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Original Paper

Use of Calcium Channel Blockers is Associated with Mortality in Patients with Chronic Kidney Disease

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Key Words
Calcium channel blockers • Chronic kidney disease

Abstract
Background/Aims: The use of antihypertensive medicines has been shown to reduce proteinuria, morbidity, and mortality in patients with chronic kidney disease (CKD). A specific recommendation for a class of antihypertensive drugs is not available in this population, despite the pharmacodynamic differences. We have therefore analysed the association between antihypertensive medicines and survival of patients with chronic kidney disease. ***Methods:*** Out of 2687 consecutive patients undergoing kidney biopsy a cohort of 606 subjects with retrievable medical therapy was included into the analysis. Kidney function was assessed by glomerular filtration rate (GFR) estimation at the time point of kidney biopsy. Main outcome variable was death. ***Results:*** Overall 114 (18.7%) patients died. In univariate regression analysis the use of alpha-blockers and calcium channel antagonists, progression of disease, diabetes mellitus (DM) type 1 and 2, arterial hypertension, coronary heart disease, peripheral vascular disease, male sex and age were associated with mortality (all $p<0.05$). In a multivariate Cox regression model the use of calcium channel blockers (HR 1.89), age (HR 1.04), DM type 1 (HR 8.43) and DM type 2 (HR 2.17) and chronic obstructive pulmonary disease (HR 1.66) were associated with mortality (all $p < 0.05$). ***Conclusion:*** The use of calcium channel blockers but not of other antihypertensive medicines is associated with mortality in primarily GN patients with CKD.

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Introduction

Current guidelines for antihypertensive drug therapy support the use of different classes of drugs in the management of hypertension for the general population [1-5] based on similar effectiveness in the prevention of cardiovascular endpoints. Data from clinical trials in small populations, selected diseases, or employing surrogate outcomes may favour a particular substance, but these trials cannot be extrapolated to cohorts that may require such drugs for a decade or longer and which are combined with other compounds for control of hypertension [6, 7].

In patients with chronic kidney disease (CKD) proteinuria is generally accepted as a marker of kidney disease progression and as a predictor for cardiovascular risk [8-11]. Improvement in proteinuria is associated with reduction in cardiovascular events [9]. In this group of patients blood pressure reduction using angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) is associated with reduction in proteinuria and slowing of nephropathy progression [12, 13]. Likewise, calcium channel blockers are effective antihypertensive agents in the general population and reduced mortality [14-16].

The effect of different classes of antihypertensive drugs on clinical endpoints has not been studied in prospective randomized trials in patients with CKD. Given that most compounds are available as generic products, a large-scale trial to assess comparative effectiveness will be of little if any attraction for commercial sponsors. In order to assess the potential for such a study we have analysed the use of ACE-inhibitors, ARB, beta-blockers, calcium channel antagonists and alpha-blockers in patients with CKD who underwent kidney biopsy.

Materials and Methods

Retrospective data from 2.687 consecutive patients who underwent kidney biopsy between 1992 and 2009 and analyzed by the department of clinical pathology were reviewed [17]. A group of 606 subjects from different nephrology centers with complete medical therapy data was identified and included into the analysis. The study protocol and data handling procedure was approved by the Ethics Committee of the Medical University of Vienna.

Patients were characterized by CKD-stages according to their kidney function prior to biopsy and during follow up. Patient visits after kidney biopsies were performed initially in a three to seven week period, extending to a three to six month period, depending on the respective histological diagnosis, consecutive immunosuppressive therapy or risk profile modification. Glomerular filtration rate (GFR) estimation was calculated via the MDRD formula. Progression of kidney disease was defined as deterioration of CKD stage ≥1 from the time of kidney biopsy to last kidney function measurement. Stable disease was regarded as constant or improved CKD stage from the time of kidney biopsy to last available kidney function measurement, without an episode of dialysis or kidney transplantation. Antihypertensive medication was maintained at least 4 weeks before and 4 weeks after kidney biopsy. Clinical endpoint data for death was obtained from the Austrian Dialysis Registry and from the central Austrian Registry for population statistics.

