Eur J Med Res (2005) 10: 161-168

Effect of Genetic Variation on Therapy with Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers in Dialysis Patients

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Abstract
Introduction: The role of interaction of polymorphisms in the Renin-Angiotensin-System (RAS) with angiotensin converting enzyme (ACE) or angiotensin receptor (AGTR1) inhibitors (RAS inhibitors) is unknown, as is the role of such therapy in end stage renal disease (ESRD) patients.
Methods: We enrolled all 445 prevalent patients with diabetic nephropathy receiving maintenance hemodialysis in 30 centers in Southern Germany from August 1999 to January 2000 for prospective survival analysis until December 2003. Blood pressure and medication was recorded at inclusion. We determined survival specific for allelic variants of the ACE (insertion/deletion), Angiotensinogen (M235T) and AGTR1 (A1166C) genes. The effect of therapy with RAS inhibitors at study inclusion was determined for the allelic variants of each gene. The primary end point was all cause mortality (ACM).
Results: For all polymorphisms, and for therapy with RAS inhibitors there was no significant effect on survival in the complete collective (n = 445), though there was an insignificant trend for improved survival in patients on AGTR1 antagonists. Increased ACM risk was associated with treatment with RAS inhibitors only in patients homozygous for the wild type AGTR1 1166A allele (HR 1.65, p=0.01). For all other polymorphisms, therapy with RAS inhibitors had no significant effect on ACM, irrespective of genotype. Similar results were obtained in patients with systolic ventricular dysfunction.
Conclusion: Our data do not show a survival advantage for type 2 diabetes hemodialysis patients receiving RAS inhibiting therapy. In addition, our data indicate that allelic variation in RAS genes and pharmacogenetic interaction with RAS inhibition does not affect mortality risk in diabetic hemodialysis patients.

Key words: hypertension, dialysis, renin-angiotensin-system, genetics, diabetes mellitus, nephropharmacology

Abbrevations: Angiotensin Converting Enzyme = ACE; Angiotensin II Receptor Type 1 = AGTR1; Renin-Angiotensin-System = RAS; Hazard Ratio = HR; Coronary Artery Disease = CAD; End Stage Renal Disease = ESRD; All Cause Mortality = ACM; Regional Wall Motion Abnormalities = RWMA; Ejection Fraction = EF

Introduction

Patients receiving maintenance hemodialysis for end stage renal disease (ESRD) have a dismal morbidity and survival prognosis [1, 2]. Cardiovascular events account for almost 50% of deaths [3]. These rates are probably higher in patients with diabetes mellitus type 2 [4]. In diabetic patients with or without renal insufficiency, pharmacological blockade of the renin-angiotensin system (RAS) has been shown to be effective in reducing cardiovascular and renal morbidity and mortality [5-8]. This effect may be due to a reduction in blood pressure [9, 10] and not applicable to patients without heart failure [11]. In a small, prospective study of the effect of perindopril and nitrendipine on pulse wave velocity in hemodialysis patients, the authors saw a reduction in mortality risk due to the ACE inhibitor that was independent of blood pressure reduction [12]. In the general dialysis population, retrospective studies have mostly shown no survival benefit of therapy with an angiotensin converting enzyme (ACE) inhibitor [13-15]. In one small study, therapy with an ACE inhibitor was associated with a decrease in mortality risk [16], while in another study on 60 patients on peritoneal dialysis, ramipril had no effect on the occurrence of the secondary outcome measure "cardiovascular events" [17]. In a retrospective analysis of the United States Renal Data System (USRDS), RAS blockade was associated with a significant decrease in 30-day mortality after acute myocardial infarction [18].

The pharmacogenetic interaction of antihypertensive therapy effectiveness with genotype of genes relevant to blood pressure physiology, specifically within the RAS, is the subject of intense research [19], yielding conflicting results typical for association studies [20]. In most publications, the outcome measure is change in blood pressure, seldomly survival or cardiovascular end points.

