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Treatment of cyclosporine induced hypertension: Results from a long-term observational study using different antihypertensive medications

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ABSTRACT

Post-transplant hypertension (PTH) is a common complication in cyclosporine immunosuppressed patients; however choosing the right antihypertensive medication is challenging. In a long-term observational study (≤13y) we examined different antihypertensive medications on graft/patient survival of kidney recipients with pre-existing and PTH. Altogether thirty-three co-variables were analyzed including dose and type of immunosuppressive and antihypertensive medication, co-medications, serum biochemistries and the glomerular filtration rate (GFR). A Cox proportional-hazard multivariable survival model was developed to detect a Hazard Ratio (HR) of 3.0 at the Bonferroni corrected level $\alpha = 0.0015$. Importantly, a significant relationship between immunosuppressive cyclosporine dose/serum concentration, systolic blood pressure (SBP) and GFR ($p < 0.001$) was observed with post-transplant hypertension being a major risk factor (HR6.1) for graft/patient survival. Although all medications lowered effectively elevated SBP the risk of graft failure/death was significantly increased when hypertension was treated with ACE inhibitors or β-blockers (HR3.3 and 3.1) but not with angiotensin receptor- and/or Ca-channel blockers. Antihypertensive medication was associated with a decline in GFR but β-blockers alone or in combination with ARB and/or CCB improved GFR. Neither BMI nor any of the drug combinations used in immunosuppression, i.e. prednisolone, mycophenolic acid, azathioprine and/or sirolimus influenced patient and/or graft survival while decision tree analyses informed on complex dependencies between immunosuppressive medications, dose of anti-hypertensive drug and diuretics in the management of hypertension. In conclusion, our study is suggestive for graft/patient survival to be influenced by the class of antihypertensive medication. A prospective randomized clinical trial is needed to confirm the results.

1. Introduction

More than 30 years ago cyclosporine (CsA) was introduced as a new class of immunosuppressive agent to revolutionize transplantation medicine [1]. This cyclic peptide inhibits calcineurin, a phosphatase, which dephosphorylates nuclear factor of activated T-cell (NFAT). As a result NFAT cannot translocate into the nucleus to control gene expression of interleukin 2 (IL2). This cytokine is a potent T-cell growth factor and repression of IL2 promotes graft acceptance. Although calcineurin inhibitors (CNI) are highly effective immunosuppressive agents their use is associated with hypertension, nephrotoxicity, metabolic alterations (hyperlipidemia and diabetes mellitus), neurotoxicity, gingival hypertrophy and hypertrichosis [2–6] that cannot be entirely controlled by dose reduction and may require switching to alternative medications such as mTOR inhibitors. Furthermore, co-medications are required to treat CNI induced adverse drug reactions. Despite the significant challenges in the control of side effects CNI-based immuno-suppressants are still commonly used with nearly 5 million defined daily doses in Germany alone in 2012 [7].

The pathogenesis of CsA induced hypertension is considered to be multifactorial [2]. Research identified cyclosporine to diminish levels of the vasodilatory prostacyclin PGI2 and endothelium derived relaxing factor and to reduce NO activity. Apart from endothelial dysfunction CsA treatment leads to increased production of the vasoconstrictive peptide endothelin-1 [8], to reduced glomerular filtration rates and to increased sodium reabsorption thereby causing greater pressure loads. There is also evidence for CsA to influence blood pressure control through the renin-angiotensin-aldosterone system (RAAS) [9].

Abbreviations: ACEi, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin receptor blocker; CCB, Calcium channel blockers; CNI, Calcineurin inhibitor; CsA, Cyclosporin A; ESKD, End-stage kidney disease; HNF4 alpha, Hepatic nuclear factor 4 alpha; HR, Hazard ratio; NFAT, Nuclear factor of activated T-cell; Tx, Transplantation

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Importantly, CsA induced hypertension has been the subject of several meta-analyses [10, 11]; however, a detailed evaluation of different antihypertensive drugs or combinations of it in the blood pressure lowering of hypertensive kidney transplant patients has not been attempted. We hypothesized that the different classes of antihypertensive medications is an important determinant in graft/patient survival and therefore analyzed clinical findings in a Cox proportional hazard multivariable model.

The primary objective of the study was to assess graft/patient survival in kidney transplant patients with pre-existing and post-transplant hypertension receiving different classes of antihypertensive medications. The secondary objective was to define the relationship between dose of immunosuppression and combinations of antihypertensive drug treatment on systolic blood pressure. The third objective was to explore the relationship between CsA dose, systolic blood pressure and doses of mono- or combined treatment regimens in the management of hypertension based on decision tree analysis.

2. Material and methods

2.1. Data collection

Approval was obtained from Hannover Medical School's ethical review board and comprehensive patient information was retrieved from the institutional database. The data were anonymized and de-identified prior to analysis. This single-center retrospective study consisted of 204 kidney transplant patients and involved 156 patients with pre-existing and 42 cases of post-transplant hypertension studied over an observation period of 13 years. Table 1 provides summary statistics describing the clinical characteristics while detailed information on the medical history and antihypertensive medication of individual patients is given in Supplementary Table S1 and S2. Furthermore, Supplementary Fig. S1 informs on the age distribution of donors and recipients and the cold ischemia time (hours). The frequency of kidney transplant patients entering the study during the entire observation period is given in Supplementary Fig. S2.

2.2. Statistical testing strategy

A comprehensive description of the statistical testing strategy is given in supplementary file S1. The drug treatment effects on transplant/patient survival was judged relevant, if associated with a hazard ratio (HR) of at least 3.0 which corresponds to a difference of 70% to 89% in the survival rate after 5 years. Taking the different observation times and a Bonferroni correction factor of 33 for multiple testing in the multivariate setting into account, a sample size of $N = 204$ patients was calculated to achieve a power of 80% for the two-sided log-rank test that would detect a Hazard Ratio (HR) of 3.0 at the level $\alpha = 0.05$ [12]. This number of patients also proved to be sufficient to investigate other co-variables (=secondary parameters) of interest. The power analysis and sample size (=PASS) was computed with the PASS software version 14 (https://www.ncss.com/software/pass/).

The following donor and patient specific criteria were considered: 1. Gender, 2. BMI, 3. Cold ischemia time, 4. Histocompatibility based on a panel of antigens, 5. Age of donor and recipient, 6. Transplant and/or patient survival, 7. Redialysis and/or re-transplantation, 8. Cause of death, i.e. malignancies or cardiovascular or others, 9. Hypertension prior to transplantation or CsA-induced the decision to treat was based on the diagnosis of hypertension, i.e. ≥140/90 mmHg. The BP measurements were recorded by healthcare professionals and 3451 measurements were considered for in-depth analysis, 10. Management of hypertension based on ACE inhibitors, calcium channel (CCB)-, angiotensin receptor (ARB)- and/or β-blockers, diuretics or a combination thereof, 11. Dose of anti-hypertensive drugs. 12. Dose of CNI and serum CsA levels. Note, the immunosuppressive treatment consisted either of CsA alone, CsA and prednisolone, CsA, sirolimus and prednisolone, CsA, prednisolone and mycophenolic acid and the combined CsA, prednisolone, mycophenolic acid and azathioprine. 13. Diabetes mellitus prior to or post-transplant with or without insulin, 14. Clinical laboratory findings to assess transplant function including estimated glomerular filtration rate.

Patient characteristics including age of donor, recipients, cold ischemia time and pharmacotherapy are given in Supplementary Table S1 and S2 as well as Supplementary Fig. S1.

2.3. Cox proportional-hazard multivariable survival model

A full description of the model is given in supplementary file S1. A series of prognostic factors in uni- and multivariate logistic regression analyses were studied as to identify single parameters and constellations of it that will impact survival. Altogether, 33 covariates were purposefully selected, and their relevance for graft and patient survival was evaluated by considering time constant basal variables marked as (1) in Table 2 and encompass gender to HLA status/matching. Additionally, time dependent variables grouped in (2) immunosuppression, (3) antihypertensive drugs, (4) systolic blood pressure and (5) laboratory parameters were considered. Importantly, dose of immunosuppression, antihypertensive medication, blood pressure recordings and laboratory parameters changed over time.