Statistical Analysis

For data description results are presented as median and 25-75% interquartile range or mean and standard deviation as appropriate. Missing variables were analyzed as blank values. For univariate analysis the Mann Whitney U test or the chi-squared test were used as appropriate. The Kaplan-Meier method was used to determine event-free survival and the log rank test was used to compare survival between subgroups. Univariate and multivariate regression analysis were performed using the Cox proportional hazard regression model to determine the effect of various variables on survival. Potential predictors were defined a priori or based on associations in the univariate analysis at a conservative threshold ($p < 0.10$). The Hosmer-Lemeshow test was used to assess goodness of model fit. We used SPSS Statistics for data management and calculations. A two sided p-value less than 0.05 was considered statistically significant. The authors performing the data analysis (D.G.H. and V.F.) were masked and were not involved in the data acquisition.

Table 1. Baseline characteristics of n = 607 patients with chronic kidney disease and undergoing kidney biopsy. Data presented as absolute numbers (%) or mean (25;75 percentile) (A). Histology findings are presented in absolute numbers (B)

A)	
Angiotensin converting enzyme (ACE) inhibitors	340 (56.0)
Angiotensin receptor blockers (ARBs)	140 (23.1)
Betablockers	165 (27.2)
Alphablockers	111 (18.3)
Calcium channel antagonists	226 (37.2)
Statins	137 (22.6)
Progression of disease	332 (54.8)
Diabetes Mellitus Type 1	18 (3.00)
Diabetes Mellitus Type 2	132 (21.7)
Arterial Hypertension	412 (67.9)
Coronary heart disease	85 (14.0)
Peripheral vascular disease	68 (11.2)
Cerebrovascular disease	19 (3.13)
Thrombembolic events	39 (6.43)
Hyperlipidemia	160 (26.4)
Chronic obstructive pulmonary disease	40 (6.59)
Male sex	372 (61.5)
Age	58 (49;70)
Proteinuria g/dl	1.8 (0.5;22.9)
Glomerular filtration rate (ml/min/1.73 m2)	52.4 (20.0;69.6)
B)	
Histology	*Absolute number*
Immunglobulin-A nephropathy	143
Membranous GN	106
Membranoproliferative GN	53
Minimal change GN	36
Primary FSGS	35
Diabetic nephropathy	89
Vasculitis	53
Goodpasture Syndrome	6
Systemic Lupus Erythematodes	49

Results

Patients were 58 years old (49;70) and 234 (38.5%) were female. Overall 114 (18.7%) patients died, 192 (31.6%) received consecutive dialysis while 97 (16%) underwent kidney transplantation during follow up. Median CKD stage at kidney biopsy was 3 (2;4). Baseline characteristics are shown in Table 1. Overall, of 108 patients without any anti-hypertensive substances 14 died (12.9%), of 205 patients with 1 substance 32 (19.4%), of 163 patients with 2 substances 33 (20.3%), of 76 patients with 3 substances 28 (36.8%), of 47 patients with 4 substances 6 (12.8%) and of 7 patients with 5 substances 1 (14.3%) patient died.

In univariate analysis the use of alpha-blockers and calcium channel antagonists, consecutive dialysis, progression of disease, diabetes mellitus type 1 and 2, arterial hypertension, coronary heart disease, peripheral vascular disease, chronic obstructive pulmonary disease, male sex, age and glomerular filtration rate were associated with mortality (all $p<0.05$, Table 2). No difference could be detected between patients with or without calcium channel blockers regarding proteinuria at baseline and follow up (Mann Whitney U and Wilcoxon rank test, both $p > 0.05$).

Table 2. Associations of mortality (n = 114) with different parameters in univariate analysis were tested via Pearson's Chi-Square Test

Parameter	p-value
Number of anti-hypertensive drugs	<0.05
Angiotensin converting enzyme (ACE) inhibitors	>0.05
Angiotensin receptor blockers (ARBs)	>0.05
Betablockers	>0.05
Alphablockers	<0.05
Calcium channel antagonists	<0.05
Statins	>0.05
Progression of disease	<0.05
Diabetes Mellitus Type 1	<0.05
Diabetes Mellitus Type 2	<0.05
Arterial Hypertension	<0.05
Coronary heart disease	<0.05
Peripheral vascular disease	<0.05
Cerebrovascular disease	>0.05
Thrombembolic events	>0.05
Hyperlipidemia	>0.05
Chronic obstructive pulmonary disease	<0.05
Male sex	<0.05
Age	<0.05
Glomerular filtration rate (ml/min/1.73 m2)	<0.05

Table 3. Multivariate cox regression analysis for mortality in patients with chronic kidney disease undergoing kidney biopsy ($p < 0.05$*)