The D allelic variant of the ACE gene is associated with elevated serum levels of ACE [21], but with inconsistent effects on therapy with an ACE inhibitor [19]. The 235T polymorphism within the angiotensino-

gen gene (AGT) is associated with increased angiotensinogen plasma levels but an influence on blood pressure only in women [22]. This allele may be associated with a greater blood pressure reduction by RAS blockade than the 235M allele [23]. The 1166C allele of the angiotensin receptor type 1 gene (AGTR1) is associated with a small effect on blood pressure [24] and possibly an improved response to ACE inhibition [25].

As is the case with studies of pharmacological RAS blockade, there is sparse, if any, pharmacogenetic data for dialysis patients, let alone for dialysis patients with diabetes mellitus type 2. In our study, we examined a) the effect of RAS inhibition, b) the effect of genotype of the AGT, ACE and AGTR1 genes and c) the effect of therapy with an ACE or angiotensin receptor inhibitor in dependence of RAS genotype on all cause mortality and on cardiovascular end points. In a substudy, we examined the role of cardiac ejection fraction and regional wall abnormalities.

Methods

Subjects and Study Design

We included 445 Caucasian patients with type 2 diabetes mellitus and ESRD from 30 dialysis centers in Southern Germany from August 1999 to January 2000 for a prospective observational, non-interventional study [26]. All prevalent patients with the diagnosis ESRD due to diabetic nephropathy were recruited and a full clinical phenotype including details of medication was determined at baseline. Patients were recruited only if age was >35 years at diagnosis of diabetes mellitus. Patients with clinical signs of systemic or overt local infection were excluded (n = 13). Blood pressure was measured before the start of the dialysis session at the date of inclusion. Medical therapy was reassessed at last follow-up in censored patients or at the time of death.

In 218 patients, echocardiography had been performed in the 6 months before study inclusion. Patients were classified as having a reduced left ventricular ejection fraction if ejection fraction was documented as being "reduced" or ≤40%. Patients were classified as having regional wall motion abnormalities if this was documented so.

All patients were followed until 4th December 2003. Primary end point was all cause mortality. Cause of death was assessed where possible. Death due to myocardial infarction, cerebral ischemia, malignant arrhythmia, intracerebral hemorrhage or acute cardiac failure was defined as the combined secondary end point "cardio- and cerebrovascular", death due to myocardial infarction, malignant arrhythmia or acute cardiac failure was defined as the combined secondary end point "cardiac", death due to pneumonia or septicaemia of any cause as "infectious" and death due to trauma, gastrointestinal bleeding, cancer or liver cirrhosis was categorised as "other". In survival analysis detailed below, patients treated with an ACE or angiotensin receptor inhibitor were compared to those without such treatment. Next, the effect of genotype of the stated ACE, AGTR1 and AGT polymorphisms on survival was determined. Patients homozygous for the ACE deletion polymorphism were compared with patients with the insertion polymorphism (recessive model for D). Patients carrying the C allele of the A1166C AGTR1 polymorphism were compared with patients homozygous for the A allele (dominant model for 1166C). Patients carrying the C allele leading to a threonine (T) for methionine (M) substitution at amino acid position 235 in AGT were compared with patients homozygous for the T (amino acid M) allele (dominant model for 235T). Finally, the effect of RAS blockade on survival was determined for each genotype group, thus yielding 6 separate survival analyses of effect of RAS blockade in dependence of genotype.

The study was approved by the Ethics Committee of the Medical Faculty of the University of Regensburg (Study Nr: 97/38. GENDIAN: "Genetic and clinical predictors of morbidity, mortality and diabetic nephropathy with end stage renal disease in diabetes mellitus type 2 – a prospective cohort study"). All patients gave informed consent to participation in the study.

Clinical Parameters

At study inclusion, we determined cardiovascular risk profile and morbidity, medication history, laboratory parameters relevant to cardiovascular diseases, dialysis filter type and weekly duration of dialysis by questionnaire and reviewing the patients' charts. We determined date of birth and of diagnosis of diabetes mellitus, of nephropathy and of begin of dialysis therapy respectively. Specifically, date of onset of diabetes mellitus was determined as the date when a test for blood glucose was first abnormally high (either fasting blood glucose or glucose tolerance testing) and when the patient first took antidiabetic drugs. In addition, the patient chart was reviewed to obtain the date of diabetes onset. PAD status was classified clinically according to the Fontaine classification. Hereby, patients with angiographically proven, asymptomatic atherosclerotic lesions of lower extremity vessels were classified as Fontaine Stage I, those with intermittent claudication as Stage II, and patients with resting claudication as Stage III. Patients with extremity necrosis or amputation due to atherosclerotic vascular disease were classified as Fontaine Stage IV. Care was taken not to misclassify patients with neuropathic foot lesions as Fontaine Stage IV.

