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ORIGINAL ARTICLE

Treatment efficacy of hypertension in kidney transplant recipients in the Netherlands

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ABSTRACT

Background: Hypertension in kidney transplant recipients jeopardises graft and patient survival. Guidelines suggest blood pressure targets of ≤130/80 mmHg and sodium intake <90 mmol/day.

Methods: Since the efficacy of antihypertensive treatment among kidney transplant recipients is unknown, we analysed data on office-based blood pressure and use of antihypertensive drugs from the Netherlands Organ Transplant Registry on 5415 kidney transplant recipients. Additionally, we studied dosages, prevalence of treatment-resistant hypertension and 24-hour sodium excretion in 534 kidney transplant recipients from our centre to explore possibilities for therapy optimisation.

Results: In patients registered in the Netherlands Organ Transplant Registry, median blood pressure was 134/80 mmHg (interquartile range 122-145/70-85). In 77.2%, the blood pressure was ≥130/80 mmHg; of these patients 10.4% had no registered use, 30.0% used one and 25.9% used ≥3 classes of antihypertensive agents. Parameters from our centre were comparable: 78.7% had a median blood pressure of ≥130/80 mmHg of whom 14.5% had no registered use of antihypertensives and 26.4% used ≥3 classes. Sub-maximal dosages were prescribed in 74.0% of the kidney transplant recipients with a blood pressure of ≥130/80 mmHg while using at least one antihypertensive agent. Treatment-resistant hypertension was present in 7.7%. Median 24-hour sodium excretion was 147 mmol/day (interquartile range 109-195).

Conclusions: This study suggests that therapeutic optimisation of antihypertensive treatment in kidney transplant recipients is, in theory, frequently possible by intensifying pharmacological treatment and by providing more advice on dietary sodium restrictions.

KEYWORDS

Antihypertensive treatment, hypertension, kidney transplantation

INTRODUCTION

Although kidney transplantation is the superior treatment for end-stage renal disease, kidney transplant recipients continue to have a high risk for cardiovascular morbidity and mortality. The annual risk for cardiovascular death is about 50-fold as compared with the general population and cardiovascular disease is the leading cause of morbidity and mortality in kidney transplant recipients.[1-3]

Hypertension is the foremost modifiable medical risk factor for cardiovascular disease in kidney disease. In addition, hypertension jeopardises renal allograft function, leading to graft loss.[4-7] Various studies, dating from before 2009, indicated that hypertension amongst kidney transplant recipients was prevalent in up to >90%.[4,8,9] Authoritative guidelines recommend a target blood pressure of <130/80 mmHg in kidney transplant recipients.[7,10] The efficacy of antihypertensive treatment in kidney transplant recipients has not been studied since. Against this background, we set out to study the efficacy of the current treatment of hypertension in kidney transplant recipients and to assess the number and dosages of prescribed antihypertensive drugs. Since sodium intake is a recognised determinant of blood pressure and sodium restriction is a major therapeutic antihypertensive intervention, we also surveyed the dietary sodium intake.

METHODS

We performed two separate, retrospective cross-sectional analyses: i.e. on data retrieved from the Netherlands Organ Transplant Registry (NOTR) and from the clinical files of kidney transplant recipients at our own institution, respectively.

Netherlands Organ Transplant Registry

The NOTR registry is a nationwide registry of kidney transplant recipients from the eight kidney transplant centres in the Netherlands, including our institution. The NOTR registry is managed by the Dutch Transplant Foundation and includes patient and donor characteristics and a variety of clinical parameters, such as office blood pressure and prevalent medications. In the first year after transplantation, registry follow-up is at month 3, thereafter on a yearly basis. We retrieved data on patient characteristics, kidney graft function, office-based systolic and diastolic blood pressure and the number of classes of antihypertensive drugs in the patients registered on 31 December 2011. For patients within the first year after transplantation, we included data from the latest visit. *Table 1* summarises these variables.

