.752, $p=0.024$) and graft survival censored for death (HR 3.866, 95% CI 1.968 to 7.598, $p<0.001$). Treatment with ACEinh/ARBs had a significant effect on proteinuria excretion after 12 months ($p=0.005$), on patient survival in the whole cohort (HR 0.437, 95% CI 0.198 to 0.967, $p=0.041$) and in patients with biopsy proven graft pathology ($p=0.029$).

Conclusions: Kidney transplant recipients benefit from receiving treatment with an ACEinh/ARB, especially in the presence of proteinuria and proven graft pathology.

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INTRODUCTION

Proteinuria – a hallmark of renal pathology contributes to progression of chronic kidney disease independent from the initial diagnosis, and is associated with higher cardiovascular and all-cause mortality /1, 2, 3/. Apart from the pathogenic treatment of the underlying conditions, a large number of randomized controlled trials evaluate the effect of additional treatment and measures to reduce proteinuria and cardiovascular risk. These include good blood pressure control, treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEinh/ARBs), calcium channel blockers (CCBs), aldosterone antagonists, lower protein and salt intake, body weight control, treatment with statins, smoking cessation. Use of renin-angiotensin aldosterone system inhibitors such and ACE inhibitors or ARBs is proved to be beneficial for lowering proteinuria levels, slowing disease progression and delaying the need for renal replacement therapy in patients with native kidneys with /4/ or without diabetes /5/. KDIGO guidelines recommend the use of ACE inhibitors or angiotensin receptor blockers in hypertensive patients with albuminuria between 30 and 300mg/24h and in normotensive patients with albuminuria above 300mg/24h /6, 7/. After renal transplantation proteinuria is an indicator for an array of conditions – from recurrent disease or de novo glomerulonephritis to specific allograft problems such as acute and chronic rejection, mTOR inhibitors treatment side effect, CNI nephrotoxicity. As with native kidneys, proteinuria is a treatment challenge after kidney transplantation. It is associated with disease progression, graft loss and worse patient outcomes. Roodnal et al prove that the risk for cardiovascular and all-cause mortality increases with 16% for a 1g/24h increase in protein excretion rate. Proteinuria 12 months after transplantation correlates with two times lower

***Corresponding author:* Vera Stamenova,**
Medical University Sofia, Nephrology and Transplantation Center, UMHAT "Alexandrovska", Sofia, Bulgaria

graft survival compared with aproteinuric patients /8/. Amer et al demonstrate that even low grade proteinuria - <500mg/24h, is associated with a fourfold increase in the risk for graft failure and nephrotic range proteinuria leads to a 19 times higher risk /9/. In a study assessing the link between early proteinuria and allograft survival, proteinuria at 3 months post transplantation, donor age and percentage of panel reactive antibodies were linked to significantly lower graft survival /10/. The importance of proteinuria management is highlighted by the frequency of monitoring after KT – once in the first month, every 3 months during the first year and annually thereafter. Kidney biopsy is recommended at new onset of proteinuria and in case of unexplained proteinuria above 3g/24h. KDIGO recommend the use of ACE inhibitors or ARBs as first line therapy only in patients with proteinuria above 1g/24h /11/.

A growing number of studies focus on the effects of RAAS-inhibition after renal transplantation with conflicting results. In a prospective double blind controlled trial Knoll et al. do not observe reduction in the risk of doubling of serum creatinine, graft failure or survival in kidney transplant recipients who received an ACE inhibitor ramipril /12/. Some studies suggest that ACE inhibitor treatment may reduce proteinuria but has no effect on slowing the progression of CKD to ESRD or improving patient survival in kidney transplant recipients /13/. In a 2009 review of 60 trials including a total number of 3802 kidney transplant patients the authors studied the effect of ACEinh/ARBs compared to placebo or calcium channel blockers (CCBs) and found no significant proteinuria reduction but a significant decline in eGFR in patients taking ACEinh/ARBs (-8.1ml/min)/14/. A metaanalysis published in 2017 is inconclusive to whether ACE inhibitors/ARBs improve outcomes in kidney transplant recipients/15/. A metaanalysis of 3 RCTs and 2 cohort studies with 20024 KTRs found that there was reduced risk of renal graft loss among renal transplant recipients who receive ACE inhibitors or ARBs but the result was not significant /16/. Other authors observed improved patient survival without any effect on long term graft function. This improved survival is explained with a lower number of cardiovascular events without any effect on delaying the need for dialysis treatment /17/. In 2013 a randomized controlled trial was published, evaluating the effect of ACE inhibitors on long term graft survival and the end points were graft loss, doubling of serum creatinine, cardiovascular event or death. For a period of 10 years 36 kidney transplant recipients treated with ACE inhibitors were followed and compared to 34 transplant patients without such therapy. A significant increase in proteinuria was observed only in the control group, as well as more cardiovascular events. No significant difference in kidney function between the two groups was observed /18/. In a rat model Hamar et al. found that ACE inhibitors delay glomerulosclerosis and tubulointerstitial injury and thus prevent some of the key mechanisms for graft injury /19/.