To define clinical significance at each stage of the analysis a stepwise backward elimination of single covariates was computed using the exclusion criterion of $p > 0.05$. The nominal alpha for Bonferroni correction was specified separately and is marked by a star in Table 2. By applying this procedure, the prognostic role of each factor could be judged within the multivariate setting. Thus, if a factor was significant at one but not the next stage of analysis its influence on survival diminished and was likely mediated by the set of the next stage variables. Vice versa, if a factor remained significant throughout all stages, its association with survival may be interpreted as specific and therefore independent of the other factors evaluated. Such a model building enables an identification of clinically relevant covariates of survival in a cohort with pre-existing and post-transplant hypertension.

3. Results

The study cohort consisted of 111 male and 93 female patients and the average recipient age was balanced, i.e. 47.9 and 47.6 years for males and females, respectively. Table 1 provides summary statistics describing the clinical characteristics; individual patient data including the medical and drug history are given in Supplementary Table S1 and S2. Note, the average follow-up period post kidney transplantation was 7.3 ± 3.0 years and included 42 patients or 21% of the cohort that was investigated over a period of ≥10 year (Supplementary Fig. S2). An additional 6 cases were included which did not develop post-transplant hypertension but received ACE inhibitors for renoprotection or β-blockers as adjuvant medications for the treatment of back pain, migraine and/or essential tremor.

During the entire observation period 29 deaths occurred in addition to 18 patients requiring dialysis; however none of these patients received a second transplant. The cancer related mortality of the entire cohort consisted of two cases of bronchial carcinoma, one case each of urothelial-, breast and clear cell renal cell carcinoma as well as one case of leiomyosarcoma. Additionally, 7 cases of cardiovascular mortality and 5 cases of septicemia were encountered while for 11 cases the cause of death could not be established.

The data were analyzed by considering (1) time constant basal variables and time dependent covariates linked to (2) immunosuppressive medication, (3) drug treatment for hypertension, (4) systolic blood pressure readings and (5) clinical laboratory findings that may highlight additional covariates to influence survival (Table 2).

Table 1
Summary patient characteristics.

Patient characteristics		Hypertension		
		preexisting	Posttransplant	Total cases
		N = 156 (76.5%)	N = 48 (23.5%)	N = 204
Gender	Female	69 (44.2%)	24 (50%)	93 (46.6)
	Male	87 (55.8%)	24 (50%)	111 (54.4%)
BMI	Minimum	15.61	18.42	15.61
	Median	25.17	24.58	24.92
	Mean	25.21	24.96	25.15
	Standard deviation	4.02	3.65	3.93
	Maximum	37.93	33.91	37.93
Recipient age [years]				N = 204
	Minimum	11.00	15.00	11.00
	Median	50.00	51.00	50.00
	Mean	46.94	50.46	47.76
	Standard deviation	14.99	11.89	14.37
	Maximum	73.00	71.00	73.00
Donor age [years]				N = 196
	Minimum	3.00	7.00	3.00
	Median	42.00	49.00	44.00
	Mean	40.98	46.07	42.20
	Standard deviation	16.87	15.98	16.77
	Maximum	74.00	74.00	74.00
Cold ischaemia time [hours]				N = 185
	Minimum	2.00	2.58	2.00
	Median	20.75	21.54	21.11
	Mean	20.16	22.12	20.64
	Standard deviation	8.43	9.85	8.82
	Maximum	39.41	60.00	60.00
Gender compatible transplantation	Female to female	24	10	34 (17.3%)
	Male to male	43	14	57 (28.9%)
Gender incompatible transplantation	Female donor/male recipient	41	10	51 (25.9%)
	Male donor/female recipient	42	13	55 (27.9%)
HLA compatibility (A1, A2, B1, B2, D1, D2)	1 out of 6	24 (16.2%)	6 (12.8%)	30 (15.4%)
	2 out of 6	42 (28.4%)	10 (21.3%)	52 (26.7%)
	3 out of 6	31 (20.9%)	12 (25.5%)	43 (22.1%)
	4 out of 6	24 (16.2%)	6 (12.8%)	30 (15.4%)
	5 out of 6	13 (8.8%)	8 (17.0%)	21 (10.8%)
	6 out of 6	3 (2.0%)	2 (4.3%)	5 (2.6%)
Outcome	Graft survival	135 (86.5%)	22 (45.8%)	157 (77%)
	Graft failure/redialysis	10 (6.4%)	8 (6.7%)	18 (8.8%)
	Death due to cancer	0 (0%)	6 (12.5%)	6 (2.9%)
	Death due to cardiovascular disease	3 (1.9%)	4 (8.3%)	7 (3.4%)
	Death due to septicaemia	3 (1.9%)	2 (4.2%)	5 (2.5%)
	Death unknown cause	5 (3.2%)	6 (12.5%)	11 (5.4%)
Comorbidities	Diabetes, non-insulin-dependent	11 (7.1%)	1 (2.1%)	12 (5.9%)
	Diabetes, insulin-dependent	24 (15.4%)	5 (10.4%)	29 (14.2%)
	Myocardial infarction	12 (7.7%)	2 (4.2%)	14 (6.9%)
	Coronary heart disease	24 (15.4%)	6 (12.5%)	30 (14.7%)
	Atrial flutter	3 (1.9%)	1 (2.1%)	4 (2.0%)
	Atrial fibrillation	11 (7.0%)	2 (4.2%)	13 (6.4%)
	Hyperlipidemia	61 (39.1%)	3 (6.3%)	64 (31.4%)
	Hyperuricemia	31 (19.9%)	1 (2.1%)	32 (15.7%)
	Stenosis	11 (7.0%)	2 (4.2%)	13 (6.4%)
	Arterial occlusive disease	19 (12.2%)	2 (4.2%)	21 (10.3%)
	Hyperparathyroidism	74 (47.4%)	10 (20.8%)	84 (41.2%)
	Valve disease	22 (14.1%)	3 (6.3%)	25 (12.3%)
	Carcinomas total of which	13 (8.3)	4 (8.4%)	17 (8.4%)
	Urothel carcinoma	1 (0.6%)	1 (2.1%)	2 (1.0%)
	Squamous cell carcinoma	3 (1.9%)	2 (4.2%)	5 (2.5%)
	Basal cell carcinoma	9 (5.8%)	1 (2.1%)	10 (4.9%)
Immune medication	CsA alone	1 (0.6%)	0 (0%)	1 (0.5%)
	CsA + prednisolone	50 (32.1%)	19 (36.6%)	69 (33.8%)
	CsA + prednisolone + mycophenolic acid	69 (44.2%)	16 (33.3%)	85 (41.7%)
	Combinations of CsA, prednisolone, mycophenolic acid, azathiopurine and tirolimus	36 (23.1%)	13 (27,1%)	49 (24.0%)
CsA serum concentration [μg/L]	Median	121.00	117.00	120.00
	Mean	127.94	124.21	127.29
	Standard deviation	59.45	58.67	59.33
	Maximum	1296.00	928.00	1296.00

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Table 1 (*continued*)

Patient characteristics		Hypertension		
		preexisting	Posttransplant	Total cases
		N = 156 (76.5%)	N = 48 (23.5%)	N = 204
Systolic blood pressure	No. of recordings	10,507.00	1974.00	12,481.00
	Minimum	90.00	100.00	90.00
	Median	130.00	130.00	130.00
	Mean	132.04	133.19	132.22
	Standard deviation	14.75	13.33	14.54
	Maximum	220.00	180.00	220.00
Antihypertensive medication *	ACEi alone or in combination with β-blockers	39 (25%)	14 (29.2%)	53 (26%)
	β-blockers alone or in combination with ARB and/or CCB	56 (35.9%)	21 (43.8%)	77 (37.7%)
	CCB in combinations with ACEi	13 (8.3%)	5 (10.4%)	18 (8.8%)
	ARB alone or in combination with CCB or ACEi	14 (9%)	2 (4.2%)	16 (7.8%)
	Combination of ACEi, β-blockers and/or CCB	34 (21.8%)	6 (12.5%)	40 (19.6%)
	Combination of antihypertensive medications and furosemide	75 (48.1%)	30 (62.5%)	105 (51.47%)
	combination of antihypertensive medications and HCT	11 (7.1%)	3 (6.3%)	14 (6.86%)
	Combination of antihypertensive medications and a mixture of different diuretics	20 (12.8%)	4 (8.3%)	24 (11.76%)

3.1. Kaplan-Meier survival statistics

The performed Kaplan-Meier statistics revealed post-transplant hypertension to be associated with a significant worse outcome (Fig. 1A, $p < 0.001$). Within the first 5 years post Tx a steep decline in the survival curve was observed; nonetheless plateaued approximately after 7 years. During the entire observation period of 13 years a total of 15 post-transplant hypertension patients died and included 6 cancers, 3 cardiovascular and 2 cases of sepsis and multi-organ failure. Moreover, 7 patients required dialysis but none received a second transplant.

