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Hospital specific factors affect quality of blood pressure treatment in chronic kidney disease

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ABSTRACT

Background: Blood pressure (BP) is the most important modifiable risk factor for cardiovascular (CV) disease and progression of kidney dysfunction in patients with chronic kidney disease. Despite extensive antihypertensive treatment possibilities, adequate control is notoriously hard to achieve. Several determinants have been identified which affect BP control. In the current analysis we evaluated differences in achieved BP and achievement of the BP goal between hospitals and explored possible explanations.

Methods: At baseline, BP was measured in a supine position with an oscillometric device in 788 patients participating in the MASTERPLAN study. We also retrieved the last measured office BP from the patient records. Additional baseline characteristics were derived from the study database. Univariate and multivariate analyses were performed with general linear modelling using hospital as a random factor.

Results: In univariate analysis, hospital was a determinant of the level of systolic and diastolic BP at baseline. Adjustment for patient, kidney disease, treatment or hospital characteristics affected the relation. Yet, in a fully adjusted model, differences between centres persisted with a range of 15 mmHg for systolic BP and 11 mmHg for diastolic BP.

Conclusion: Despite extensive adjustments, a clinically relevant, statistically significant difference between hospitals was found in standardised BP measurements at baseline of a randomised controlled study. We hypothesise that differences in the approach towards BP control exist at the physician level and that these explain the differences between hospitals.

KEYWORDS

Chronic kidney disease, therapeutic inertia, centre differences, blood pressure, epidemiology

INTRODUCTION

Blood pressure (BP) is considered to be the most important modifiable cardiovascular (CV) risk factor. In large population studies a reduction of systolic BP of 20 mmHg is associated with a 33% reduction in stroke and ischaemic heart disease in patients aged 80 to 89 years and an even greater reduction of 62% in stroke and 51% in ischaemic heart disease in those aged 50 to 59 years.[1] The prevalence of hypertension is high in patients with chronic kidney disease (CKD) and increases with CKD stage from 79% in CKD stage I to 95% in CKD stages IV and V.[2] In patients with CKD, reduction of BP is not only important to prevent CV events but also to attenuate the decline of kidney function.[3,4]

Nowadays, physicians can use a multitude of effective BP-lowering agents and, in addition, focus on lifestyle

changes. Despite this armamentarium, the large majority of patients do not achieve treatment goals.[5-7] Several factors have been identified to be associated with poor BP control, including more advanced kidney dysfunction, poor adherence, absence of health insurance and physicians not adhering to guidelines or showing therapeutic inertia.[5,8-10] Recently, we reported in CKD patients that the hospital where a patient receives treatment was independently associated with a quality of care score based on 11 different risk factors.[11] In the current analyses, we evaluated the BP and the degree that BP goals were achieved, compared results between centres and explored possible explanations for the observed differences.

SUBJECTS AND METHODS

MASTERPLAN study

The MASTERPLAN study [Trial registration ISRCTN registry: 73187232 (http://isrctn.org)] is a randomised, controlled trial conducted in nine hospitals with a nephrology department in the Netherlands. Rationale and design have been published elsewhere.[12,13] Ethical approval was given by the ethics board of the University of Utrecht with additional endorsement of local applicability by the ethical boards of each of the participating hospitals.

In brief, adult patients with CKD (estimated GFR between 20 and 70 ml/min) were included in the study.

The effects of a multi-targeted treatment regimen executed by a specialised nurse under the supervision of, and in collaboration, with a nephrologist are compared with the care delivered by the patients own physicians, also mostly nephrologists. In both arms of the study, the same sets of guidelines apply. The primary endpoint is a composite of fatal and nonfatal myocardial infarction, stroke and cardiovascular mortality. Secondary endpoints are all-cause mortality, achievement of treatment goals for the various risk factors, decline of kidney function and quality of life. Follow-up will continue for five years.

All participating hospitals are teaching hospitals that offer a full range of nephrology treatment including kidney replacement therapy (both haemodialysis and peritoneal dialysis) and are involved in the care of kidney transplant recipients. Three hospitals are university clinics that offer tertiary care and have kidney transplant programs. The number of beds per hospital ranges from 414 to 953.