Table 1. *Kidney transplant recipient characteristics*

	NOTR n=5415	AMC n=534	P value
Age	48 (36-58)	54.5(43-64)	<0.001
Gender (male) (%)	59.6	56.4	0.154
Height (cm)	172 (166-180)	172 (165-179)	0.087
Weight (kg)	73 (64-83)	76 (65-88)	<0.001
Living donor (%)	44.5%	34.1%	<0.001
Time after kidney transplantation (years)	5.0 (2-11)	4.4 (1.3-9.7)	<0.001
Unilateral nephrectomy (%) Bilateral nephrectomy (%)	Unknown Unknown	6.4 5.4	- -
No diabetes mellitus (%)	91.8	72.1	<0.001
Caucasian (%) (of whom native born Dutch (%))	Unknown	76 (64)	-
Plasma creatinine (μmol/l)	126 (101-163)	143 (112-183)	<0.001
eGFR >60 ml/min/1.73m² (%)	18.2	15.2	0.485
eGFR 45-59 ml/min/1.73m² (%)	25.9	27.7	0.485
eGFR 30-44 ml/min/1.73m² (%)	34.4	34.6	0.485
eGFR 16-29 ml/min/1.73m² (%)	18.3	18.9	0.485
eGFR <15 ml/min/1.73m² (%)	3.1	3.6	0.485
Proteinuria g/l	0.11 (0.03-0.30)	0.09 (0.06-0.18)	0.831
Sodium excretion (mmol/24 h)	Unknown	147 (109-195)	-
Systolic blood pressure (mmHg)	134 (122-145)	134 (124-146)	0.171
Diastolic blood pressure (mmHg)	80 (70-85)	81 (76-88)	<0.001
Number of anti-hypertensive drugs	2 (1-2)	2 (1-3)	0.381
Diuretic (%)	21.1	31.7	<0.001
Alpha or beta blocking agent (%)	60.1	53.9	0.006
Prednisolone (%)	89.5	93.6	0.004
Prednisolone (mg/day)	Unknown	10 (5.0-10.0)	-
Tacrolimus (%)	58.2	53.4	<0.001
Cyclosporine (%)	36.9	20.8	<0.001
MMF (%)	73.8	58.1	<0.001
Azathioprine (%)	5.3	14.0	<0.001
mTOR inhibitor (%)	5.1	4.1	0.359

Interquartile ranges 25% and 75% shown. NOTR = Netherlands Organ Transplant Registry; AMC = Academic Medical Centre Amsterdam; DM = diabetes mellitus: either DM type I or II or new-onset DM after transplantation; MMF = mycophenolate mofetil; mTOR inhibitor= mammalian target of rapamycin.

Local data

To provide additional information about determinants of hypertension that could not be retrieved from the NOTR, we performed a retrospective survey on the medical files of the prevalent kidney transplant recipients at our kidney transplant centre in Amsterdam in September 2012. On average these patients visit the outpatient clinic four times per year. We collected data on patient characteristics including ethnicity, kidney graft function, office-based systolic and diastolic blood pressure and prevalent classes of antihypertensive and immunosuppressive drugs and their dosages.

In all patients 24-hour urine collections are routinely performed at each outpatient clinic visit. Therefore we were able to assess daily sodium excretion as a proxy of dietary intake parallel to the blood pressure readings. Urine sodium excretion was measured at least four weeks after adjustment or initiation of diuretic treatment. Therefore these measurements represented a steady state in which

Table 2. *Advised maximal daily dosages of antihypertensive medications in kidney transplant recipients according to the local protocol (Academic Medical Centre Amsterdam) The protocol allows higher dosages if clinically indicated*

Class	Name	eGFR 60-15 ml/min	eGFR >60 ml/min
Calcium antagonists	Nifedipine	90 mg	90 mg
	Amlodipine	10 mg	10 mg
	Barnidipine	20 mg	20 mg
Diuretics	Furosemide	120 mg	80 mg
	Bumetanide Chloro-talidone	5 mg 50 mg	2 mg 50 mg
	Hydrochloro-thiazide	25 mg	25 mg
ACE inhibitors	Enalapril	20 mg	30 mg
	Lisinopril	20 mg	40 mg
Beta blockers	Metoprolol	200 mg	200 mg
	Nebivolol	10 mg	10 mg
Alpha blockers	Doxazosine	8 mg	8 mg
Angiotensin II antagonists	Losartan	100 mg	100 mg
Central antihy-pertensives	Moxonidine	0.2 mg	0.4 mg
Central antihy-pertensives	Methyldopa	2250 mg	2250 mg

sodium intake and excretion were equal. We defined the possibility for optimisation of antihypertensive treatment as the option to initiate antihypertensive treatment or the option to increase the number and/or dosage of the prescribed antihypertensive agents up to the maximum recommended dosage in our local protocol (*table 2*).