Specimen Collection and SNP Genotyping

10 mL whole blood samples were drawn prior to hemodialysis sessions, and centrifuged within 6 h. Serum was frozen at –80°C until analyses were performed. For determination of the AGT polymorphism at amino acid position 235 (M235T; dbSNP: rs699), of the AGTR1 polymorphism at position 1166 (A1166C, dbSNP: rs5186) and of the ACE 287 bp insertion/deletion polymorphism within intron 16, we used genomic DNA extracted by standard methods. Genotyping was performed by Taqman RT-PCR (AGT, AGTR1) and by the method described by Rigat et al. [21]. Except for the ACE I/D polymorphism, the distribution of genotypes did not deviate from that

expected from a population in Hardy Weinberg equilibrium. There were significantly more patients homozygous for the deletion polymorphism (n = 136) than expected (n = 120) by χ^2 analysis (p = 0.003).

Statistical Analysis

Results are expressed as mean (± 1 standard deviation), unless stated otherwise. Comparisons of continuous variables between groups were performed by Student's T-test, ANOVA or by Kruskal-Wallis test and of categorial variables by χ^2 or Fisher's exact test where applicable. Statistical significance in all tests was accepted at $p<0.05$. Power calculations for survival analysis were performed separately for each patient subgroup with the "PS Power and Sample Size Calculations" software package, Version 2.1.30 [27]. For the analysis of effect of RAS inhibition on survival, the study was powered with 0.8 to detect a hazard ratio of 1.8 with a 0.05 Type I error probability, given a 31.5% cumulative control survival rate at the end of the study, an accrual period of 6 months, a follow up of 52 months and considering the observed crossover from treated to control group and vice versa (see Results).

Survival analysis was performed by the Kaplan Meier method, comparing groups using the log-rank test. Censoring occurred for lost-to-follow-up, renal transplantation and if alive at the final examination. Duration of dialysis therapy from study inclusion onwards was the time variable. To correct for covariates, a Cox proportional hazard ratio model was applied. Covariates used for survival analysis and explorative statistics for comparison of patient groups were medication with ACE or AT-II receptor 1 antagonists, HMG-CoA-reductase inhibitors, platelet inhibitors (acetylsalicylic acid, ticlopidin or clopidogrel), calcium channel antagonists and betablockers (reference: no therapy), log CRP (log of CRP value measured in mg/L), age at start of dialysis therapy (years), duration of previous dialysis therapy and of diabetes at study inclusion (years), gender (reference: female), smoking history (reference: never-smoker), body mass index, systolic-diastolic blood pressure difference prior to the dialysis session at inclusion (mmHg), serum albumin (g/L), interaction term [history of myocardial infarction]*[presence of coronary artery disease], history of cerebral ischemia (reference: no such history) and history of coronary intervention including bypass surgery (reference: no intervention). Since we have shown significant interaction between log CRP and presence of peripheral arterial disease stage IV [26], we included the interaction term "[log CRP]*[PAD IV status]" as a covariate (reference of PAD status: no PAD IV).

First, the univariate hazard ratio was determined for each variable in the cohort (data not shown). Variables with a significant effect on HR ($p<0.1$), the variable "medication with RAS blocking therapy at baseline" and 2 variables selected by a-priori considerations of epidemiology (gender, smoking history) were included in the final model. Therapy with ACE- or AT-II recepor and HMG-CoA-reductase inhibitors, log CRP, [log CRP]*[PAD IV status], [history of myocardial infarction]*[presence of coronary artery disease], age at start of dialysis therapy, previous duration of dialysis therapy at study inclusion, gender, smoking history, body mass index were thus included in the regression model. Serum albumin and history of coronary intervention were subjected to stepwise backward selection since there was significant ($p<0.05$) interaction with body mass index and history of myocardial infarction respectively. The remaining variables were also subjected to stepwise backward selection by the LR method, with the threshold for exclusion being $p>0.1$.