Patient evaluation

Baseline measurements consisted of a questionnaire to obtain information on smoking behaviour, physical activity and medication use. Physical examination consisted of measurement of height, weight and BP (oscillometric BP measurements after 15 minutes of supine rest, mean of five measurements in the following 15 minutes). BP was concluded to be on target if oscillometric BP level was ≤125/80 mmHg in patients without proteinuria and ≤120/70 mmHg in patients with ≥1 g proteinuria / 24 hours (guidelines indicate goals of 130/85 and 125/75 mmHg respectively for office measurement; an additional 5 mmHg adjustment for both systolic and diastolic BP is applied for the period of supine rest and use of an oscillometric device).[14,15] Also the BP of the patient measured during the last outpatient visit prior to randomisation (screening visit) was retrieved. These were sphygmomanometric office measurements, usually taken in a sitting position by an experienced internist during the visit to the centre. The sphygmomanometric devices were of the aneroid mechanical type.

All devices (both oscillometric and sphygmomanometric) are validated annually in participating centres. Aneroid devices were validated by local technical services in the respective centres. Most centres retained a mercury sphygmomanometer in their technical department to allow for correct validation. Additional validation of the oscillometric devices was performed prior to the start of the study. Per centre different types of oscillometric devices are used: BP100 (Gambro, Lund, Sweden), Critikon (Critikon, Tampa, Florida), Dinamap Procare (GE Medical Systems Information Technologies Inc., Milwaukee, Wisconsin), Accuratorr plus (Datascope, Mahwah, New Jersey).

Blood was drawn and a 24-hour urine sample was collected. Blood and urine samples were analysed by the centre's laboratory. Medical history was obtained from the medical records. History of CV disease was defined as a history of myocardial infarction, stroke or vascular intervention. Diabetes mellitus at baseline (DM) was defined as the use of glucose-lowering drugs or a fasting glucose >7.0 mmol/l. Adherence to the Dutch Guidelines of Healthy Physical Exercise was determined with the validated SQUASH questionnaire.[16] The underlying diagnosis of kidney disease was determined by the treating physician and categorised using the ERA-EDTA (European Renal Association) registration criteria. To allow comparisons with other studies, we report the estimated glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) formula.[17]

Data analysis

Baseline characteristics were given for the study population by participating hospital and expressed as means (SD) or proportions. For non-parametric data medians [range] were supplied. Differences between centres in risk factors were studied using analysis of variance adjusted for age and gender if applicable.

With regard to missing data, two analyses were performed: one complete case analysis (all complete data) and one in which missing data were imputed. The presented data

are based on imputed data. Five separate imputations were performed and analyses were carried out on each imputation separately.[18] Results were then pooled via the statistical software (SPSS 17).

Since patients cluster within hospitals, we applied general linear modelling for continuous dependent variables and included hospital as a random effect.[19] As a measure for the explanation of the variability in the model η^2 is used, since for this type of analysis η^2 is considered more appropriate than R^2.

For multivariate analyses of the centre effect, different models have been constructed. Based upon known determinants of systolic and diastolic BP, both from literature and our own analyses, we came to the following models (which can be viewed online as appendix A):

Model 0: no adjustment;

Model 1 (patient characteristics): age, gender, race, history of CV disease, history of DM, body mass index (BMI), income, current smoking, physical activity, left ventricular hypertrophy (LVH) on ECG;

Model 2 (additional kidney disease characteristics): Model 1 + diagnosis, history of kidney transplantation, eGFR, proteinuria, serum potassium;

Model 3 (additional treatment characteristics): Model 2 + sodium excretion in urine, number of visits in the year prior to randomisation, number of antihypertensives, renin angiotensin system (RAS) intervention, use of diuretics;

Model 4 (additional hospital characteristics): Model 3 + hospital size, academic status.

Adjusted means were calculated for systolic and diastolic BP measured at baseline and at the screening visit. Adjustment was performed for age, gender, race, history of CV disease, history of DM, BMI, income, current smoking, physical activity, LVH on ECG, nephrological diagnosis, history of kidney transplantation, eGFR, proteinuria, sodium excretion in urine, number of visits in the year prior to randomisation, number of antihypertensives, RAS intervention, use of diuretics and hospital size. The analyses were performed with SPSS 17.0 (SPSS inc., Chicago, USA).

RESULTS

A total of 793 patients were included in the study between April 2004 and December 2005. Three patients did not meet inclusion criteria and two patients withdrew consent directly after randomisation, leaving 788 patients available for the analyses.