Most of the studies in this literature review state that due to the small number of trials, patients and short period of observation, they could not make a conclusive recommendation on ACE inhibitors/ARBs use after kidney transplantation. Until now a study on proteinuria and ACEinh/ARB treatment effects on graft and patients survival in Bulgarian kidney transplant recipients had not been done. The aim of the article is to study the effect of proteinuria on graft and patient survival and to look at the possibilities to improve survival with an ACE inhibitor or ARB treatment.

MATERIALS AND METHODS

In a retrospective single center study in UMHAT "Alexandrovska", Sofia, Bulgaria, we included all KTRs who received a kidney graft between 01.01.2005 and 31.12.2010 (N 277) and compared survival rates depending on proteinuria excretion on the 3rd month post transplantation (N 240). We divided the patients into two groups – with normal proteinuria excretion rates (bellow 0.15g/24h) and with overt proteinuria (above 0.15g/24h) and compared survival rates of the patient and graft (censored for death and overall). In the Wilcoxon signed rank test we looked at protein excretion rate change after the start of ACEinh/ARB therapy. Using Cox regression analysis we identified factors that affected graft and patient survival and in the multivariate regression analysis looked for the effects of proteinuria and treatment with ACE inhibitors or ARBs. Further we identified 91 KTRs with biopsy proven graft pathology and studied the effect of at least 12 month ACEinh/ARB treatment on survival rates using Log rank test and Cox regression analysis. Statistical analysis of the data was performed using IBM SPSS Statistics 2010 and Microsoft Excel 2010. Categorical data was compared using chi-square test, quantitative data with normal distribution - with paired sample t-test, or Mann-Whitney U-test when the distribution differed from normal. We used Kaplan Meier log rank test to look at survival rates and univariate and multivariate Cox regression to report hazard ratios.

RESULTS

To see the effect of proteinuria on patient and graft survival, we identified 240 KTRs who received a kidney graft between 01.01.2005 and 31.12.2010 and compared survival rates depending on proteinuria excretion on the 3rd moth post transplantation. Patients without graft function on the 3rd month were, naturally, excluded. We divided the patients into two groups – with normal proteinuria excretion rates (bellow 0.15g/24h) and with proteinuria (above 0.15g/24h). The characteristics of the patients are summarized in Table 1. There was a significant decline in patient survival (p=0.021), graft survival censored for death (p=0.004) and overall graft survival (p<0.001) in the group of patients with proteinuria above 0.15g/24h 3 months after kidney transplantation – Figure 1. Using Wilcoxon Signed ranks test we found statistically significant reduction in proteinuria after 12, 24 and 36 months of treatment with an ACEinhibitor or ARB in patient with proteinuria at the start of treatment – from 0.901g/24h SD 0.825 to 0.533g/24h SD 0.710 (p=0.009) after 12 months, after 24 months –0.0.694g/24h SD 0.721 (p=0.001) and 36 months – 0.642g/24h SD 0.740 (p=0.016), after 60 months the significance was lost- proteinuria was 0.584g/24h SD 0.801 (p=0.128). For patients without proteinuria (N 60) ACEinh/ARB treatment did not prevent its occurrence - we compared proteinuria at the start of treatment (0.143g/24h SD 0.021) with proteinuria at 12 (0.213g/34h SD 0.241, p=0.010), 24 (0.277g/24h SD 0.312, p<0.001), 36 (0.295g/24h SD 0.365, p=0.002) and 60 months (0.266g/24 SD 0.280, p<0.001) and found significant rise in proteinuria excretion. The overall effect, however, was proteinuria reduction – significant after 12 months of treatment with an ACEinhibitor or ARB – from 0.513g/24h SD 0.688 to 0.365g/24h SD 0.540 (p=0.005), later

the significance was lost but proteinuria remained lower compared to the beginning - after 24 months –0.467g/24h SD 0.575 (p=0.807) and 36 months – 0.448g/24h SD 0.584 (p=0.997), after 60 months – proteinuria was 0.403g/24h SD 0.585 (p=0.465) - Fig. 2.

Using Paired sample T-test we did not find significant change in eGFR with ACEinh/ARB treatment – eGFR at the beginning was 57.95 ml/min/1,73m^2 SD 23.065, at 12 months was 55.18 ml/min/1,73m^2 SD 17.419 (p=0.078), at 24 months – 56.61 ml/min/1,73m^2 SD 18.993 (p=0.549), at 36 months – 56.55 ml/min/1,73m^2 SD 19.125 (p=0.489) and at 60 months – 56.48 ml/min/1,73m^2 SD 18.412 (p=0.395). We performed Cox regression analysis and in the univariate analysis found statistical significance for the following factors affecting patient survival- Table 2. From the multivariate analysis factors that remained significant were: diabetes (HR 3.682, 95% CI 1.610 to 8.422, p=0.002), treatment with an ACE inhibitor/ARB (HR 0.437, 95% CI 0.198 to 0.967, p=0.041) and treatment with corticosteroids (HR 5.126, 95% CI 1.194 to 22.016, p=0.028). Factors significant for graft survival censored for death are presented in Table 3. From the multivariate analysis factors that remained significant were alloantibodies (HR 2.471, 95% CI 1.056 to 5.786, p=0.037) and proteinuria at 3 months (HR 3.866, 95% CI 1.968 to 7.598, p<0.001) Factors significant for overall graft survival are listed in Table 4.