Panel B and C of Fig. 1 depicts the distribution of patients with first time systolic blood pressure readings of ≥140 and/or ≥130 mmHg after kidney transplantation. Patients with pre-existing hypertension had more frequent elevated systolic blood pressure when compared to post-transplant hypertensive patients the difference being statistically significant for ≥130 mmHg readings ($p < 0.046$). However, the curves followed a similar pattern. One year after kidney transplantation approximately 65% and 35% of patients with pre-existing and post-transplant hypertension, respectively had systolic blood pressure readings of ≥130 mmHg.

None except one of the drug combinations used in immunosuppressive therapies, i.e. prednisolone, mycophenolic acid, azathioprine and combinations of CsA with the mTOR inhibitor sirolimus influenced patient/graft survival (Fig. 2A). Given that prednisone possesses potent diuretic effects [13] the combined use of prednisolone and furosemide was also evaluated and such combinations were associated with an increased risk for graft loss/death (Fig. 2B). Typical prednisone doses were 5 mg/day whereas furosemide doses ranged between 20 and 500 mg with the majority of patients receiving 20 (6%), 40 (42%), 80 (26%), 125 (11%) and 250 mg/d (6%), respectively.

3.2. Cox proportional-hazards regression analysis

In a step wise approach different time constant and time dependent covariates were assessed. Post-transplant hypertension was a significant risk factor for graft lost/death in uni- (HR 4.9; $p < 0.001$) and multivariate analysis (HR > 6 stage 3 onwards, $p < 0.001$). As shown in Table 2 incremental rises of 10 mmHg in systolic blood pressure were associated with a significant increased risk for graft failure/death in uni-(HR 1.377, $p < 0.001$) and multivariate analysis (stage 4, HR 1.29, $p = 0.011$). However, the significant relationship disappeared when other laboratory parameters were considered (stage 5,Table 2). Additional covariates associated with worse outcome were cold ischemia time (HR 1.5 per 10 min time increment) and blood urea (HR 1.1); however, only proteinuria and serum creatinine remained statistically significant at stage 5 in multivariate analyses and the associated hazard ratios are 6.4 and 1.1, respectively after Bonferroni correction. The Cox regression analysis revealed a modestly increased HR with increased serum creatinine concentration and creatinine based estimates of glomerular filtration rates (eGFR) while univariate analysis confirmed increased GFR to be a predictor variable for better outcome (HR 0.6). Multivariate analysis also indicated serum cholinesterase activity to be a predictor variable of patient/graft survival (HR 0.7, Table 2).

A statistically significant relationship between age of recipient and survival was determined in uni- and multivariate analysis. However, the variables donor age and cold ischemia time were only significant in uni- and multivariate analysis up to stage 3 to possibly influence graft survival (Table 2). Neither HLA incompatibility nor gender affected graft survival. Likewise, diabetes mellitus was not a significant covariate and did not influence patient and/or graft survival and involved 27 cases of T2DM and 14 cases of post-transplant new onset DM.

3.3. Antihypertensive medication

Management of hypertension followed target levels of ≤140/90 mmHg. All antihypertensive medications were effective in lowering systolic blood pressure. However, > 70% of patients required more than a single antihypertensive agent to lower systolic blood pressure to target values of ≤140 mmHg. A therapy consisting of ACE inhibitors (ACEi) alone or in combination with other antihypertensive medications was associated with a statistically significant increased HR of 2.1 in uni- and 3.4 in multivariate analysis at stage 5 (Table 2). This indicates ACEi to be a specific and independent factor for worse outcome. Moreover, a minor and statistically insignificant increase in HR was observed at an ACEi dose increment of 10%. Note, therapeutic doses differ among the various agents; therefore the 10% increment of dose is calculated on the basis of maximum daily dose for a given drug to determine its relevance for HR.

Alike, treatment of hypertensive kidney transplant patients with β-blockers alone or in combination with other antihypertensive drugs was unfavorable; the HR for graft failure/death was 2.3 (stage 3) and 3.1 (Table 2, stage 5 multivariate analysis). Once again this suggests β-blockers to be a specific and independent factor for worse outcome even though dose increment did not influence the HR significantly. With CCB a statistically insignificant worse outcome (HR = 1.4, Table 2) was computed though incremental doses did not influence HR. Importantly,

Table 2
Cox proportional-hazards regression analysis for survival.

Variable [unit]	Univariate		Multivariate (Stepwise backward selection at p<0.05)									
			Stage 1		Stage 2		Stage 3		Stage 4		Stage 5	
	P	HR	P	HR	P	HR	P	HR	P	HR	P	HR
1) basal variable												
gender	0.710	0.896										
BMI	0,263	0.959										
post-transplant hypertension	<0.001*	4.891	<0.001*	4.829	<0.001*	4.445	<0.001*	6.898	<0.001*	6.087	<0.001*	6.376
post-transplant diabetes	0.295	1.457										
distribution of gender	0.864											
age of recipient increment [10 years]	<0.001*	1.724	0.001*	1.774	<0.001*	1.692	<0.001*	1.724	<0.001*	1.673	<0.001*	2.419
age of donor increment [10 years]	0.018	1.255					0.016	1.331				
CIT [10 min]	0.010	1.509					0.041	1.438				
HLA status / matching	0.185	1.143										
2) immunosuppression												
CsA + prednisolone (=IMM1)	0.818											
IMM1 + mycophenolate (=IMM2) versus IMMI	0.621	0.845										
others versus IMM1	0.892	1.052										
prednisolone +furosemide	0.002	2.758			0.025	2.109			0.032	2.056		
CsA dose [10 mg]	0.202	0.970										
CsA level [10 µg/l] (serum)	0.025	0.904			0.023	0.899	0.049	0.904	0.016	0.897		
3) antihypertensive drugs												
ACE-blocker dose **	0.198	1.069										
ACE-blocker	0.017	2.100					<0.001*	3.902	0.002*	2.817	0.001*	3.337

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Table 2 (*continued*)

ß-blocker dose **	0.682	0.985								
ß-blocker	0.310	1.377			0.020	2.283	0.007	2.447	0.003	3.069
ARB dose **	0.084	0.887								
ARB	0.359	0.717								
CCB dose **	0,879	0.994								
CCB	0,225	1,444								
4) systolic blood pressure [10 mmHg]	<0.001*	1,377					0.011	1.285		
5) laboratory parameters										
Urea [mmol/l]	<0.001*	1.130								
Creatinine [10 µmol/l]	<0.001*	1.127							<0.001*	1.145
AST [10 U/l]	0.007	0.516								
ALT [10 U/l]	0.082	0.631								
γ-GT [10 U/l]	0.602	1,012								
GLDH [U/l]	0.225	0.942								
ChE [U/l]	<0.001*	0.662							0.011	0.767
Bilirubin [10 µmol/l]	0.097	0.562								
PTT [10 %]	0.797	1.002								
proteinuria [g/l]	<0.001*	3.573							<0.001*	6.442
GFR [10 ml/min]	<0.001*	0.633							0,047	1,226
Nominal alpha for Bonferroni correction	0.0015		0.0055	0.0038	0.0024		0.0023		0,0015	

*p < 0.05 after Bonferroni correction.
**10% increment of the dose based on maximum daily dose.

angiotensin receptor blockers (=sartans) did not influence graft or patient survival but were most effective in the treatment of hypertension as determined in multivariate analysis as detailed below.

The management of hypertension also included different classes of diuretics such as the loop diuretic furosemide (N = 105), the thiazide HCT (N = 14) and combinations of others (N = 23). Based on Kaplan-Meier survival statistics a treatment strategy that consisted of the combined use of prednisolone and furosemide was associated with a statistically significant (p < 0.036) worse outcome (Fig. 2B). Likewise, in Cox proportional-hazard regression analysis the combined use of prednisolone and furosemide was associated with HR of 2.758 (p < 0.002) in univariate and 2.056 (p = 0.032, Table 2) at stage 4 in multivariate analysis. Moreover, univariate analysis revealed an increment of 10 mg/d furosemide to be associated with a statistically significant increase in HR = 1.049 (p < 0.001).