Baseline characteristics are given in *table 1*. The majority of patients are male (68%) and Caucasian (92%). Mean BP is 135 (±20)/78 (±11) mmHg. The proportion of patients considered to have achieved the treatment goals based on the oscillometric BP measurement is 28%, varying between centres from 12 to 42% *(table 1)*.

Differences in BP between hospitals

In the general linear modelling analysis with centre as a random factor, systolic BP was significantly lower in all hospitals compared with the reference centre (Centre B) *(table 2a)*.

Models 1 and 2 showed that some of the differences are explained by patient and kidney disease-related characteristics, respectively *(table 2a)*. Factors added in models 3 and 4 did not seem to contribute much. For diastolic BP, patient-related characteristics (Model 1) have the greatest contribution. Adjustment for pharmacotherapy (i.e. the use of RAS intervention (either an ACE inhibitor or angiotensin receptor blocker) or diuretics) did not explain the differences between hospitals (Model 3). A table with the results of the various models can be viewed online as appendix B.

In the final full multivariate model (Model 4) a clear centre effect remained present, i.e. hospitals A, C, D, G and H showed significantly lower systolic BP levels compared with the reference centre. The centre effect explained about half of the variability that can be explained by the regression model; η^2 for the full model is 0.21 and 0.10 for the model without adjustments. Also in a reverse fashion for the fully adjusted model without centre η^2 was 0.13, whereas the fully adjusted model with centre had an η^2 of 0.21. The range of the differences in adjusted systolic BP between hospitals was 15 mmHg.

For diastolic BP a centre effect was found with centre I having the highest diastolic BP and centre G the lowest (*table 1*, appendix B). After adjustment for additional determinants the differences remained. The difference between highest and lowest diastolic BP after adjustment is 11 mmHg. Hospitals A, D, E and G also had a significantly lower diastolic BP compared with hospitals F and I.

Differences in oscillometric and sphygmomanometric (office) BP measurements

Based on the previous findings we performed additional analyses to explore the following issues as potential explanations of these findings.

1. Are there not only centre differences in the oscillometric BP measurements (BP obtained with the BP measuring device at baseline of the study), but also in the sphygmomanometric BP measurements performed at the outpatient clinics during the last visit prior to entry into the study (median 32 days before inclusion (IQR 20-53 days). *Figure 1* shows that on average oscillometric BP is lower than office BP (p=0.05 for systolic BP and p=0.006 for diastolic BP). Yet, the centre effect remained present in both methods of BP assessment.