Statistical analysis

All data were included in a master file and statistical analyses were performed using SigmaStat (Jandel Scientific Software, San Jose, California USA). Normally distributed data are represented as mean and SD; non-normally distributed data as median and interquartile ranges. Under Dutch law this retrospective, descriptive study was exempt from medical ethics review.

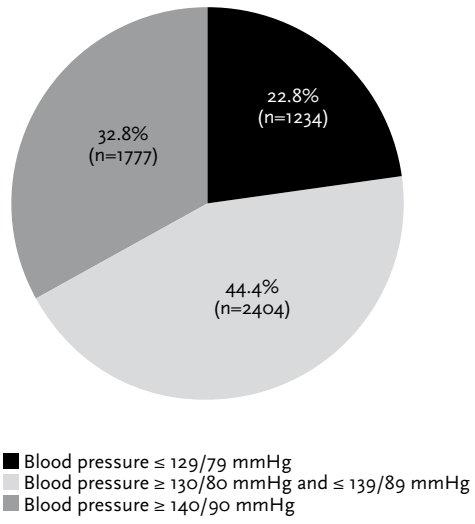
RESULTS

Netherlands Organ Transplant Registry data

On 31 December 2011, 5770 patients of 18 years and older were registered in the NOTR as living with a functioning kidney transplant. Recent blood pressure measurements were missing in 355 patients (6.2%), who were excluded from further analysis. Median age was 48 years (interquartile range (IQR) 36-58) and time after transplantation 5.0 years (IQR 2-11). Median plasma creatinine was 126 µmol/l (IQR 101-163) and proteinuria was 0.11 g/l (IQR 0.03-0.30). Most patients were treated with a calcineurin inhibitor (CNI). Tacrolimus was prescribed in 58.2% and cyclosporine in 36.9% of the patients. Prednisolone was prescribed in 89.5% of the patients, mostly in combination with a CNI. Mycophenolate mofetil (MMF) was used in addition to the CNI and/or prednisolone regimen in 73.8%. Azathioprine was given to 5.3% of the kidney transplant patients and a mammalian target of rapamycin (mTOR) inhibitor to 5.1%.

Median blood pressure was 134/80 mmHg (IQR 122-145 / 70-85). These data are summarised in *table 1* and *figure 1*. The examination of the numbers of classes of antihypertensive drugs prescribed showed that at least one class of blood pressure lowering agents was prescribed in 87.8% of the patients. Of all kidney transplant recipients with a blood pressure ≥130/80mmHg, 10.4% had no prescription for any antihypertensive drug, 30.0% used one antihypertensive agent, 33.7% used two and 25.9% used three or more different classes of antihypertensive drugs (*figure 2*).

Figure 1. *Blood pressure of kidney transplant recipients (data from the NOTR)*



Blood pressure is classified into three categories (≤ 129/79 mmHg, > 130/80 - ≤ 139/89 mmHg and ≥ 140/90 mmHg).

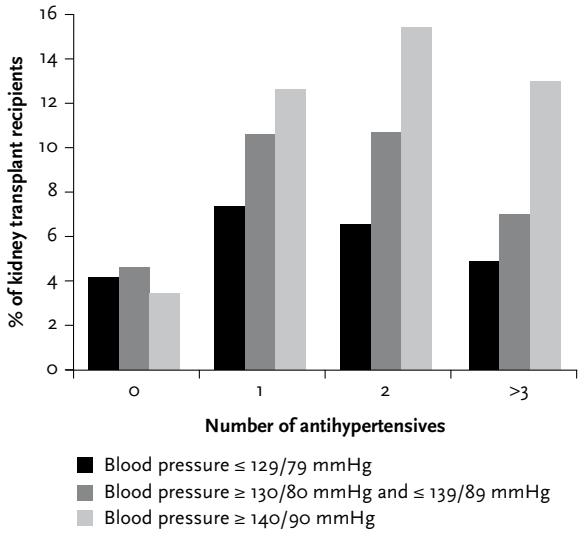
Local data

Patient characteristics are shown in *table 1*. Data on n=539 prevalent patients living with a functioning kidney transplant on 1 September 2012 were included. There were missing data on recent blood pressure in five patients. Therefore, we further analysed the data on 534 patients. There were nine patients who had missing data on 24-hour urine specimens. In this cohort, the median age of 54.5 years (IQR 43-64) was slightly higher and time after transplantation of 4.4 years (IQR 1.3-9.7) was shorter than in the NOTR survey. Ethnic diversity was broad with 76% being Caucasian and of whom 64% were of Dutch descent. Median plasma creatinine was 143 µmol/l (IQR 112-183) and proteinuria was 0.09 g/l (IQR 0.06-0.18).