Statistical analysis was performed with the SPSS® Version 11.5 software package (Chicago, USA).

Results

Patient Characteristics and Genotype Distribution

For ACE I/D polymorphism, 116 (26.2%) patients had the ACE II genotype, 189 (42.5%) the ID genotype and 136 (30.1%) the DD genotype. For the AGT M235T polymorphism, 107 (24.0 %) patients had the 235MM genotype, 228 (51.2%) the 235MT genotype and 110 (24.6%) the 235TT genotype. For the AGTR1 A1166C polymorphism, 238 (53.5%) patients had the 1166AA genotype, 178 (40.1%) the 1166AC genotype and 28 (6.4%) the 1166CC genotype.

The patient characteristics by RAS inhibiting therapy are presented in Table 1. Patients with RAS inhibiting therapy (n = 288) were treated significantly more frequently with platelet and calcium channel antagonists. In all other variables there was no significant difference between RAS inhibitor treatment groups.

Patients heterozygous for the ID polymorphism in the ACE gene were younger and had been on dialysis longer. Patients with the AGTR1 1166CC genotype had significantly less a history of cerebral ischemia. For all other variables, there were no significant differences between genotypes (data not shown).

Therapy with ACE or Angiotensin II Receptor Inhibitors

There was no significant difference in numbers treated with an ACE or AR inhibitor between the genotypes of the three polymorphisms.

At baseline, 59 patients were being treated with captopril (mean: 31 mg ± 23 mg per day), 61 patients with enalapril (mean: 9 ± 6 mg per day), 38 patients with ramipril (mean: 4 ± 3 mg per day), 33 patients with fosinopril (mean: 16 ± 5 mg per day), 26 patients with benazepril (mean: 9 ± 7mg per day), 6 patients with perindopril (mean: 2 ± 1mg per day), 1 patient with lisinopril, 4 patients with cilazapril (mean: 2 ± 1mg per day), 15 patients with losartan (mean: 49 ±18 mg per day), 9 patients with candesartan (mean: 11 ± 5 mg per day), 22 patients with valsartan (mean: 102 ± 62 mg per day), 11 patients with irbesartan (mean: 177 ± 69 mg per day) and 3 patients with eprosartan (mean: 400 ± 173 mg per day).

After study inclusion, 42 patients started treatment with RAS inhibiting medication in the course of the study and 56 patients discontinued treatment. In a comparison of patients remaining on initial RAS in-

Table 1. Clinical characteristics of patients with and without RAS inhibitor.

	+ ACE/AR-Inh N=288	- ACE/AR-Inh N=155	p
Blood pressure (systolic/diastolic, mmHg)	140 ± 23 / 74 ± 11	140 ± 24 / 74 ± 11	0.9 / 0.99
Male Sex	54.5%	55.8%	0.82
Age at inclusion (years)	67.2 ± 8.4	68.0 ± 7.9	0.3
Duration HD at inclusion (years)	2.45 ± 2.0	2.7 ± 2.2	0.18
Diabetes duration (years)	17.8 ± 9.5	18.1 ± 9.7	0.79
BMI	26.3 ± 4.3	27.1 ± 4.8	0.07
HbA1c (%)	6.9 ± 1.2	6.8 ± 1.1	0.47
CRP (mg/L)	13.5 ± 16.2	12.8 ± 14.7	0.65
Serum albumin (g/L)	42.2 ± 5.4	43.14.9	0.07
present- or ex-smoker	44.7%	43.6%	0.82
CAD	54.6%	63.2%	0.09
Myocardial infarction	28.7%	27.6%	0.81
Coronary intervention	17.7%	19.1%	0.73
Cerebral ischemia	30.9%	31.6%	0.88
PAD Stage IV	41.7%	44.2%	0.6
Reduced EF (≤40%)*	26.3%	29.6%	0.59
RWMA *	37.5%	41.5%	0.56
Platelet-Inh.	60.1%	46.8%	0.007
HMG-Co-A-Inh.	27.8%	26.9%	0.85
Calcium channel blocker	53.1%	35.3%	<0.001
Betablocker	26.0%	25.0%	0.81