From the multivariate analysis factors with significance for overall graft survival were proteinuria at 3 months (HR 1.718, 95% CI 1.072 to 2.752, p=0.024), corticosteroid use (HR 4.399, 95% CI 1.703 to 11.362, p=0.002), diabetes (HR 3.107, 95% CI 1.597 to 6.048, p=0.001), eGFR at 3 months (HR 0.985, 95% CI 0.970 to 1.000, p=0.046) and use of statins (HR 0.206, 95% CI 0.072 to 0.590, p=0.003). We wanted to see if ACEinh/ARBs prescription would add some benefit to graft survival in patients, who had biopsy proven graft pathology. We identified 91 patients with biopsy-proved graft pathology (acute or chronic rejection, CAN, glomerulonephritis relapse or de novo, CNI toxicity) and divided them into two groups – patients who were treated with an ACEinh/ARB for at least 12 months and started treatment in the first 24 months after KT (N 36) and a control group (N 33). Mean duration of ACEinh/ARB treatment was 35 months SD 4.421. The characteristics of the patients are shown on Table 5. No patients died in the treatment group for the study period. In the log rank test the overall graft survival was higher in patients who received treatment but not significantly p=0.070, 72 month survival rate in the treatment group was 88.9%, compared to 72.7% in the control group Fig.3. Graft survival censored for death was still higher in the treatment group but not significantly p=0.474, with 72 month survival rates of 88.9% versus 83.4%. Patient survival was significantly higher in the treatment group (no event for 72 month period) p=0.029 (from the log rank and Breslow tests) - 100% in the treatment group and 87.2% in the control group Fig 3.

Table 1. Patient characteristics

Factor	Proteinuria below 0.15g/24h	Proteinuria above 0.15g/24h	P value
NUMBER	147	93	
AGE	36.90 SD 13.108	41.15 SD 12.546	0.016
SEX			0.202
Men	95 (64.6%)	68 (73.1%)	
Women	52 (35.4%)	25 (26.9%)	
Months on HD	38.55 SD 35.172	39.63 SD 39.458	0.826
Donor type			0.065
cadaveric	55 (37.4%)	37 (39.8%)	
living	92 (62.6%)	56 (60.2%)	
Donor age	39.71 SD 13.936	44.69 SD 11.075	0.032
Donor sex			0.329
Men	88 (59.9%)	48 (51.6%)	
Women	59 (40.1%)	45 (48.4%)	
HLA mismatches	3.34 SD 1.078	2.67 SD 1.33	0.040
Alloantibodies	30 (20.4%)	13 (14%)	0.206
Systolic pressure	129.31 SD 15.134	131.98 SD 16.105	0.200
Diastolic pressure	82.07 SD 9.567	82.53 SD 12.096	0.747
BMI	24.56 SD 5.25	24.88 SD 4.06	0.612
Kidney biopsy	57 (38.78%)	32 (34.41%)	0.487
Acute rejection	15 (26.32%)	10 (31.25%)	ns
Chronic rejection	9 (15.78%)	8 (25%)	ns
Chronic nephropathy	18 (31.58%)	5 (15.62%)	ns
CNI tox	8 (14.04%)	3 (9.38%)	ns
GN (relapse or de novo)	7 (12.28%)	6(18.75%)	ns
eGFR at 3 months	59.48 SD 22.51	50.88 SD 23.056	0.005
eGFR 12months	60.03 SD 19.39	52.74 SD 19.31	0.009
eGFR 24months	61.05 SD 18.26	52.81 SD 19.31	0.002
eGFR 36months	60.23 SD 20.55	53.17 SD 20.94	0.021
eGFR 60 months	59.67 SD 21.33	54.89 SD 18.54	0.133
Hemoglobin	136.16 SD 17.71	132.97 SD 15.86	0.244
DGF	22 (15%)	29 (31.2%)	0.003
Immunosuppression			
CS	101 (68.7%)	74 (79.6%)	0.065
AZA	14 (9.5%)	12 (12.9%)	0.412
MMF	116 (78.9%)	79 (84.9%)	0.243
CsA	68 (46.3%)	49 (52.7%)	0.332
Tacrolimus	62 (42.2%)	35 (37.6%)	0.063
mTORinhibitor	19 (12.9%)	9 (9.7%)	0.187

Table 2. Factors significant for patient survival (Cox regression analysis)