Table 1. *Baseline characteristics of the MASTERPLAN cohort*

Variable	Total (n=788)	A (n=94)	B (n=100)	C (n=100)	D (n=100)	E (n=104)	F (n=91)	G (n=66)	H (n=65)	I (n=68)
Age (years)	59.1 (13.0)	54.3 (13.2)	60.9 (11.6)	59.3 (11.8)	52.5 (12.6)	59.9 (13.2)	61.9 (10.5)	66.9 (12.6)	58.5 (14.3)	60.3 (12.2)
Gender (male %)	68	64	76	76	68	59	77	64	55	66
Caucasian (%)	92	93	95	94	99	73	95	88	95	100
KTR (%)	14	32	3	10	30	14	8	3	0	21
Prior CV disease (%)	29	29	38	30	16	29	36	30	23	34
Cause of kidney disease (%)										
Unknown	20	31	20	52	8	12	20	14	14	4
Glomerulonephritis	15	16	6	17	31	14	7	8	14	22
Interstitial	9	11	5	6	23	8	4	5	11	3
Cystic	10	18	7	5	13	4	8	6	20	12
Other cong	2	3	0	0	7	1	0	0	5	3
Renovascular	27	6	49	15	4	43	35	42	11	38
Diabetes	10	9	9	4	9	12	14	18	5	16
Other multisystem	5	4	3	1	3	4	8	3	19	2
Other	2	2	1	0	2	4	4	5	3	0
BMI (kg/m^2)	27.1 (4.7)	26.1 (4.6)	26.7 (4.2)	28.6 (4.5)	27.1 (5.6)	27.2 (5.3)	27.2 (4.0)	27.6 (5.1)	25.6 (4.3)	27.3 (4.0)
Oscillometric BP (mmHg)	135(20)/78(11)	127(16)/75(8)	145(22)/82(12)	136(18)/80(10)	128(16)/76(8)	140(23)/77(11)	140(19)/81(9)	131(25)/72(10)	128(19)/76(13)	141(17)/84(11)
Office BP (mmHg)	137(20)/79(10)	132(17)/82(9)	145(23)/81(8)	138(23)/80(11)	135(15)/79 (7)	134(20)/79(11)	139(23)/78(11)	135(23)/73(12)	134(19)/79(10)	138(16)/80(8)
No. of visits in year prior to inclusion	3 [0-31]	3 [1-31]	2 [0-5]	3 [1-8]	4 [2-31]	3 [0-8]	3 [0-8]	3 [0-8]	3 [0-10]	3 [1-8]
Creatinine (µmol/l)	182 (68)	201 (74)	186 (68)	182 (55)	168 (83)	184 (83)	160 (58)	180 (78)	191(74)	188 (60)
eGFR by MDRD (ml/min/1.73 m^2)	37 (14)	33 (13)	37 (15)	36 (11)	40 (13)	38 (16)	44 (16)	37 (13)	34 (11)	34 (10)
Proteinuria (mg/24 h)	300 [0-9300]	400 [100-9300]	163 [0-7000]	300 [20-7400]	600 [0-6640]	221 [0-9000]	100 [0-3700]	300 [0-6800]	400 [30-7000]	305 [0-6300]
Urinary sodium excretion (mmol/24 h)	150 [29-419]	139 [29-261]	158 [57-283]	162 [51-419]	160 [46-340]	129 [31-343]	148 [44-297]	130 [34-279]	148 [48-318]	163 [48-366]
Serum potassium (mmol/l)	4.4 (0.6)	4.5 (0.6)	4.5 (0.6)	4.2 (0.5)	4.7 (0.6)	4.7 (0.5)	4.3 (0.5)	4.3 (0.6)	4.5 (0.6)	4.4 (0.5)
LVH on ECG (%)	15	21	13	22	10	21	11	9	5	13
Monthly income (euro)	1900 [1000-8500]	2100 [1000-7000]	1880 [1200-3900]	1900 [1100-3400]	1970 [1200-4900]	1800 [1000-4700]	1800 [1100-4000]	2050 [1200-5100]	1900 [1100-8500]	1900 [1100-2800]
Physical activity (met/min x min/week)	5190 [80-41940]	6460 [240-21480]	4020 [600-17340]	6420 [600-17340]	5430 [800-19765]	4690 [120-16380]	4920 [300-18300]	4400 [80-28560]	4974 [120-16800]	6000 [240-41940]
Smoking (%)	21	19	24	18	14	28	24	15	26	19
Antihypertensives										
No. antihypertensives	2.4 (1.3)	2.3 (1.0)	2.6 (1.5)	2.4 (1.3)	2.1 (1.2)	2.5 (1.3)	2.4 (1.4)	2.4 (1.4)	2.2 (1.3)	2.5 (1.2)
RAS intervention (%)	79	89	83	64	78	84	85	80	79	71
Beta-blocker (%)	50	37	57	63	57	45	43	39	42	62
Calcium channel blocker (%)	35	21	47	31	25	39	46	36	32	38
Diuretics (%)	50	60	45	56	37	56	40	53	46	60
Loop or thiazide (%)	49	59	44	54	37	53	36	53	46	57
Alpha-blockers (%)	9	3	15	7	1	17	11	8	8	10
Other antihypertensives (%)	1	0	1	3	1	1	2	0	0	0

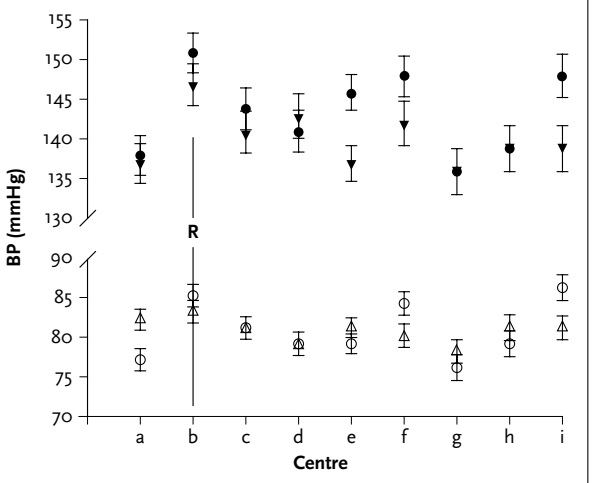
Values given are mean (SD) or % or median [range].
KTR = kidney transplant recipient; CV = cardiovascular; GN = glomerulonephritis; IN = interstitial nephritis; PKD = polycystic kidney disease; MDRD = modification of diet in renal disease; BP = blood pressure; BMI = body mass index; oscillometric BP = oscillometric assessment after 30 min of supine rest; office BP = sphygmomanometric BP during the last outpatient clinic prior to randomisation.