The CNI tacrolimus was prescribed in 53.4% of the patients, with median dosages of 6 mg/day (IQR 4-8) and with associated plasma trough levels of 7.4 µg/l (IQR 5.5-9.2). Cyclosporine was prescribed in 20.8%, and 93.6% of the kidney transplant recipients were treated with prednisolone with median daily dosages of 10 mg (5-10 mg). In our centre, 58.1% of our kidney transplant recipients received MMF, 14.0% azathioprine and 4.1% an mTOR inhibitor.

Kidney transplant recipients had a median blood pressure of 134/81 mmHg (124-146/76-88). In 420 patients (78.6%) blood pressure was ≥130/80 mmHg, of whom 14.5% were not taking an antihypertensive drug, 29.3% used one, 29.8% two and 26.8% used three or more different classes of blood pressure lowering agents. Blood pressure ≥140/90 mmHg was found in 43.8% of our patients. Of the 420 patients with blood pressure ≥130/80 mmHg, 24.8% were taking three or more antihypertensive drugs while having their antihypertensive drugs prescribed at dosages that were lower than the highest permitted dose, as indicated by the local protocol (*table 2*). Resistant hypertension (defined as blood pressure >130/80 on either three antihypertensives including a diuretic, all in highest permitted dose, or on four antihypertensives regardless of the dose) was present in 7.7% of all our kidney transplant recipients. Median sodium intake as inferred in 24-hour urine specimens was 147 mmol/24 h (109-195).

Figure 2. *Number of classes of antihypertensive drugs prescribed (data from the NOTR)*



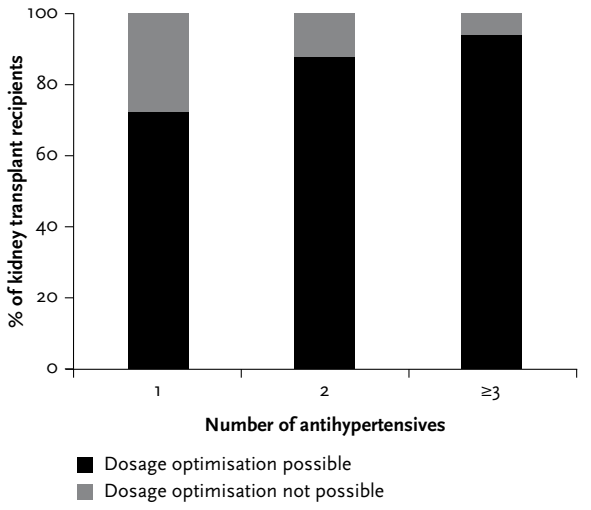
Blood pressure is classified in three categories (≤ 129/79 mmHg, ≥ 130/80 and 139/89 mmHg and ≥ 140/90 mmHg). The number of patients per group was n=659 without an antihypertensive agent and n=1650, n=1763 and n=1343 in the groups on one, two, three or more than three antihypertensive drugs respectively.

DISCUSSION

The main findings of our study include the following. Firstly, 22.8% of the kidney transplant recipients had office-based blood pressure measurements <130/80 mmHg (regardless of the use of antihypertensive drugs) while in the remaining 77.2% treatment targets are not reached. Secondly, this might be due to the prescription of too low numbers of antihypertensive drugs and/or in too low dosages. Thirdly, only 7.7% of patients fulfil the criteria of treatment-resistant hypertension. And fourthly, sodium intake targets appear not to be reached in the majority of transplant recipients.