Parameter	HR (CI)	p-value
Alphablockers	1.33 (0.83;2.15)	0.24
Calcium channel antagonists	1.89 (1.20;2.98)	0.006*
Diabetes Mellitus Type 1	8.43 (3.02;23.5)	<0.01*
Diabetes Mellitus Type 2	2.17 (1.10;4.28)	0.03*
Arterial Hypertension	0.84 (0.47;1.49)	0.55
Coronary heart disease	0.87 (0.51;1.49)	0.61
Peripheral vascular disease	1.41 (0.78;2.56)	0.25
Chronic obstructive pulmonary disease	1.66 (1.06;2.61)	0.03*
Male sex	0.85 (0.53;1.34)	0.47
Age	1.04 (1.03;1.06)	<0.001*
Glomerular filtration rate (ml/min/1.73m2)	0.99 (0.98;1.01)	0.26
Minimal change glomerulonephritis	0.60 (0.13;2.67)	0.50
Diabetic nephropathy	1.17 (0.57;2.41)	0.64
Number of anti-hypertensive drugs	0.96 (0.73;1.26)	0.76

We further tested the influence of histological diagnoses after kidney biopsy on mortality in our patient cohort but only minimal change glomerulonephritis and diabetic nephropathy showed an influence on mortality in univariate analysis (both $p < 0.05$, Pearson's Chi-Square Test). These parameters were therefore included in the multivariate analysis.

In the multivariate analysis regression model we included all parameters showing an association with mortality from the univariate analysis. As glomerular filtration rate defines

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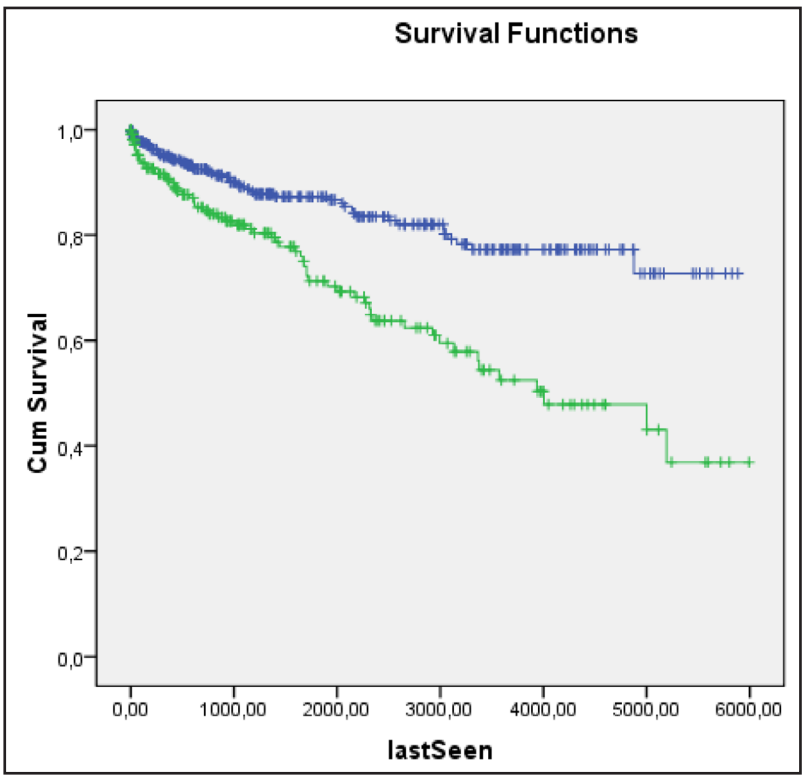

Fig. 1. Kaplan-Meier curve of patients with chronic kidney disease after kidney biopsy with (green line) and without (blue) calcium channel blocker use ($p < 0.001$).

CKD stage, stable or progression of disease, only GFR was implemented in the multivariate regression model (Table 3). After multivariate adjustment the use of calcium channel blockers (HR 1.89), age (HR 1.04), diabetes mellitus type 1 (HR 8.43) and 2 (HR 2.17) and chronic obstructive pulmonary disease (HR 1.66) were associated with mortality in our patients cohort (all $p < 0.05$, Table 3).

We further tested any interactions between substances patients were prescribed. We could only detect an univariate association of alpha-Blockers with mortality ($p < 0.05$, Pearson's Chi-Square Test). We could not confirm this in a multivariate regression model ($p > 0.05$, 0.09 (0.34;2.43).