Table 2. *Univariate and multivariate general linear modelling for systolic BP with hospital as a random effect*

Centre	Model 0: η^2=0.10		Model 1: η^2=0.17		Model 2: η^2=0.20		Model 3: η^2=0.21		Model 4: η^2=0.21		
	B	p	B	p	B	p	B	p	B	p	95% CI
A	-18	<0.001	-15	<0.001	-15	<0.001	-13	<0.001	-13	<0.001	-19;-8
B	Ref		Ref		Ref		Ref		Ref		
C	-9	0.001	-9	<0.001	-8	0.004	-8	0.004	-8	0.004	-13;-2
D	-17	<0.001	-12	<0.001	-11	<0.001	-10	0.001	-10	0.001	-15;-4
E	-6	0.04	-6	0.02	-6	0.02	-4	0.11	-4	0.11	-9;1
F	-5	0.06	-6	0.04	-3	0.18	-3	0.20	-3	0.20	-9;2
G	-15	<0.001	-16	<0.001	-16	<0.001	-15	<0.001	-15	<0.001	-21;-9
H	-17	<0.001	-13	<0.001	-12	<0.001	-11	<0.001	-11	<0.001	-17;-5
I	-4	0.19	-3	0.30	-4	0.20	-3	0.30	-3	0.30	-9;3

Model 0: no adjustment; model 1: patient characteristics: age, gender, race, history of CV disease, history of DM, BMI, income, current smoking, physical activity, LVH on ECG; model 2: Model 1 + kidney disease specific: diagnosis, history of kidney transplantation, eGFR, proteinuria, serum potassium; model 3: model 2 + treatment related: sodium excretion in urine, no. of visits in the year prior to randomisation, no. of antihypertensives, use of renin angiotensin-modulating drugs, use of diuretics; model 4: model 3 + centre related: centre size, academic status. η^2 = is a measure of effect size for use in ANOVA, B = unstandardised regression coefficient (representing difference in BP in mmHg with centre B), p = p-value in statistical analysis.

Figure 1. *Adjusted BP values (according to model 4, table 2) in different centres*

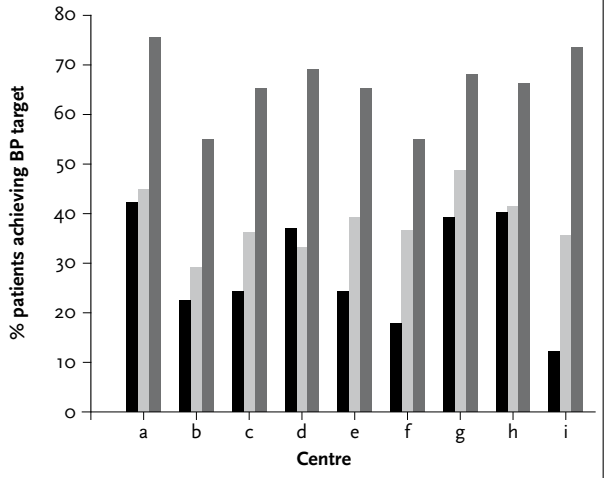


• = systolic oscillometric BP; o = diastolic oscillometric BP; ▼ = systolic office BP; Δ = diastolic office BP; ⊤ = 1 standard error of the mean. R = reference centre. Adjustment for: age, gender, race, history of CV disease, history of DM, BMI, income, current smoking, physical activity, LVH on ECG, nephrological diagnosis, history of kidney transplantation, eGFR, proteinuria, sodium excretion in urine, no. of visits in the year prior to randomisation, no. of antihypertensives, use of ACEs or ARBs, use of diuretics and centre size.