Factor	HR	P value	95% CI
eGFR at month 3 (above 56ml/min/1,73m2)	0.977	0.015	0.959 to 0.995
Proteinuria above 0.15g/24h at month 3	2.952	0.013	1.260 to 6.918
Corticosteroid	5.785	0.017	1.378 to 24.293
Tacrolimus	0.266	0.007	0.102 to 0.696
Cyclosporin A	2.795	0.010	1.279 to 6.106
Azathioprine	3.800	0.001	1.684 to 8.574
ACEinh/ARB	0.396	0.020	0.182 to 0.866
Nondihydropyridine CCBs	4.546	0.001	1.853 to 11.150
Diabetes	3.212	0.003	1.470 to 7.017

Table 3. Factors significant for graft survival censored for death (Cox regression analysis)

Factor	HR	P value	95% CI
eGFR at month 3(above 56ml/min/1,73m2)	0.958	<0.001	0.936 to 0.980
Proteinuria at month 3 (above 0.338g/d)	2.924	<0.001	1.915 to 4.466
Proteinuria at month 6 (above 0.306g/d)	3.172	<0.001	2.130 to 4.724
Alloantibodies	3.214	0.003	1.476 to 7.000
Corticosteroid	3.426	0.045	1.028 to 11.413
Cyclosporin A	2.876	0.013	1.250 to 6.616
Azathioprine	4.720	<0.001	1.975 to 11.280
Systolic BP (above 130.339)	1.024	0.038	1.001 to 1.046
Diastolic BP (above 82,246)	1.043	0.015	1.008 to 1.080

Table 4. Factors significant for overall graft survival (Cox regression analysis)

Factor	HR	P value	95% CI
eGFR at month 3 (above 56ml/min/1,73m2)	0.969	<0.001	0.955 to 0.983
Proteinuria at month 3(above 0.338g/d)	2.242	<0.001	1.576 to 3.190
Proteinuria at month 6(above 0.306g/d)	2.459	<0.001	1.686 to 3.587
Corticosteroid			
Tacrolimus	0.352	0.001	0.186 to 0.666
Cyclosporin A	2.832	<0.001	1.602 to 5.009
Azathioprine	4.193	<0.001	2.312 to 7.604
MMF	0.466	0.009	0.263 to 0.824
ACEinh/ARB	0.503	0.014	0.291 to 0.869
Nondihydropyridine CCBs	3.798	<0.001	1.857 to 7.767
Diabetes	2.363	0.007	1.270 to 4.397
Statin use	0.221	0.004	0.060 to 0.611

Table 5. Patient characteristics

Factor	ACEinh/ARB treatment	Control group	P value
NUMBER	36	33	
AGE	34.20 SD 12.4	36.13 SD 14.378	0.560
SEX			0.099
Men	28 (77.8%)	20 (60.6%)	
Women	8 (22.2%)	13 (39.4%)	
Months on HD	33.94 SD 29.262	28.7 SD 32.174	0.484
Donor type			0.672
cadaveric	11 (30.6%)	11 (33.3%)	
living	25 (69.5%)	22 (66.7%)	
Donor age	41.24 SD 13.274	36.12 SD 10.885	0.209
Donor sex - male	19 (52.8%)	24 (72.7%)	0.141
HLA mismatches	3.22 SD 0.972	3.00 SD 1.41	0.595
Alloantibodies			0.177
None	29 (80.6%)	22 (66.7%)	ns
HLA class I/II	7 (19.4%)	11 (33.3%)	ns
DGF	11 (30.6%)	5 (15.2%)	0.130
Systolic pressure	133.61 SD 14.223	135.78 SD 18.144	0.583
Diastolic pressure	84.03 SD 8.436	85.63 SD 11.76	0.519
BMI	24.65 SD 4.94	25.68 SD 6.286	0.450
Diabetes	5 (13.9%)	6 (18.2%)	0.804
eGFR 12months	57.92 SD 18.698	53.57 SD 19.98	0.365
eGFR 24months	56.36 SD 17.150	51.52 SD 17.54	0.267
eGFR 36months	52.11 SD 17.297	48.93 SD 18.8	0.489
eGFR 60months	55.53 SD 18.836	48.0 SD 21.18	0.156
Proteinuria month 12	0. 428 SD 0.558	0.193 SD 0.133	0.807
Proteinuria month 24	0.360 SD 0.441	0.171 SD 0.060	0.516
Proteinuria month 36	0.638 SD 1.734	0.276 SD 0.363	0.390
Proteinuria month 60	0.359 SD 0.389	0.655 SD 0.799	0.799
Statin	9 (25%)	4 (12.5%)	0.191
Imunosuppression			
Corticosteroid	28 (77.8%)	26 (78.8%)	0.919
MMF	33 (91.7%)	28 (84.8%)	0.377
AZA	1 (2.8%)	3 (9.1%)	0.262
Tacrolimus	15 (41.7%)	13 (39.4%)	0.848
CsA	14 (38.9%)	16 (48.5%)	0.422
mTOR inh	8 (22.2%)	4 (12.1%)	0.269
Kidney biopsy			
Acute rejection	9 (25%)	10 (30.3%)	ns
Chronic rejection	8 (22.2%)	8 (24.2%)	ns
Chronic nephropathy	7(19.4%)	9 (27.3)	ns
CNI toxicity	7 (19.4%)	3 (9.1%)	ns
GN- relapse or de novo	5 (14%)	3 (9.1%)	ns