3.4. Cyclosporine induced hypertension

To explore the relationship between cyclosporine immunosuppression, hypertension, pharmacological class and dose of antihypertensive medication a multivariate linear mixed model was developed. A significant ($p < 0.001$) relationship between CsA dose/serum concentrations and systolic blood pressure was established (Table 3). This relationship was significant in uni- and multivariate analysis (Tables 3 and 4), and the analysis is based on 14,086 CsA serum as well as 3451 blood pressure measurements derived from 204 patients.

Specifically, increased therapeutic CsA doses were associated with a significant rise in systolic blood pressure by about 0.46 mmHg per 10 mg CsA oral dose. Correspondingly, a 200 mg CsA oral dose is expected to raise systolic blood pressure by about 9.2 mmHg. Fig. 3 exemplifies the relationship between CsA oral dose and serum concentration and systolic blood pressure readings. In univariate analysis we next considered the class of antihypertensive medication (Table 3). This revealed all medications to lower elevated systolic blood pressure effectively though ARB tended to be best (−8.6 mmHg). Due to the fact that > 70% of patients received more than one antihypertensive medication we evaluated the effects of different drug combinations. Once again all combinations were effective and a combination of ACEi, β-blockers, ARB and or/CCB tended to be best in lowering systolic blood pressure.

We next considered the effects of diuretics either given in monotherapy or in combination with other antihypertensive agents (Supplementary Table S3). Given that prednisolone also functions as potent diuretic the combinations of different diuretics with prednisolone were evaluated. HCT and combinations of other diuretics with prednisolone had no effect on BP; however the combination of prednisolone and furosemide was associated with a significant increase in systolic blood pressure by about 4.1 mmHg. Shown in Supplementary Table S3 are also the different combinations of antihypertensive medications and diuretics and essentially all were effective in lowering systolic blood pressure; however for patients on prednisolone and furosemide the combination of CCB and ACEi tended to be best (−18.2 mmHg).

Furthermore, we considered the effects of dose escalation in uni- and multivariate analysis and all medications were effective in lowering CsA induced hypertension (Table 4). However, the β-coefficient differed by 2 and 5-fold in uni- and multivariate analysis with ARB being most effective as compared to CCB or β-blockers in lowering elevated systolic blood pressure.

Apart from determining the link between CsA dose and systolic blood pressure we also interrogated this relationship by considering systemic serum CsA concentrations. As shown in Table 5 any of the antihypertensive medications improved CsA induced rises in systolic BP (denoted by the β-coefficient), however only ARB was effective in completely offsetting the rise in RR due to CsA immunosuppression. Supplementary Tables S4 and S5 provide additional information on the relationship between antihypertensive medication and systolic BP readings.

Additional information regarding the relationship between CsA dose/serum concentration and systolic blood pressure is given in Fig. 3. As shown in panels B&C a CsA dose dependent increase in systolic blood pressure was observed while sustained target systolic blood pressure readings of ≤140 mmHg were observed approximately 4 years of antihypertensive medication (Fig. 3, panel A).

We also considered cyclosporine doses/serum concentrations over the entire observation period of 13 years. Fig. 4 depicts mean CsA dosage and corresponding serum concentrations (panel A) for the entire study cohort. With time the CsA dosages and corresponding serum concentrations were lowered and comparable between kidney recipients with pre-existing and post-transplant hypertension (panel B). Note, there were 5 hypertensive patients prior to Tx which required higher CsA doses to achieve therapeutic serum concentrations in the first year post Tx. However, over the entire observation period mean serum concentrations did not differ between prior to Tx hypertensive and post-transplant hypertensive patients (Fig. 4B).

As mentioned above any of the antihypertensive medications reduced systolic blood pressure (Tables 3–5). Furthermore, a small but significant reduction in systolic blood pressure ($p = 0.010$) was observed for each additional antihypertensive drug given with some patients receiving up to 4 different pharmacological classes of antihypertensive drugs in addition to diuretics. In univariate analysis incremental doses of different classes of antihypertensive medications reduced systolic blood pressure significantly ($p < 0.001$). However, in multivariate analysis only medications involving ACEi and/or AT-receptor blockers were associated with sustained reduction of systolic blood pressure (Table 4, $p < 0.001$) whereas β-blockers were borderline and CCB failed to be significant.

3.5. Glomerular filtration rates in hypertensive CsA immunosuppressed patients

To explore the relationship between CsA dose/serum concentration, antihypertensive medication and estimated GFR (eGFR) a linear mixed model of variance for repeated measurements was developed. In univariate analysis all medications lowered GFR significantly with ACE inhibitors having the strongest effect (Table 6). Except for β-blockers a similar reduction in GFR was observed in multivariate analysis in patients on monotherapy. Note, 23 patients developed ACE inhibitor intolerance and were switched to ARB. Such a change in pharmacotherapy is in line with current recommendations for the treatment of hypertension in chronic kidney disease [14]. When treatment regimens consisting of more than one antihypertensive agent were considered a similar picture emerged (Table 6). Once again, ACE inhibitors in combinations with β-blockers, ARB and CCB had the strongest effect in worsening GFR in uni- and multivariate analysis. A similar marked reduction in GFR was observed with the combined use of ACEi and CCB while β-blockers alone or in combination with CCB or AT-receptor blockers improved GFR (Table 6). Notwithstanding, a significant reduction ($p < 0.001$) in proteinuria was achieved with the use of ACE inhibitors (Supplementary Fig. S3).

3.6. Decision tree analyses

Unlike the Cox regression model in which general linear effects on the hazard are considered the tree analysis is designed to identify constellations and main interactions of co-variables associated with marked changes leading to elevated or reduced risks.

For this purpose data derived from multiple measurements of 204 kidney transplant patients were analyzed. When the cyclosporine serum trough level was considered patients at the age of ≥50 years, and a cyclosporine serum concentration of < 195 ng/mL was associated with a higher risk of graft loss (Supplementary Fig. S4). Equally, decision tree analysis revealed a cyclosporine serum trough level of < 76 ng/ mL to be associated with higher risk of death/graft lost in patients with hypertension prior to kidney transplantation. Cold ischemia time was another co-variable. Cyclosporine serum concentration of < 76 ng/mL and a cold ischemia time of ≥15.8 h were associated with graft loss (Supplementary Fig. S4, unpruned tree analysis). Conversely, a favorable constellation for graft survival was an average systolic blood pressure of < 145 mmHg, proteinuria < 0.09 mg/mL and urea of < 23.6 mmol/L (Supplementary Fig. S5, pruned tree analysis).

Additionally, the effects of dose of ACE-inhibitors, β-blockers and/or AT-receptor antagonists were investigated. Note, dose regimens changed over time and therefore at each time point the actual dose was entered into the analysis. Supplementary Table S2 informs on the typical clinical doses employed for each patient. The management of hypertension was better with an AT-receptor blocker (Supplementary Fig. S6, pruned tree analysis). Conversely, treatment of hypertension