2. Do hospital differences disappear above a certain level of achieved BP goals? Such a finding might be interpreted as indicating that different targets are used in the hospitals. *Figure 2* shows percentages of patients achieving treatment goals per centre for three separate goals: a goal of 125/80 mmHg (120/70 mmHg if proteinuria >1 g/day) for oscillometric BP, a goal of 130/85 mmHg (125/75 mmHg if proteinuria >1 g/day) for sphygmomanometric office BP, and a goal of 140/90 mmHg for sphygmomanometric office BP (independent of proteinuria). *Figure 2* illustrates that differences between centres were present for all three treatment goals, although the smallest range was found when 140/90 mmHg as treatment goal is applied. In some centres a marked difference between achievement of the oscillometric BP goal and office BP goal could be appreciated (e.g. hospitals F and I) *(figure 2)*.

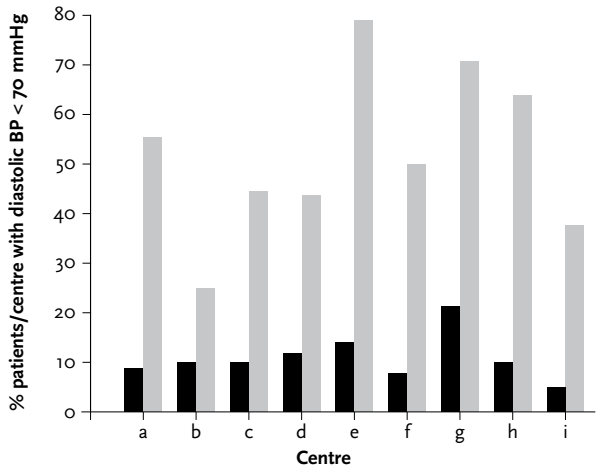
3. Could low diastolic BP be a factor obstructing achievement of treatment goals?
A diastolic BP <70 mmHg was present in 170 (21.6%) patients. This is shown per hospital for patients who do and do not meet the study treatment goal *(figure 3)*.

Figure 2. *Percentage of patients achieving BP goals in different centers*



Black bars represent the oscillometric BP goal, light grey bars represent the office guideline derived goals and dark grey bars represent a goal of 140/90 mmHg.

Figure 3. *Percentage of patients with diastolic BP <70 mmHg in different centres*



Black bars represent the patients not achieving the study treatment goal and the light grey bars represent patients who do meet the study goal.

In 62 of 587 patients not on target (10.6%) diastolic BP was below 70 mmHg with no significant differences between hospitals.

DISCUSSION

The present study shows that there are substantial and clinically relevant differences between centres with regard to achieved systolic and diastolic BP levels in CKD patients and percentages of patients achieving adequate BP control. These differences persist after adjustment for various patient, kidney disease, treatment and hospital characteristics.

Adequate BP control in hypertensive patients is notoriously difficult and may show important differences between populations. Even more so in the CKD population because of the added disturbed sodium and water handling. Differences between countries may be attributed to the use of different guidelines, differences in lifestyle factors, healthcare organisation and racial distribution.[20] In the present study, all patients were subject to the same set of guidelines, to the same healthcare organisation and mostly of Caucasian race. It seems fair to conclude that these factors cannot explain the differences observed between hospitals. In addition, potential differences in several lifestyle factors between patients in centres were taken into account in our analysis.

In the present analysis, we went at length to take possible confounders into account.[5] Patient characteristics including socioeconomic status (Model 1) and characteristics of kidney disease (Model 2) did contribute and explained partially the differences between hospitals. Treatment- and hospital-related factors (Models 3 and 4) did not markedly change the observed associations. The fact that BP-lowering therapy did not affect differences between centres may be explained by the high prevalence of the use of both diuretics and agents that interfere with RAS in all the hospitals. So, Model 4 showed that despite adjusting for multiple factors, differences between hospitals persist. These results necessitate the consideration of yet additional factors, which may be of relevance.

Firstly, we addressed the question whether the technique/device is the source of the difference. For that purpose, we also studied the last BP measured by the physician during the visit to the outpatient clinic prior to inclusion (a manual sphygmomanometric measurement using an aneroid device). *Figure 1* showed that these office BPs substantially differed between hospitals, indicating that the observed difference between hospitals was not explained by the different oscillometric devices. Moreover, BP differences existed between centres that use the same oscillometric device (e.g. centres A and I both used the Datascope device, centres D, E, G an H all used the Critikon device).