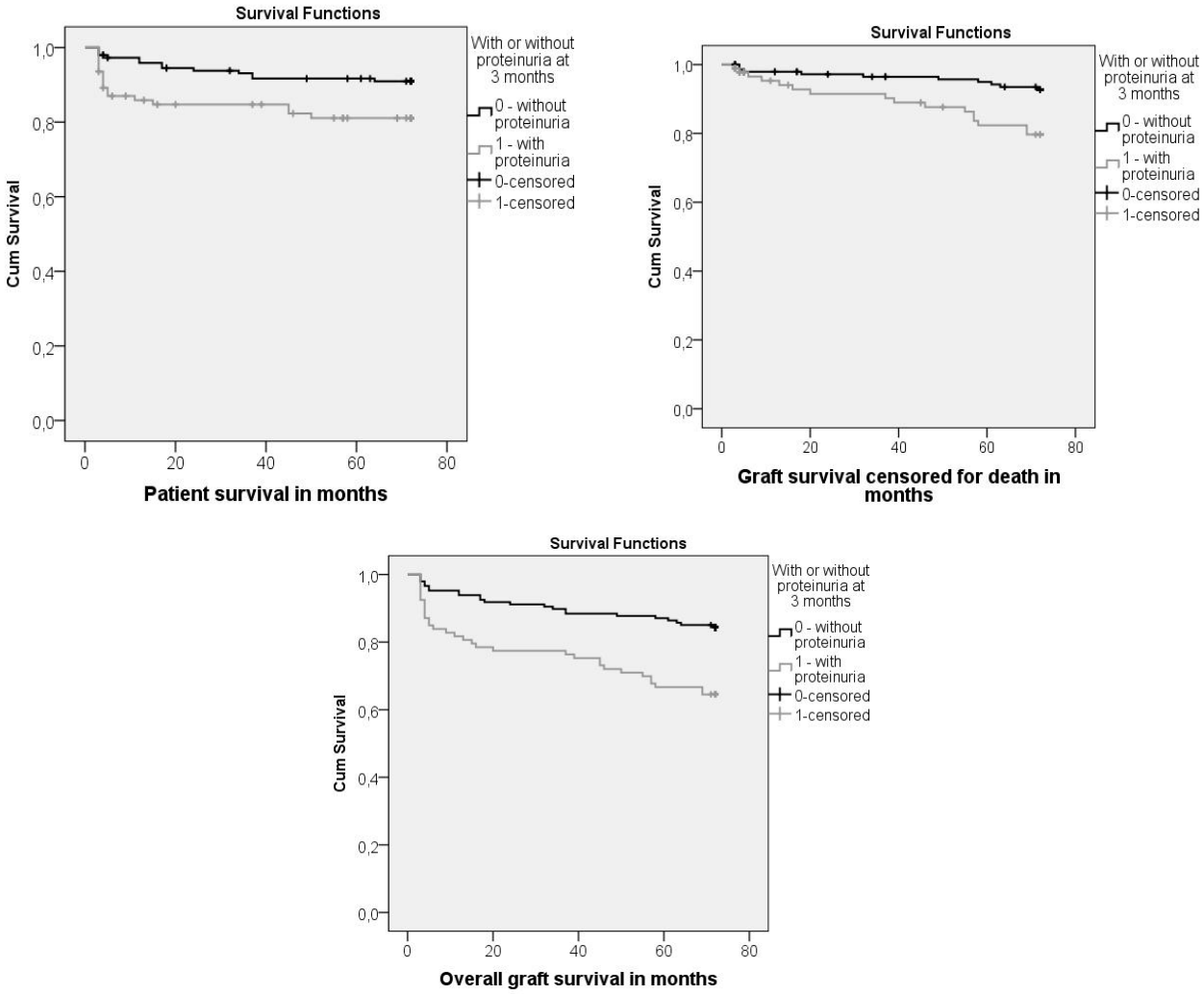

Figure 1. Statistically significant decline in patient and graft survival in patients with proteinuria above 0.15g/24h 3 months after KT