CAD: coronary artery disease. Coronary intervention: PTCA, Stent or coronary bypass operation. BMI: body mass index. HD: hemodialysis. EF: ejection fraction. RWMA: regional wall motion abnormalities. * Data on RWMA and EF were available in n=218 patients. Statistical testing was performed with $\chi 2$ or two-sided t-test, where applicable.

hibiting therapy with patients discontinuing this treatment and with patients started after study inclusion, significant differences were noted only in systolic blood pressure at baseline: in patients newly started on an ACE or AR inhibitor blood pressure was higher than in the other patients (147 ± 21 mmHg vs. 140 ± 23 mmHg in patients with unchanged treatment vs. 134 ± 24 mmHg in patients with discontiuation of RAS blockade, p = 0.018). In all other anthropometric variables, there were no differences between the subgroups.

Cohort Survival

Of the 445 patients, 305 (68.5%) had died by the final examination of all patients on 4th December 2003. Overall mean survival from study inclusion onwards was 2.5 ± 1.4 years. Mean survival for patients with an event, defined as all cause mortality, was 1.84 (± 1.13) years, and 3.90 (± 0.77) years for patients without an event. 118 deaths were classified as "cardio- and cerebrovascular", 55 as "infectious" and 19 as "other". In 113 patients, the cause of death could not definitely be determined. In the majority of these cases, the patients died as a consequence of cardiac failure with concomitant infection.

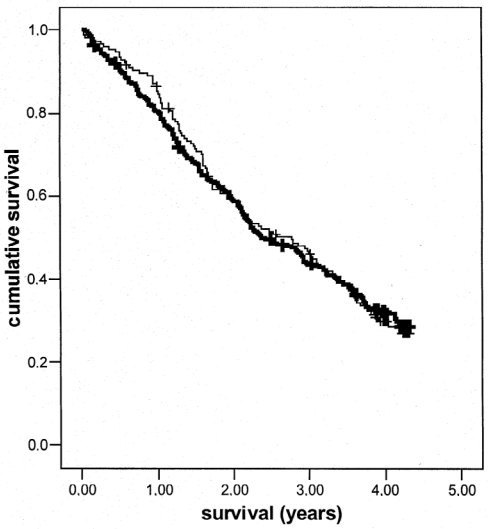

Fig. 1. Kaplan Meier analysis of survival on hemodialysis therapy (n=445) and effect of treatment with RAS inhibitors. End point is all cause mortality. Patients are censored for renal transplantation (n=11), lost to follow-up (n = 2) or if alive on December 4th, 2003 (n = 127). Patients treated with RAS inhibitors: bold line. Patients not treated with RAS inhibitors: thin line. Crosses represent censored patients. Log rank statistic = 0.01, df = 1, p = 0.97.

Table 2. Cox proportional hazard regression model of survival on hemodialysis therapy – multivariate analysis of effect of RAS blockade.

Covariate	HR	95% CI	p
Therapy with ACE or AT-II-receptor inhibitor (ref: no therapy)	1.07	0.84-1.37	0.6
Log CRP	1.32	0.99-1.74	0.05
[Log CRP] * [PAD IV status (ref: no PAD IV)]	1.44	1.14-1.8	0.002
[history of CAD] * [history of myocardial infarction]	1.7	1.3-2.23	<0.001
Age at dialysis initiation (per year increase)	1.03	1.01-1.05	0.001
dialysis duration prior to study (per year increase)	1.09	1.03-1.15	0.004
Body mass index (per unit increase)	0.98	0.95-1.01	0.18
Coronary intervention or surgery (ref: no intervention)	0.59	0.42-0.84	0.003
Gender (ref: female)	1.05	0.78-1.42	0.75
Smoking history (ref: never-smoker)	0.96	0.72-1.28	0.78
Therapy with HMG-co-A-reductase-inhibitors (ref: no therapy)	0.78	0.59-1.03	0.08

The time variable is survival from study inclusion onwards. All cause mortality is defined as event (n=305). Censoring is performed for renal transplantation (n=11), loss to follow-up (n=2) and if the patient is alive at the last examination (n=127). Cox regression modelling was performed as described in the Methods section. HR = hazard ratio.