This is the first study on the prevalence and treatment efficacy of hypertension in kidney transplant recipients in the Netherlands. Previous studies have reported prevalences of 45.5% in a kidney transplant recipient cohort studied between 1976-2002.[4] The landmark study by Opelz *et al.* analysing a large international multicentre kidney transplant recipient cohort also showed a prevalence of hypertension of ~46% at both 1 and 5 years post-transplantation.[9] In more recent studies, this prevalence has been surpassed without exception. In the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) study, 92% of 4107 American kidney transplant recipients had hypertension. Of them, 69% had a blood pressure of ≥130/80 mmHg regardless of the use of antihypertensive drugs.[8] A Spanish study showed that hypertension was more prevalent in more recent years (1994 and 1998 compared with 1990) although simultaneously a greater number of antihypertensive agents were prescribed.[11] In another ten-year follow-up study, hypertension after kidney transplantation was present in 74%.[12] A large analysis of the use of cardiovascular drugs in kidney transplant recipients, including lipid-lowering and antiplatelet agents, showed a nearly fourfold increase between 2000-2006 compared with the early 1990s.[13] These findings imply that our

Figure 3. *The possibilities for optimising the dosages of antihypertensive drugs prescribed in kidney transplant recipients with blood pressure ≥130/80 mmHg*



This chart shows the theoretical possibility to optimise dosage(s) of the class(es) of antihypertensive drugs that are prescribed in kidney transplant recipients using one, two or three or more antihypertensive drugs while having office-based blood pressure ≥130/80 mmHg (data from our cross-sectional analysis in our kidney transplant unit in Amsterdam). The number of patients per group was comparable (n= 123, n=125 and n=111 in the groups using one, two or three or more antihypertensive drugs respectively). Possibilities to optimise the dosage were based on the local protocol prescription recommendations (table 2).

results are in agreement with the data shown in literature. The prevalence of treatment-resistant hypertension is in accordance with the single published study on this topic.[14] Our data on daily sodium excretion are also in agreement with a recent survey on sodium excretion of Dutch kidney transplant recipients by Van den Berg *et al*. They showed that urinary sodium excretion was 156±62 mmol/24 hours in 660 kidney transplant recipients.[15]

Our study is the first to directly identify the prescription behaviour of the attending physicians as an opportunity for improving blood pressure control. *Figure 3* shows the optimisation possibilities of antihypertensive medications, i.e. the prescribed dosage of the class of antihypertensive drugs. According to our local protocol, a theoretical dose optimisation of the prescribed class of antihypertensive agent(s) seemed possible in 74.0% of our kidney transplant recipients with an office-based blood pressure ≥ 130/80 mmHg (*figure 3*).

The present study has some methodological limitations. First of all there is the question of setting the target blood pressure. The target of < 130/80 mmHg was derived from observational studies and therefore we should regard this threshold with caution. Especially in patients with extensive atherosclerosis, blood pressure < 130/80 mmHg may be too low. However, even if we regard measurements above 140/90 mmHg as hypertension, still about 44% of the kidney transplant recipients remain hypertensive. Secondly, the feasibility of implementing a restriction in daily sodium intake in all patients is uncertain; however, lowering sodium intake to approximately 90 mmol/day has been shown to be feasible.[16,17] Thirdly, the retrospective design and the use of single office-based blood pressure measurements may have limited the quality of the source data (as compared with for example prospective data collection including 24-hour ambulatory blood pressure measurements).[18] Fourthly, we assumed that patients using antihypertensive medications fulfilled the diagnosis 'hypertension'. However, some of these medications may have been prescribed for indications other than hypertension (e.g. renin-angiotensin system inhibition for proteinuria and beta-blockers for coronary artery disease). By these assumptions we may have overestimated the prevalence of hypertension. Furthermore, our data did not address the attending physicians' rationale for choosing a certain sub-maximal antihypertensive drug dosage e.g. due to intolerance, allergies, toxicity or comorbidities. Ultimately, the sodium excretion from 24-hour urine collections depends on the assumption that such collections have been performed adequately.

These limitations should be addressed in future prospective studies. Because adherence to antihypertensive agents may be low as compared with adherence to immunosuppressive medications future work should also address strategies to improve patients' adherence to antihypertensive therapy regimens and behavioural factors concerning medication intake.[19]

CONCLUSION

Hypertension as the foremost cardiovascular and renal risk factor in kidney transplant recipients is highly prevalent and only a minority of patients reach target blood pressures with current therapy. We have identified physicians' prescription behaviour and the patients' daily sodium intake as possible mediators to improve blood pressure control. Intensifying pharmacological therapy often seems possible and more stringent advice for lowering their daily sodium intake should be given to and followed by kidney transplant recipients.

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DISCLOSURES

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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