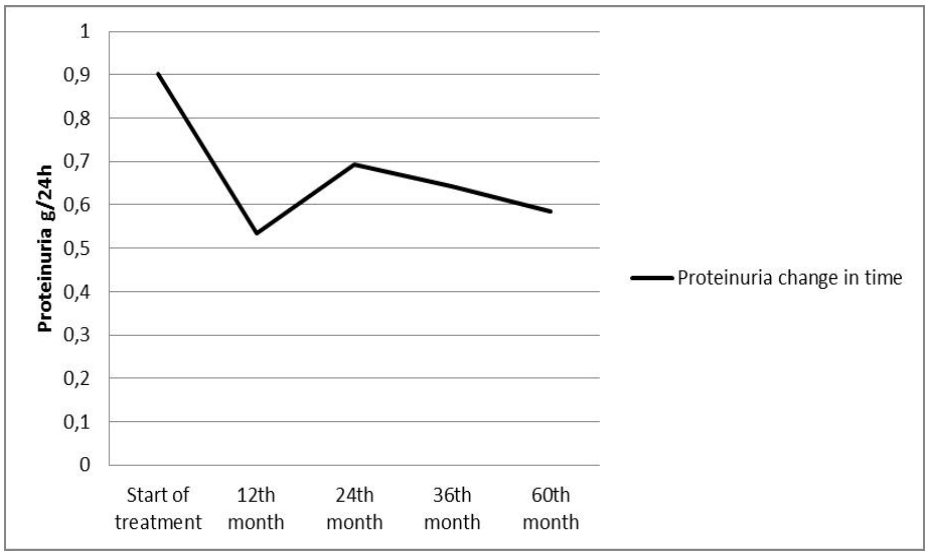

Figure 2. Change in proteinuria levels in time in patients treated with an ACE inhibitor or ARB

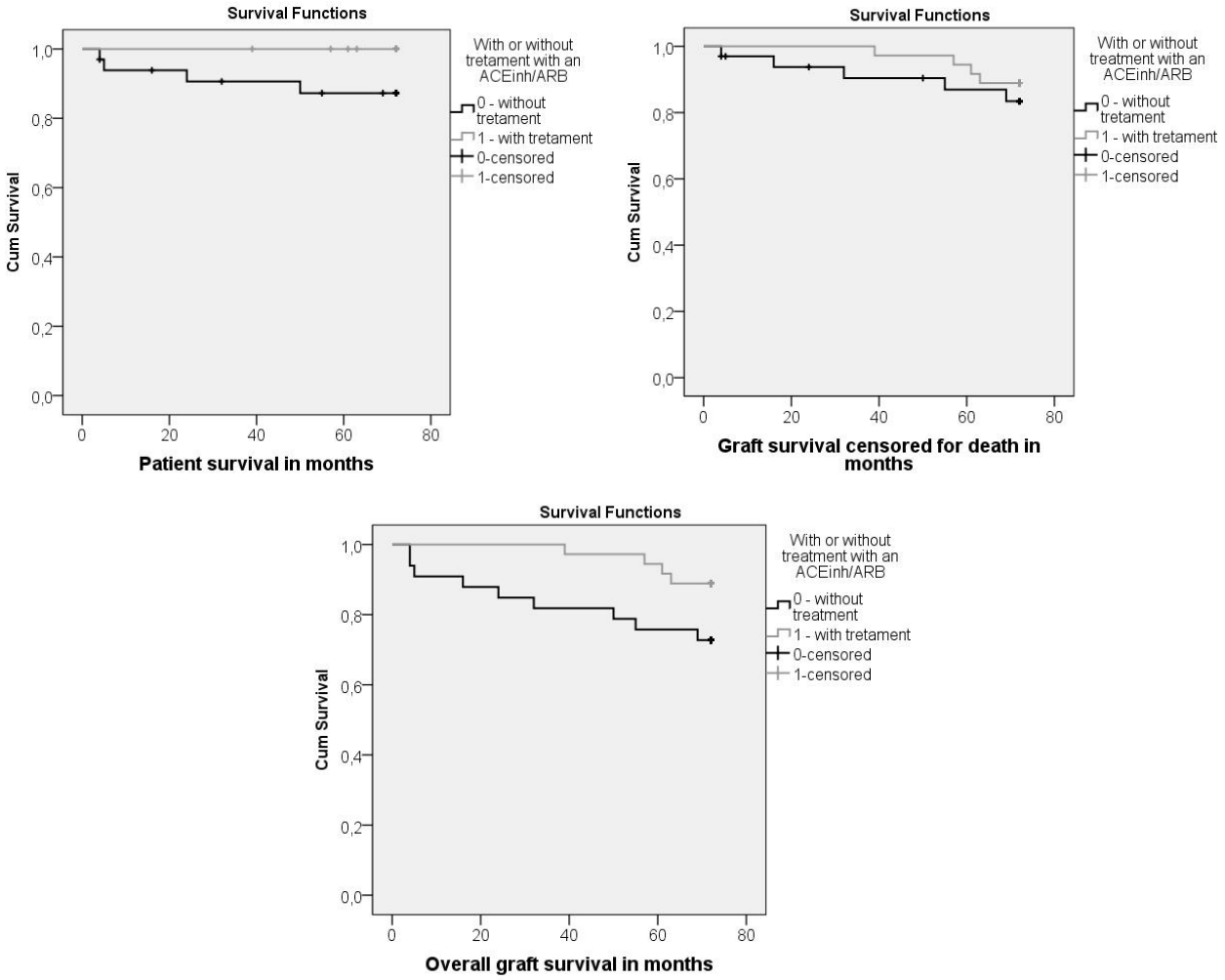

Figure 3. Patient and graft survival (censored for death and overall) – with and without ACEinh/ARB treatment in patient with biopsy proven graft pathology