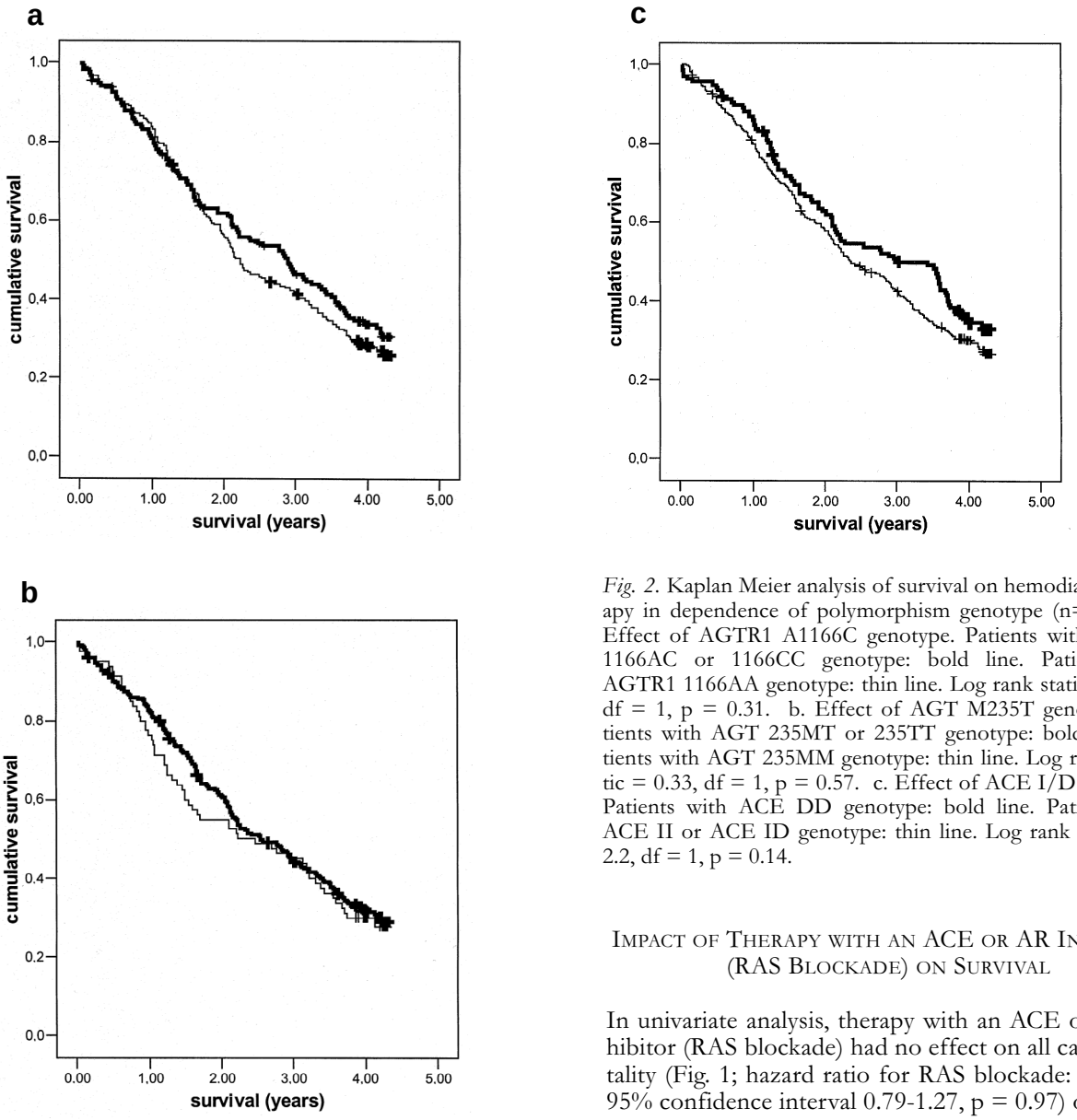

Fig. 2. Kaplan Meier analysis of survival on hemodialysis therapy in dependence of polymorphism genotype (n=445). a.: Effect of AGTR1 A1166C genotype. Patients with AGTR1 1166AC or 1166CC genotype: bold line. Patients with AGTR1 1166AA genotype: thin line. Log rank statistic = 1.0, df = 1, p = 0.31. b. Effect of AGT M235T genotype. Patients with AGT 235MT or 235TT genotype: bold line. Patients with AGT 235MM genotype: thin line. Log rank statistic = 0.33, df = 1, p = 0.57. c. Effect of ACE I/D genotype. Patients with ACE DD genotype: bold line. Patients with ACE II or ACE ID genotype: thin line. Log rank statistic = 2.2, df = 1, p = 0.14.