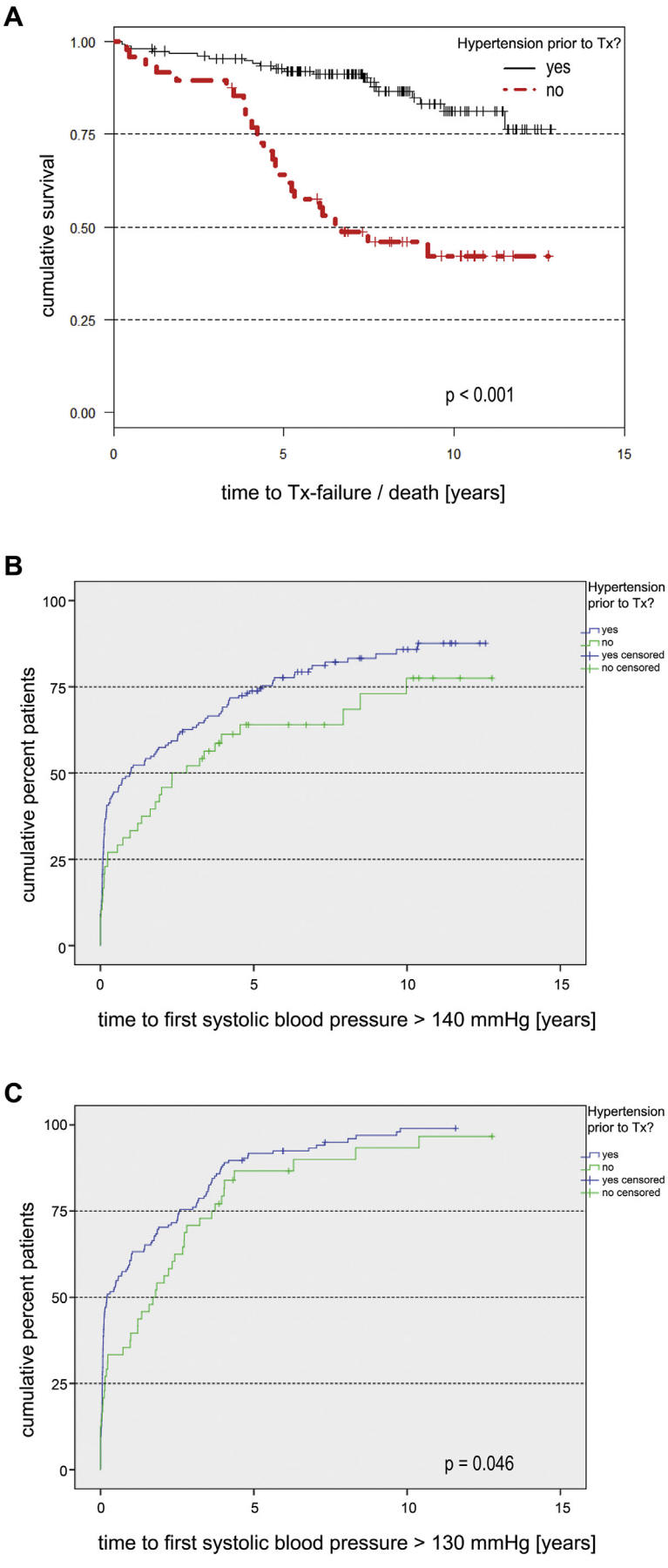


Fig. 1. Kaplan-Meier survival curves for kidney transplant patients.
(A) The survival/freedom of Tx-failure of kidney transplant patients with pre-existing hypertension (black line) is compared with patients who developed cyclosporine induced post-transplant hypertension (red line). A statistically significant reduced graft and/or overall survival was observed for patients with cyclosporine induced post-transplant hypertension.
(B) Depicted is the cumulative percent of patients with either pre-existing (black line) or cyclosporine induced post-transplant hypertension (red line) with time to onset of systolic blood pressure > 150 mmHg.
(C) Depicted is the cumulative percent of patients with either pre-existing (blue line) or cyclosporine induced post-transplant hypertension (green line) with time to onset of systolic blood pressure ≥140 mmHg.
(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

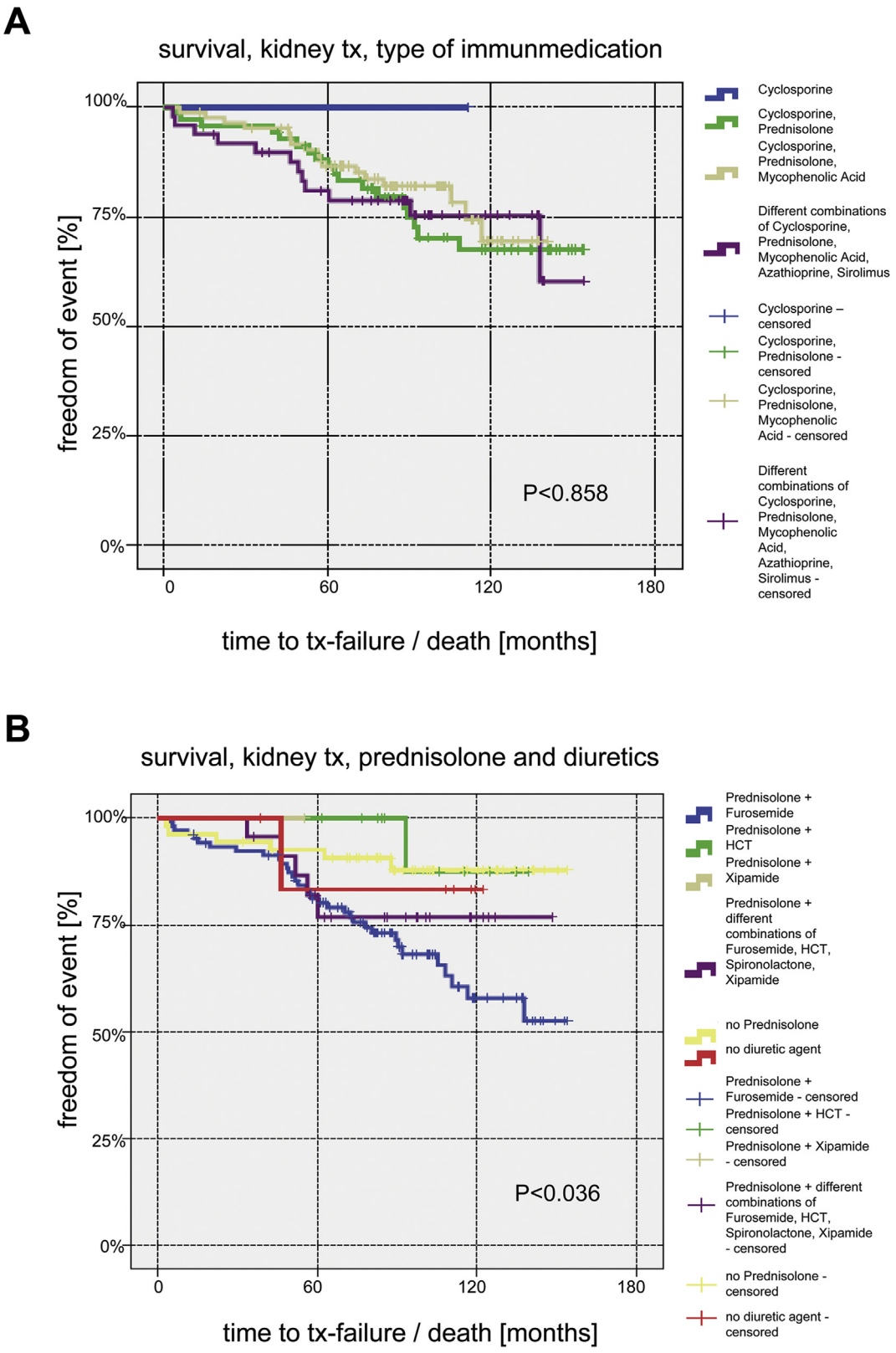


Fig. 2. Kaplan-Meier survival curves for kidney transplant patients given different antihypertensive medications.
(A) Patient/graft survival does not differ by the various immune medications ($p < 0.858$).
(B) Drug regimens involving the combined use of prednisolone and furosemide was associated with a significant risk for graft loss/death ($p < 0.036$).

Table 3
The effects of immune suppression and antihypertensive medication on systolic blood pressure in kidney transplant patients with either pre-existing or post-transplant hypertension. Univariate analysis.

Parameter	β-coefficient	P-value
Hypertension prior to Tx	−2,7	0.088
Cyclosporin dose[a]	0.46	< 0.001
Cyclosporin serum concentration per [10 μg/L] increment	0.21	< 0.001
ACE[b]	−5.4	< 0.001
ARB[b]	−8.6	< 0.001
β-blocker[b]	−6.9	< 0.001
CCB[b]	−6.0	< 0.001
ACE Inhibitors alone or in combination with β-Blockers[b]	−5.3	< 0.001
β-Blockers alone or in combination with AT2 and/or CCB[b]	−6.0	< 0.001
AT2 Receptor blockers alone or in combination with CCB and/or ACE[b]	−4.7	< 0.001
CCB in combination with ACE Inhibitors[b]	−6.7	< 0.001
A combination of ACE Inhibitors, β-Blockers AT2[b] and/or CCB	−9.9	< 0.001

[a] Per [10 mg] increment.
[b] Reference group: patients not receiving this class of medications.

with ACEi was associated with an increased risk of graft loss/death. Treatment with β-blockers was also associated with an increased risk of graft lost/death, if no or low doses of AT and ACE blockers were given (Supplementary Fig. S6, 17 events). Furthermore, a systolic blood pressure of < 146 mmHg treated with ACE inhibitor and β-blocker was a better constellation than treatment with ACE inhibitor alone or with lower β-blocker doses (Supplementary Fig. S7, pruned tree analysis).