From the univariate Cox regression factors significant for graft survival censored for death were alloantibodies (HR 4.771, 95% CI 1.190 to 19.121, p=0.027), proteinuria at 6 months (HR 3.270, 95% CI 1.295 to 8.254, p=0.012) and treatment with dihydropyridine calcium channel blockers (HR 5.322, 95% CI 1.105 to 25.641, p=0.037). From the multiple regression analysis only proteinuria at six months remained significant – HR 3.898, 95% CI 1.216 to 12.494, p=0.022. For patient survival we did not run Cox regression. For overall graft survival significant factors were proteinuria at 6 months (HR 2.899, CI 1.186 to 7.088, p=0.020) and use of dihydropyridine calcium channel blockers (HR 4.915, 95% CI 1.351 to 17.874, p=0.016) in the univariate and multivariate analysis.

DISCUSSION

This is the first study in kidney transplant recipients in Bulgaria observing the effect of proteinuria on patient and graft survival (overall and censored for death). Similar to reports in the literature we found lower patient and graft survival in patients with protein excretion above 0.15g/24h even in the early period (3 months) post transplantation. Patients with protein excretion above 0.15g/24h had lower graft function and were older compared to aproteinuric patients. In the multivariate analysis, however, proteinuria at 3 months had a significant negative effect on overall graft survival (HR 1.718, 95% CI 1.072 to 2.752, p=0.024) and graft survival censored for death (HR 3.866, 95% CI 1.968 to 7.598, p<0.001), independent from age or graft function at 3 months. Age did not have a significant effect on survival in any of the groups. Graft function at 3 months post transplantation had a significant effect on overall graft survival (HR 0.985, 95% CI 0.970 to 1.000, p=0.046). Treatment with ACE inhibitors or ARBs lowered protein excretion significantly after 12 months of treatment (p=0.005), although it did not prevent new onset of proteinuria. From the multiple regression treatment with these medications was a significant factor positively affecting patient survival (HR 0.437, 95% CI 0.198 to 0.967, p=0.041). In the univariate analysis ACE inhibitors/ARBs had a significant effect on overall graft survival (HR 0.503, 95% CI 0.291 to 0.869, p=0.014) but in the multivariate analysis this significance was lost. Treatment with ACE inhibitors or ARBs did not have significant effect for graft survival censored for death. From the multivariate analysis treatment with corticosteroids had a negative impact on patient survival (HR 5.126, 95% CI 1.194 to 22.016, p=0.028) and overall graft survival (HR 4.399, 95% CI 1.703 to 11.362, p=0.002), which probably reflects the fact that corticosteroid withdrawal is considered only for stable patients with low immunologic risk and without proteinuria. In the light of experimental data of ACE inhibitors slowing glomerulosclerosis and IF/TA/19/ in animal models, we identified patients with biopsy proven graft pathology and divided them into two groups - treatment and control group. Again, we found benefit only for patient (p=0.029) but not for graft survival. The study conducted in

our nephrology and transplantation center confirmed the results of larger studies about the reductions of proteinuria in kidney transplant recipients treated with ACEinh/ARBs. In some larger studies, however, no improvement in graft function and patient survival was observed. The authors state that CCBs may have benefits as first line medications for hypertension in kidney transplant patients compared to ACE inhibitors/14/. From the performed analysis in the current study, we conclude that ACEinh/ARB treatment in kidney transplant recipients has a statistically significant benefit for the patient but not for death censored graft survival. Treatment with dihydropiridine calcium channel blockers had a negative effect on graft survival censored for death (HR 5.322, 95% CI 1.105 to 25.641, p=0.037) and overall graft survival (HR 4.915, 95% CI 1.351 to 17.874, p=0.016) in patients with biopsy proven graft pathology. We would be cautious to use this class of antihypertensive medications as first line therapy in this group of patients.

Conclusion

In the kidney transplant patients in Bulgaria we found:

1. Significant reduction of patient and graft survival (overall and sensored for death) in patients with proteinuria above 0.15g/24h
2. Significant negative effect of proteinuria at 3 months on graft survival censored for death and overall graft survival from the multivariate analysis.
3. Statistically significant reduction of proteinuria 12 months after the start of treatment with an ACEinh/ARB without significant reduction in eGFR.
4. Significant positive effect of ACE inhibitor/ARB treatment on patient survival from the multivariate analysis.
5. Significant positive effect of ACE inhibitor/ARB treatment on patient survival in patients with graft pathology proven with biopsy.
6. Treatment with dihydropyridine calcium channel blockers has a significant negative effect on graft survival censored for death and overall graft survival in patients with biopsy proven graft pathology.