Impact of Therapy with an ACE or AR Inhibitor (RAS Blockade) on Survival

In univariate analysis, therapy with an ACE or AR inhibitor (RAS blockade) had no effect on all cause mortality (Fig. 1; hazard ratio for RAS blockade: HR=1.0, 95% confidence interval 0.79-1.27, p = 0.97) or on any

Table 3. Cox PH regression model of survival on hemodialysis therapy – multivariate analysis of effect of RAS blockade for each genotype group.

Genotype group		RAS blockade Multivariate Hazard Ratio for ACM	95% CI	p
AGTR1	1166AA	1.65	1.12-2.4	0.01
	1166AC + 1166CC	0.82	0.54-1.24	0.34
AGT	235MM	1.19	0.6-2.38	0.62
	235MT + 235TT	1.27	0.91-1.77	0.15
ACE	II + ID	0.99	0.73-1.35	0.96
	DD	1.35	0.84-2.19	0.22

Cox regression modelling was performed as described in the Methods section. ACM: all cause mortality.

of the secondary end points. Similar results were obtained in multivariate analysis (Table 2). There was a non-significant trend for improved survival in patients receiving an AR inhibitor in comparison with patients with an ACE inhibitor or without RAS inhibiting therapy ($p = 0.09$).

The lack of significant effect of RAS inhibitors on survival was also observed in the subgroup of patients with known regional wall motion abnormalities ($n = 85$; patients with RAS inhibitor: $n = 51$) and with a known reduced EF ($n = 60$; patients with RAS inhibitor: $n = 36$). In both subgroups $p>0.05$ in univariate analysis.

Impact of Genotype on Survival

In univariate and multivariate analysis, there was no effect of any polymorphism genotype on all cause mortality or the secondary end points (Fig. 2).

Impact of RAS Blockade on Survival by Genotype

In patients with the AGTR1 genotype 1166AA, therapy with RAS blockade led to an increase in risk for all cause mortality which was significant only in multivariate analysis (Table 3: multivariate HR = 1.65, 95% confidence interval: 1.12-2.42, $p = 0.01$). RAS inhibition showed a trend for increased risk for the combined secondary end point "cardiac death and death of indeterminate cause" (multivariate HR = 1.59, 95% confidence interval: 1.0-2.5, $p = 0.05$). For all other patients grouped by genotype, RAS inhibition had no effect on risk for all cause death or for any of the secondary end points in univariate or multivariate analysis (Table 3).

Discussion

Therapy with ACE and AR inhibitors has been shown to reduce morbidity and mortality after acute myocardial injury [28] and in patients with high cardiovascular risk including patients with diabetes [5-7]. The mechanisms by which this occurs appear to be manifold, including attenuation of myocardial remodeling [29], preservation of ischemic preconditioning [30], improvement of endothelial function [31] and of fibrinolysis [32], reduction of oxidative stress [33] and possibly by inhibiting chemokine-associated local vascular inflammation [34].

In the hemodialysis population, endothelial dysfunction, inflammation and severe atherosclerosis are prominent problems placing the patients at high risk for cardiovascular events [35-37]. Theoretically, RAS blockade in these patients would thus appear to provide a significant survival benefit. In a small, retrospective study, ACE inhibitors provided a significant survival benefit to hemodialysis patients [16]. In a large database search study, another group observed a reduction in mortality in ESRD patients treated with ACE inhibitors [18] after acute myocardial infarction. In contrast, we observed no survival benefit due to RAS blockade in our high risk cohort of diabetic dialysis patients. Importantly, the same applies if only patients are analysed with known ventricular dysfunction. One possible reason may be the fact that blood pressure in our cohort was fairly well – though not optimally – controlled and that, given its non-interventional design, the study was not a blood pressure lowering study. Interestingly, patients placed on RAS inhibitors after study inclusion had a higher mean blood pressure at baseline and showed a trend for improved survival in comparison with patients on RAS inhibitors throughout the study (data not shown).