4. Discussion

CNI-induced hypertension is a common complication in kidney transplant patients [9, 15–17]. However, a comprehensive survival analysis that takes different classes of antihypertensive drugs and combinations of it into account has not been attempted. Based on power analysis to determine sample size for statistical testing a total of 204 transplant patients were deemed to be sufficient for in-depth evaluation. We analyzed survival and risk of graft failure in kidney recipients in relation to dose and type of antihypertensive medication by examining 33 covariates in patients with pre-existing and post-transplant hypertension. Our findings highlight the complexities and interdependencies between cyclosporine immunosuppression, systemic hypertension and antihypertensive medication in a long term follow-up, and we evidence survival and graft failure to be influenced by the class of antihypertensive drugs.

Specifically, a multivariate Cox proportional-hazard model with time constant and time variable covariates was developed. Varying hazards were observed when the age of recipient and donor, cold ischemia time and serum creatinine was considered (Table 2 and Fig. 5 for interdependencies among the major co-variables). Previous studies already established cold ischemia time and recipient age to influence graft survival [18, 19]. Conversely, HLA mismatch, new onset diabetes mellitus, and a BMI > 25 was not a risk factor for graft loss/death.

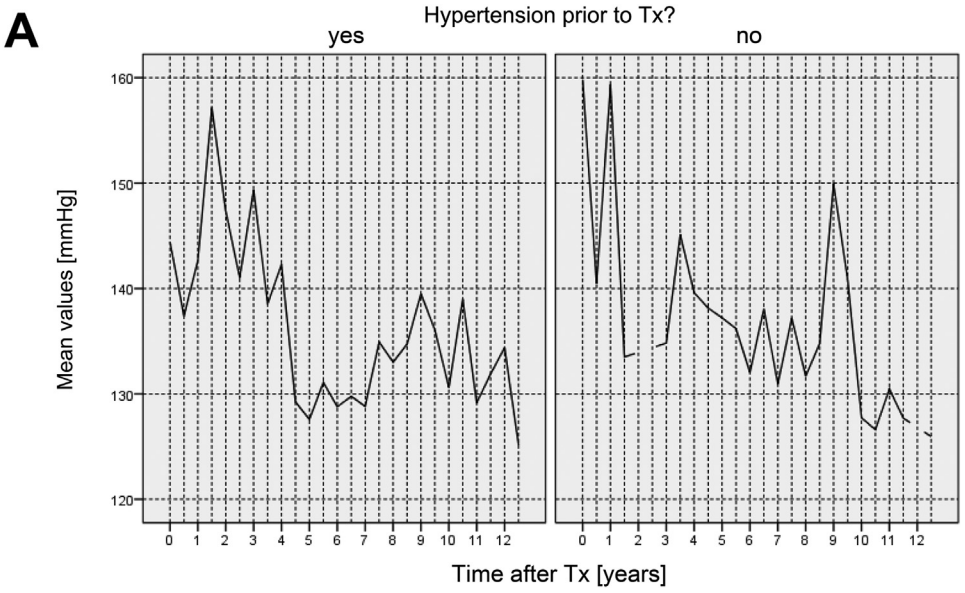
Overwhelmingly, CsA induced post-transplant hypertension was a major determinant for patient survival (Table 2). A disproportionate mortality, i.e. 36% as compared to 7% was observed when compared with the group of patients with pre-existing hypertension. Furthermore, the distribution of cases requiring re-dialysis differed between these two groups, i.e. 16.7% versus 6.4% in post-transplant hypertensive patients even though mean CsA serum levels were similar, i.e. 130.26 versus 125.34 μg/L among the two groups (Fig. 4).

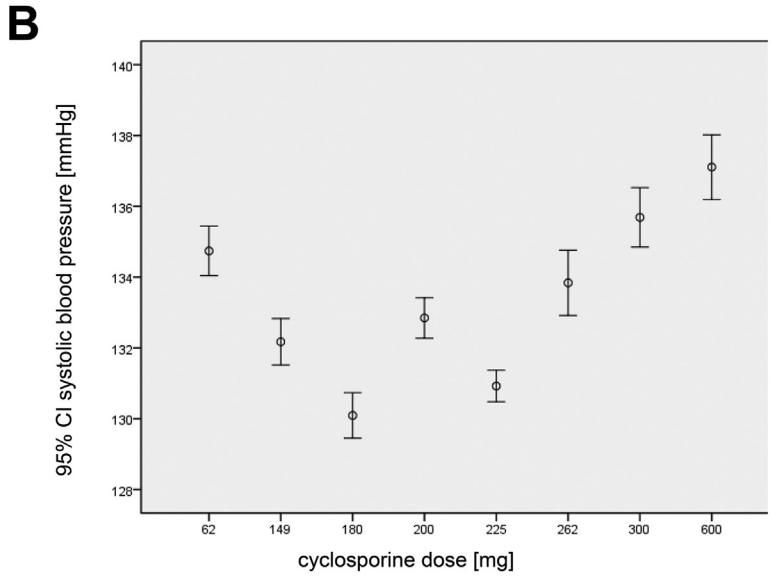
A statistically significant association was observed between CsA dose/serum concentrations and drug-induced hypertension (Tables 3–5, Fig. 3). This relationship reinforces the need to optimise cyclosporine serum levels without fear of graft rejection as to reduce risk of drug

Table 4
The effects of immune suppression and antihypertensive medication on systolic blood pressure in kidney transplant patients with either pre-existing or post-transplant hypertension.

	Univariate		Multivariate analysis prior to co-variable selection		Multivariate analysis after co-variable selection	
Parameter	β-coefficient	P-value	β-coefficient	P-value	β-coefficient	P-value
Hypertension prior to Tx	−2.7	0.088	−2.25	0.183		
Cyclosporin dose[a]	0.46	< 0.001	0.37	< 0.001	0.37	< 0.001
Cyclosporin serum concentration per [10 μg/L] increment	0.21	< 0.001	0.08	< 0.001	0.08	< 0.001
ACE dose[b]	−0.75	< 0.001	−0.35	< 0.001	−0.35	< 0.001
ARB dose[b]	−0.72	< 0.001	−0.47	< 0.001	−0.48	< 0.001
β-blocker dose[b]	−0.30	< 0.001	−0.002	0.968		
CCB dose[b]	−0.28	< 0.001	−0.14	< 0.001	−0.14	< 0.001

The following points require consideration:
(a) Higher cyclosporine dose and increased cyclosporine serum levels are associated with increased systolic blood pressure; note an increased cyclosporine dose alone is also associated with an increased systolic blood pressure even if the cyclosporine serum concentration is unchanged.
(b) All antihypertensive medications except β-blockers reduced systolic blood pressure in multivariate analysis.
(c) For hypertensive patients prior to kidney Tx and when compared to post-transplant hypertensive patients the systolic blood pressure is insignificantly reduced by 2.7 mmHg.
(d) Figs. 3 and 4 display the relationship between cyclosporine serum concentrations and systolic blood pressure.
[a] Per [10 mg] increment.
[b] 10% increment of the dose based on maximum daily dose.





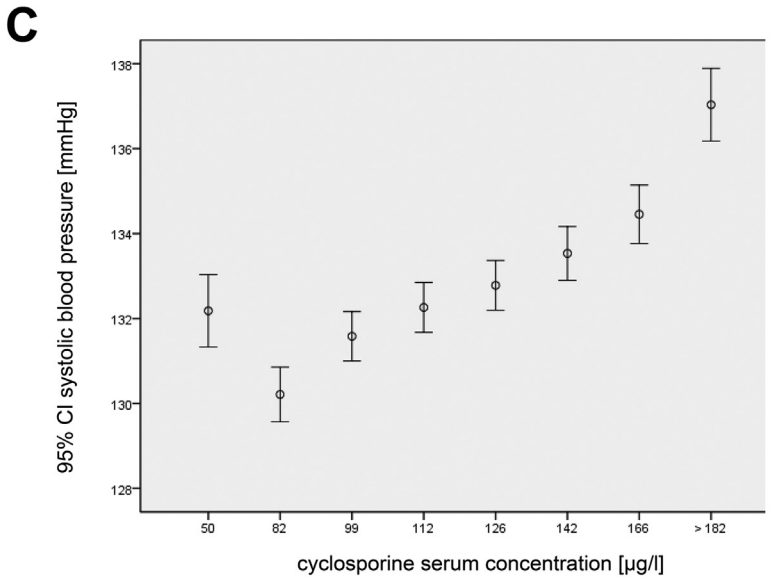


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Fig. 3. Relationship between CsA immunosuppression and systolic blood pressure (Panel A) Systolic blood pressure of kidney transplant patients with pre-existing and post-transplant hypertension during an observation period of 13 years. (Panel B) Systolic blood pressure in relation to CsA dose. (Panel C) Systolic blood pressure in relation to CsA serum concentration.

induced hypertension. Given the inverse relationship between increased CsA serum concentrations and GFR (Table 6) a dose reduction will also reduce risk for CsA-induced changes in glomerular filtration rates.