The Kaplan Meier curve shows that the increase in mortality in patients with use of calcium channel blockers becomes apparent between the 1st to 2nd years after kidney biopsy (Fig. 1).

Discussion

Our study demonstrates an association between the use of calcium channel blockers and mortality in patients with chronic kidney disease. We could further detect associations with both types of diabetes, age and chronic obstructive pulmonary disease.

Calcium channel blockers have been demonstrated to exert beneficial effects on the reduction of proteinuria, reducing mortality, or effective blood pressure control in end stage renal disease [18-20]. This was, however, not consistent across all studies [21, 22]. In our study we detected an association of the use of calcium channel blockers and mortality. These controversial findings are also reported for long-acting agents in broader patient populations [3, 23, 24]. Observational studies as well as some systematic overviews report an increased risk for cardiovascular events with the use of some calcium antagonists [25-27]. Some of the earlier data primarily addressed the increased cardiovascular risk associated with immediate-release nifedipine, and the hazard in high-risk patient subsets such as patients

in the immediate post myocardial infarction period or those with unstable angina. One may speculate that the differences might be due to different calcium channel blocker antagonist substances e.g. amlodipine or nifedipin. While especially amlodipine has been demonstrated to exert beneficial effect, especially when added to ACE-I treatment, nifedipin use might be associated with a detrimental outcome [18, 26].

In our study we could not detect an association of statin use and mortality in our patients' cohort. However, Statins have been demonstrated to lower death and major cardiovascular events in people with CKD not requiring dialysis and have an important role in primary prevention of cardiovascular events and mortality in people who have CKD [28]. On the other hand, some important factors such as baseline creatinine level, baseline GFR, and cardiovascular disease history may affect the results. The effects of statin therapy on cardiovascular disease in patients with baseline creatinine levels >1.5 mg/dL was not statistically significant [29]. Similar effects were also found in a subgroup analysis of total mortality in patients with baseline creatinine levels >1.5 mg/dL, baseline GFR <60 mL · min^{-1} · 1.73 m^{-2}, and a cardiovascular disease history [29]. Therefore, to date data regarding study use in CKD patients is still conflicting.

Further, we could not detect an association of ACE-I or ARB use on mortality in our study. The effect of treatment with ACEI or ARBs on CKD or dialysis patients' survival is controversial. These drugs may have positive effects on residual renal function, vascular access and the uraemic myocardium, which in turn may be reflected in better survival, although other studies have not been able to demonstrate this benefit [30-32]. However, in a cohort of nondialysis-dependent patients with CKD, ACEI/ARB administration was associated with greater survival [33].

One limitation of our study is the lack of single substance monitoring. As for calcium channel blockers or ACE-I or ARB use one may speculate that our contradictory findings might relate to the substance-class-group-analysis we performed and not analyzing single substances. Further, the medication patients were on might have differed over time e.g. one patients with 8 month duration another with 2 years. However, when compared with other studies, comparable differences appear when substances were investigated singularly. In addition our study setting was chosen to assess medication influence when kidney function is declining and further strategies appear urgent. Further, one may criticize that our study collective appears to be very heterogeneous because of a broad range of risk profiles. On the other hand, the point of kidney biopsy where kidney function worsens, either via a GFR decline or presence of macroalbuminuria, carries the potential chance to evaluate the effectiveness of different treatment strategies. Therefore, the potential bias might rather be related to study inclusion or moderate patient numbers. Last, our study may carry a selection bias because of two factors. We only included patients where kidney biopsy appeared to be suitable or carried the potential chance of curative options. Patients with non-albuminuric CKD-stage 3 or stable kidney function were not included. Discriminating diuretic therapy indications was not assessed in our study. Differentiation of the indication these substances were given either for hypertension or CKD was difficult because of the retrospective design of our study and no information about this was given in the questionnaire. Further, sample size especially in subpopulations might have been a limiting factor as we e.g. could not detect an association of coronary heart disease with mortality.

In patients undergoing kidney biopsy calcium channel blocker use was associated with mortality. We could detect no interactions among the antihypertensive agents and no association of mortality/survival with ACE-I or ARB use.

Disclosure Statement

The authors state that they have no conflict of interest and had full access to data. The authors state that the work is original; the work has not been, and will not be published, in

whole, or in part, in any other journal; and all the authors have agreed to the contents of the manuscript in its submitted form.

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