There is mounting evidence against an effect of RAS blockade that is independent of simple blood pressure lowering [10, 11], which would be in support of our data. However, we cannot exclude that RAS blockade may have a positive effect in dialysis patients that is smaller than our study was powered to detect. Considering the high mortality observed in our cohort, this small effect would be clinically irrelevant.

In addition to the above, our study provides first evidence that mortality risk in diabetic dialysis patients is not significantly affected by polymorphisms in the ACE, AGTR1 and AGT genes and that genotype has only a small, if any, role in determining efficacy of RAS inhibiting therapy in a high risk dialysis population. Interestingly, the distribution of ACE I/D polymorphism genotype deviated significantly from that expected from a population in Hardy Weinberg equilibrium. The DD genotype was overrepresented, suggesting that DD genotype may be associated with a

high risk for ESRD. In a similarly designed study on patients with advanced ventricular systolic dysfunction, McNamara and colleagues found an improved heart transplant-free survival in patients with the ACE DD genotype if treated with a beta-blocker [38], and a maximal benefit from ACE inhibitors and betablockers in patients with the DD genotype [39]. Thus, pharmacological attenuation of the effects of increased ACE activity observed in patients with DD genotype appears relevant in patients with advanced heart failure. In contrast, this strategy appears to be markedly less important in dialysis patients including the patients in our study with left ventricular dysfunction, possibly since inflammation, infection and atherothrombotic events, and not end stage ventricular dysfunction, are the main causes of mortality.

The main limitation of our study is the lack of randomisation to RAS inhibiting therapy and the observational, non-interventional study design. Significant selection bias for treatment with an RAS inhibitor cannot be excluded. Accordingly, our results should be regarded as exploratory for future randomised, controlled studies. However, patients in the therapy subgroups were comparable in their anthropometric variables, thus reducing the risk of bias [40]. As discussed above, the study's power may have been too low to detect treatment effects. However, considering the Kaplan Meier survival plots, significant differences between groups in a larger study population should be small and clinically irrelevant.

We conclude that, whilst our data does not show any relevant survival benefit, also by genotype, of therapy with RAS inhibitors, RAS inhibition appears safe in diabetic hemodialysis patients. Even though the role of pharmacogenetic interaction in the RAS in a high risk diabetic dialysis population appears negligible in our study, controlled trials of antihypertensive medication randomised for genotype of other hypertension genes will be important to optimise treatment in this growing population of dialysis patients.

Acknowledgements: The support of the physicians, the patients, and the staff of the dialysis centers KfH Amberg, KfH Bayreuth, KfH Deggendorf, KfH Donauwörth, KfH Freising, KfH Freyung, KfH Fürth, KfH Hof, KfH Ingolstadt, KfH Kelheim, KfH München Elsenheimerstraße, KfH München-Schwabing, KfH Neumarkt, KfH Neusäß, KfH Oberschleißheim, KfH Passau, KfH Plauen, KfH Regensburg Günzstraße, KfH Regensburg Caritas-Krankenhaus, KfH Straubing, KfH Sulzbach-Rosenberg, KfH Weiden, Dialysezentrum Augsburg Dr. Kirschner, Dialysezentrum Bad Alexandersbad, KfH Bamberg, Dialysezentrum Emmering, Dialysezentrum Klinikum Landshut, Dialysezentrum Landshut, Dialysezentrum Pfarrkirchen, Dialysezentrum Schwandorf is gratefully acknowledged for participating in the study.

We wish to thank Claudia Strohmeier and Gabriele Spatar for expert technical assistance.

Conflict of interest statement: The authors have no conflict of interest to declare that would inappropriately influence or bias the content of the manuscript.

This study was supported in part by grants from the ReForM-C-Program of the Medical Faculty of the University of Regensburg, and by Ortho-Biotech (Janssen Cilag) to CAB.

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Received: February 4, 2005 / Accepted: March 10, 2005

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