Although all antihypertensive medications were effective in lowering systolic blood pressure their use in the long-term was associated with different outcomes. A major finding was the significant worse outcome associated with the use of ACE inhibitors (Tables 2 and 3). Note, similar results were reported by the Cochrane Database of Systematic Reviews [20]. Their meta-analysis involved 60 studies enrolling 3802 kidney recipients on ACE inhibitors. Independent studies therefore confirm ACE inhibitors to be detrimental in the management of hypertension in kidney recipients. However, in their meta-analysis the authors did not employ the complex approach that was taken in the present study, i.e. we considered 33 covariates including dose and type of immunosuppressive and antihypertensive medication, co-medication, serum biochemistries and the glomerular filtration rate (GFR) to arrive at this conclusion. Additionally, the American Heart Association issued a scientific statement on the different mechanisms in the worsening of renal function during ACEi therapy [21] thus reinforcing the notion to be cautious in the use of ACE inhibitors in kidney recipients. Importantly, in 2017 the American College of Cardiology and the American Heart Association Task Force on Clinical Practice Guidelines lowered the treatment goal for hypertension from < 140/90 to < 130/80 mmHg. The committee also concluded the use of ACE inhibitors in chronic kidney disease patients with > 300 mg/d proteinuria to be reasonable. This recommendation is based on strength IIa and a quality of evidence based on randomized and non-randomized clinical studies (Level B-NR) [14]. Alike, for kidney transplant patients the treatment goal for hypertension is < 130/80 mmHg and CCB are recommended on the basis of improved GFR and kidney survival [14]. However, in the present study therapy of hypertension with ACEi was associated with worse outcome and CCB failed to lower effectively PTH in multivariate analysis (Table 4).

Specifically, a complex interplay exists between CsA induced vasoconstriction and modulation of the renin angiotensin system by ACE inhibitors. Their effect on afferent and efferent arterioles causes a decrease in GFR. In uni- and multivariate analysis ACE inhibitors alone or in combination with other drugs reduced GFR significantly (Table 6). A marked reduction in GFR was observed in the combined use of ACEi, ARB and/or CCB and a similar renal impairment was observed with a therapy consisting of ramipril and telmisartan as observed in the Ontarget trial [22]. Alike, the combined use of ACE inhibitors and CCB was associated with a significant worsening of GFR (Table 6). Conversely, β-blockers given alone or in combination with AT-receptor blockers and/or CCB improved GFR. It is tempting to speculate that such medications enable good control of blood pressure and sufficient inhibition of RAAS.

A previous study compared ACE inhibitors and β-blockers for the treatment of hypertensive renal allograft recipients and both drugs were found to be effective [23]. Notwithstanding, ACE-inhibitors have proven benefits beyond blood pressure control in the treatment of proteinuria [24] and protection against progressive kidney disease [15,25]. While dose of ACE inhibitors and β-blockers did not influence overall survival the principal use of these drugs either given alone or in combination was associated with a statistically significant increased HR in multivariate Cox proportional-hazard regression analysis (Table 2). The multivariate analysis also revealed treatment regimens involving ACE inhibitors, Ca-channel and AT receptor blockers to be effective in lowering elevated systolic blood pressure (Table 3). Although statistically insignificant pharmacotherapy based on ARB was associated with a small reduction in the hazard ratio (Table 2). Note, an earlier study did not observe improved outcome on patient/graft survival with AT receptor blockers [26]; however the two studies are not directly comparable, i.e. a smaller follow-up of only 5 years and most covariates analyzed in the current study were not considered.

A recent review highlights the potential of AT receptor blockers for renal protection and the pharmacological effects involve vasodilation, increased renal blood flow, lowered intraglomerular pressure and reduced angiotensin II levels in the kidney [27].

In the present study 70% of the cohort (see Supplementary Table S2) received diuretics in the long term, and the combined use of CsA, prednisolone and furosemide was associated with an increased risk for graft loss/death (Table 2, stage 4) that may have been aggravated by ACE therapy in volume depleted patients [21]. Given that loop diuretics can cause renal vasoconstriction and activation of the RAAS system, a dose reduction of furosemide may improve clinical outcome as was shown in patients with stable systolic heart failure, fluid overload and renal dysfunction [28]. Our study revealed dose increments of 10 mg/d furosemide to be associated with worse outcome HR = 1.049 ($p < 0.001$). A similar relationship was reported for heart failure patients with exposure to higher furosemide doses to be associated with increased morbidity and death [29].

The management of post-transplant hypertension was the subject of an independent review [16] and there are obvious and less obvious reasons why benefits and harms of medications may differ between kidney recipients and other hypertensive patients. For example,

Table 5
Relationship between CsA-serum concentration, systolic blood pressure and anti-hypertensive medication.

	Change in systolic blood pressure [mmHg] per 10 μg/L increment of CsA-serum concentration	
	β-coefficient	p-value for the reduction of the β-coefficient[a]
Systolic blood pressure increase [mmHg] associated with an increment of 10 μg/L of CsA-serum concentration in the absence of anti-hypertensive medication: β-coefficient	0.28	
Reduction of the β-coefficient in the presence of treatment with		
ACE: reduction to	0.20	< 0.001
β-blocker: reduction to	0.17	< 0.001
ARB: reduction to	−0.06	< 0.001
CCB: reduction to	0.21	< 0.001

[a] The medications differed in their ability to lower CsA- induced elevations in systolic blood pressure. ARB was most effective and completely reversed CsA induced rises in systolic blood pressure. Conversely, the other medications were similar but less effective in ameliorating systolic BP rises.