Drawback of the study is that it is retrospective. To eliminate early post transplantation complications we included patients who had proteinuria 3 months after KT. Information concerning 6 year kidney graft survival in Bulgaria is published for the first time. In the future more patients will be included in the study with a longer observation period.

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REFERENCES

1. Gorriz, Jose Luis et al. Proteinuria: detection and role in native renal disease progression. *Transplantation Reviews*, Volume 26 , Issue 1 , 3 - 13
2. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis *The Lancet*, Volume 375, Issue 9731 , 2073 - 2081
3. Brad C. Astor, Stein I. Hallan, Edgar R. Miller, III, Edwina Yeung, Josef Coresh; Glomerular Filtration Rate, Albuminuria, and Risk of Cardiovascular and All-Cause Mortality in the US Population. *Am J Epidemiol*., 2008; 167 (10): 1226-1234. doi: 10.1093/aje/kwn033
4. Eboh, C., & Chowdhury, T. (2015). Management of diabetic renal disease. *Annals of Translational Medicine*, 3(11). doi:10.21037/6863
5. Dattolo, P.C., Gallo, P., Michelassi, S. et al. *J Nephrol*., (2016) 29: 809. doi:10.1007/s40620-016-0290-9
6. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease volume 2 issue 5 December 2012
7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1-150
8. Roodnat JI, Mulder PG, Rischen-Vos J et al. Proteinuria after renal transplantation affects not only graft survival but also patient survival. Transplantation. 2001 Aug 15;72(3):438-44
9. Amer H, Cosio Fernando G. Significance and Management of Proteinuria in Kidney Transplant Recipients J Am Soc Nephrol. 2009 Dec;20(12):2490-2. doi:10.1681/ASN.2008091005. Epub 2009 Oct 9.
10. Pierre Galichon, Yi-Chun Xu-Dubois, Serge Finianos, Alexandre Hertig, Eric Rondeau; Clinical and histological predictors of long-term kidney graft survival. *Nephrol Dial Transplant,* 2013; 28 (6): 1362-1370. doi: 10.1093/ndt/gfs606
11. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *American Journal of Transplantation,* 2009; 9 (Suppl 3): S1–S157.
12. Knoll, Greg A et al. Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial. 2016 *The Lancet Diabetes & Endocrinology*, Volume 4 , Issue 4 , 318 - 326
13. Paoletti E, Bellino D, Marsano L, Cassottana P, Rolla D, Ratto E. Effects of ACE inhibitors on long-term outcome of renal transplant recipients: a randomized controlled trial. Transplantation. 2013 Mar 27;95(6):889-95. doi: 10.1097/TP.0b013e3182827a43
14. Cross, Nicholas B. Antihypertensives for Kidney Transplant Recipients: Systematic Review and Meta-Analysis of Randomized Controlled Trials Transplantation: 15 July 2009 - Volume 88 - Issue 1 - pp 7-18
15. Hiremath S, Fergusson DA, Fergusson N, Bennett A, Knoll GA. Renin-Angiotensin System Blockade and Long-term Clinical Outcomes in Kidney Transplant Recipients: A Meta-analysis of Randomized Controlled Trials. *Am J Kidney Dis*. 2017 Jan;69(1):78-86. doi: 10.1053/j.ajkd.2016.08.018. Epub 2016 Oct 4.
16. Cheungpasitporn W1, Thongprayoon C1, Mao MA1, Kittanamongkolchai W1, Sathick IJ1, Erickson SB1. The Effect of Renin-angiotensin System Inhibitors on Kidney Allograft Survival: A Systematic Review and Meta-analysis. *N Am J Med Sci*., 2016 Jul;8(7):291-6. doi: 10.4103/1947-2714.187141
17. Heinze G, Mitterbauer C, Regele H, Kramar R, Winkelmayer WC, Curhan GC, Oberbauer R: Angiotensin converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol.,* 17: 889–899, 2006
18. Zhang R, Laguardia H, Paramesh A, Mills K, Killackey M, McGee J, Alper B, Simon E, Lee Hamm L, Slakey D. Early

inhibition of the renin-angiotensin system improves the long-term graft survival of single pediatric donor kidneys transplanted in adult recipients. *Transpl Int*., 2013 Jun;26(6):601-7. doi:10.1111/tri.12087. Epub.2013,Mar 19.

19. Hamar P1, Kerjaschki D2. Blood capillary rarefaction and lymphatic capillary neoangiogenesis are key contributors to renal allograft fibrosis in an ACE inhibition rat model. Am *J Physiol Heart Circ Physiol*., 2016 Oct 1;311(4):H981-H990.doi:10.1152/ajpheart.00320.2016. Epub 2016, Aug 5.

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