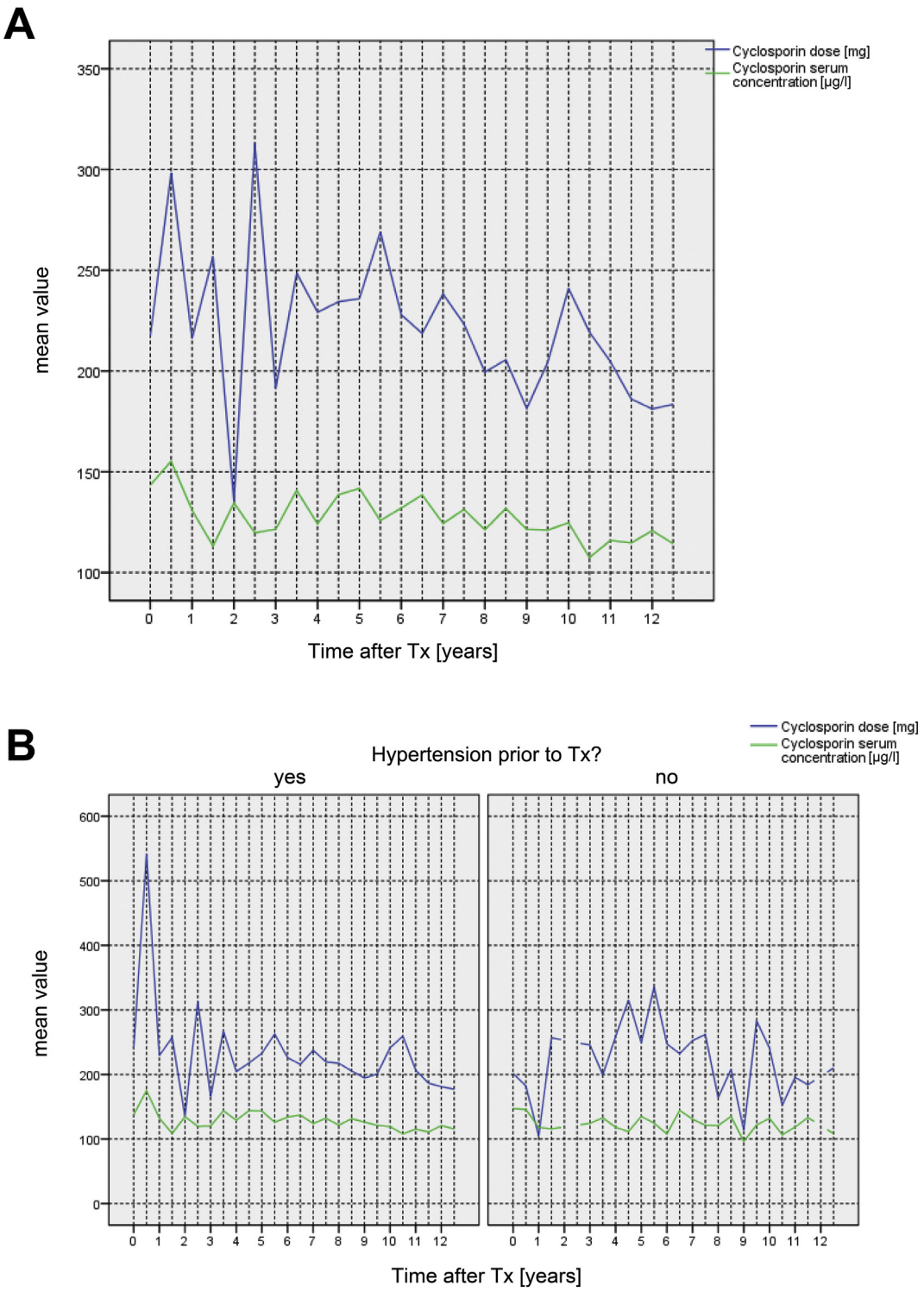

Fig. 4. Relationship between CsA dosages and corresponding serum concentrations.
(Panel A) Follow-up among all kidney transplant patients over an observation period of 13 years. (Panel B) Kidney transplant patients with pre-existing and post-transplant hypertension.

calcium channel blockers promote vasodilation of afferent arterioles of the kidney, which may counteract afferent arteriolar vasoconstriction and interstitial fibrosis induced by cyclosporine immunosuppression [16, 17, 30].

Given the importance of the sympathetic nervous system in renal blood flow and glomerular filtration the use of β-blockers appears rational in the management of chronic kidney disease. Although benefits of certain β-blockers in hypertensive kidney disease have been reported [31] they are not recommended as first-line treatment for hypertension. Specifically, certain β1-selective blockers like metoprolol lower effectively renal vascular resistance (RVR) and improve GFR. β-blockers cause vasodilation and renoprotection through binding to adrenergic receptor and/or stimulation of NO release from the endothelium. Altogether a complex interplay exists with activation of the sympathetic nerve system and the release of catecholamines, i.e. norepinephrine and the secretion of epinephrine by the medulla of the adrenal glands to

Table 6
The effects of immune suppression and antihypertensive medication on glomerular filtration rates in kidney transplant patients.

Parameter	Univariate analysis		Multivariate analysis			
			Monotherapy		Combination therapy	
	β-coefficient	P-value	β-coefficient	P-value	β-coefficient	P-value
Cyclosporine serum concentration increment [10 μg/L]	0.08	< 0.001	−1.329	< 0.001	−0.117	< 0.001
ACE	−8.35	< 0.001	−5.59	< 0.001		
ARB	−5.79	< 0.001	−2.59	< 0.001		
Beta	−3.78	< 0.001	1.67	< 0.001		
CCB	−5.19	< 0.001	−1.37	0.001		
ACE inhibitors alone or in combination with β-blockers	−3,54	< 0.001			−1.184	0.005
β-blockers alone or in combination with ARB and/or CCB	1.61	< 0.001			3.217	< 0.001
ARB alone or in combination with CCB and/or ACE	−1.94	0.005			−0.867	0.203
CCB in combination with ACE inhibitors	−11.30	< 0.001			−8.074	< 0.001
A combination of ACE inhibitors, β-blockers, ARB and/or CCB	−12.35	< 0.001			−8.027	< 0.001

The minus sign of the β-coefficient refers to a reduction in eGFR.

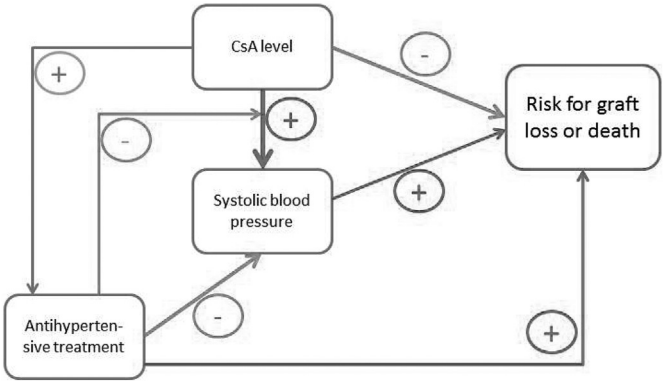

Fig. 5. Positive and negative effectors influencing post-transplant hypertension and graft survival.
The results of the multivariate analysis are represented as schemata to illustrate the influences of immunosuppression, post-transplant hypertension and antihypertensive medication on the risk for graft failure; (+) denote increased risk; (−) denotes a reduced risk.

function as agonists of adrenergic receptors in the control of vascular tone and GFR. The present study highlights improved GFRs in kidney transplant patients treated with β-blockers (primarily metoprolol and carvedilol) either given alone or in combination with ARB and/or CCB (Table 5). However, none of the other antihypertensive medications improved GFR. Unfortunately, not all β-blockers are equally renoprotective with propoanol increasing RVR but lowering GFR whereas the non-selective β-blocker carvedilol decreases RVR to improve GFR [31]. Furthermore, β-blockers reduce cardiac output and therefore may impair renal perfusion. Adding to complexity are the differing pharmacological properties of individual β-blockers that need to be considered in CKD and post-transplant hypertension. [32]. In the present study 143 patients were on β-blockers of which 43 received this class of drug as first-line therapy for myocardial infarction, cardiomyopathy, coronary heart disease, congestive heart failure, bypass surgery, atrial fibrillation and atrial flutter. For the remaining patients β-blockers were part of a complex medication in the management of hypertension and renoprotection. Importantly, a recently published Cochrane review compared β-blockers to other antihypertensive medications. Their meta-analysis does not support the use of β-blockers as an initial therapy for hypertension though the study was considered to be biased towards atenolol [33]. Moreover, the renoprotective effects of β-blockers and ACE inhibitors were compared with β-blockers and considered to be inferior as judged by GFR and proteinuria [31, 34]. In the present study ACE inhibitors proved to be effective in reducing proteinuria (Supplementary Fig. S3) while β-blockers alone or in combination with ARB and or CCB improved GFR.

Collectively, β-blockers are not recommended as antihypertensive agents in patients with proteinuria and this further exemplifies the complexities in the management of hypertension in CKD and post-transplant hypertension.

4.1. A molecular rationale for CsA induced hypertension

The key central and peripheral mechanisms in CsA induced hypertension have been reviewed [35]. In pursue of mechanisms of adverse drug reactions studies from our group revealed cyclosporine to repress DNA binding activity of the hepatic nuclear factor 4 alpha (HNF4α) [36]. This Zink-finger protein functions as a transcription factor to control gene expression of the vasoactive peptide angiotensin as well as members of the insulin and glycogenic signaling pathway. Therefore, a regulatory loop exists whereby CsA influences activity of the transcription factor NFAT, and this transcription factor also controls activity of HNF4α. Consequently, cyclosporine inhibits NFAT and HNF4α activity at the same time. Given the interdependence of these transcription factors and their function in regulatory networks a decisive role in CsA induced hypertension and diabetes was proposed [36, 37]. It should be noted that HNF4α expression levels vary considerable, i.e. > 200-fold among individual patients. Accordingly, patients with lower levels of HNF4α are at higher risk of developing CsA induced post-transplant hypertension [36, 37].

Fig. 5 summarizes the interdependencies between cyclosporine immunosuppression, systemic hypertension and antihypertensive medication.

4.2. Study limitations

The following caveats need to be considered: First, our findings are based on a single center retrospective study. A prospective multicenter study is needed to confirm the initial data independently. Second, we considered comprehensively possible confounders by analyzing 33 covariates in a staged approach (see Table 2, stages 1 to 5); nonetheless, we cannot completely rule out an indication bias that may have influenced the outcome even though time constant and time dependent variables were considered in a multivariate Cox-regression model. Third, patients were not randomized to different classes of antihypertensive medications as most patients required a combination therapy to achieve treatment goals in the management of hypertension. Notwithstanding a significant relationship between immunosuppressive cyclosporine therapeutic dose/serum concentration and systolic blood pressure ($p < 0.001$) was observed, and the management of hypertension was influenced by the type of antihypertensive medication.

In conclusion, our study is suggestive for the survival of kidney transplant patients to be influenced by the class of antihypertensive medication. A prospective randomized clinical trial is needed to confirm the results.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vph.2018.06.012.

Declarations of interest

none.

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