It must be noted that in some centres a marked difference between oscillometric BP and office BP was present. This might indicate that the technique and situation of measurement affected results to a certain extent as stated recently by Becker and Wheeler, although all office measurements were performed in the office during the visit by the internist using an aneroid sphygmomanometric device *(figure 2)*.[21] A second factor is that a yet unmeasured patient characteristic may have (partially) contributed to the centre effect. These factors may include ethnicity, living environment and adherence to the prescribed treatment. Our cohort included patients from North-Africa, the Middle-East, Turkey and Northern Europe and all these different ethnicities were classified as Caucasian. The prevalence of these ethnicities is variable in the various regions of the Netherlands and may have been different between hospitals, which might have affected the results.[22,23] Non-adherence to therapy is a well-known cause for not achieving BP goals and may be different between hospitals and possibly also affected by ethnicity.[24,25] Also environmental issues (i.e. crime, street noise, crowded housing) could affect BP and be distributed unevenly between the regions in which the hospitals are located.[23] However, these factors have not been specifically addressed in this study.

A third and most relevant factor in explaining the centre differences may have been the attitude of the physician towards BP management. We have analysed the data at the level of the hospital, not the physician. As such detailed data have not been collected in the MASTERPLAN study, the

present dataset does not allow such an analysis. The hospitals were, however, comparable with regard to the number of visits and the number or type of prescribed antihypertensive agents. Although all physicians had access to and were familiar with the same set of guidelines, we unfortunately had no data on the target levels of BP that physicians in hospitals actually pursue.[26] Part of the observed differences could therefore be explained by different treatment goals: for example, in one hospital the physicians might target BPs below 130 mmHg systolic, whereas in another hospital a systolic BP of 140 mmHg was considered adequate. *Figure 2* showed that centre differences appeared less obvious when applying a goal of 140/90 for the office BP measurement, possibly illustrating this phenomenon. Since the difference between hospitals was still statistically significant, this factor does not fully explain the hospital effect.

The perceived importance of BP control could differ between physicians and hospitals and might possibly explain centre differences. Physician inertia (i.e. the tendency not to adjust the intensity of treatment, despite the fact that a risk factor does not meet the treatment goal) has been identified as an important factor affecting BP control and is also part of the physician attitude towards BP management.[8,9] However, as no information has been collected on these aspects, it was not addressed in this study.

A fourth aspect that could have affected treatment efficacy was the attainment of a low diastolic BP. Several studies have cautioned against lowering diastolic BP below 70 mmHg, especially in patients with vascular disease. This trend may hamper treatment of patients with high pulse pressure, since adequate lowering of systolic BP in these patients will often cause diastolic BP below 70 mmHg. Our data did not allow for a definite conclusion on this issue.

LIMITATIONS

Our study has some limitations. The present analysis was performed on baseline data of CKD patients who consented to participate in a randomised controlled trial. Therefore, the results might not be generalisable to the general CKD population. Further, all automated devices were validated within the centres, but were not all from the same manufacturer. We cannot exclude the possibility that this is of relevance.

Finally, at the start of the study, we did not expect to find this centre effect. Therefore, we may not have collected sufficient data to evaluate this finding in much more depth; for instance, daily defined dosages of antihypertensives could have illustrated some differences in treatment. Because of the numerous different antihypertensives applied in the cohort at baseline, daily defined dosages could not be calculated. However, it seems reasonable to assume that this centre effect is to be explained on the level of the physician.

In conclusion, the present data indicate that there are substantial and most likely clinically relevant differences between centres in the quality of BP control in CKD patients. Our analysis suggests that this may be explained by differences at the level of the physician. Further studies are necessary to address this possibility in more detail. It is attractive to hypothesise that this reveals additional opportunities to improve the quality of care.

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CONFLICTS OF INTEREST/DISCLOSURE

None.

REFERENCES

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002 Dec 14;360(9349):1903-13.
2. Sarafidis PA, Li S, Chen SC, Collins AJ, Brown WW, Klag MJ, et al. Hypertension awareness, treatment, and control in chronic kidney disease. Am J Med. 2008 Apr;121(4):332-40.

3. Klahr S, Levey AS, Beck G, Caggiula AW, Hunsicker L, Kusek JW, et al. The Effects of Dietary Protein Restriction and Blood-Pressure Control on the Progression of Chronic Renal Disease. N Engl J Med. 1994 Mar 31;330(13):877-84.

4. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Lancet. 1998 Oct 17;352(9136):1252-6.

5. Muntner P, Anderson A, Charleston J, Chen Z, Ford V, Makos G, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2010 Mar;55(3):441-51.

6. Tonelli M, Bohm C, Pandeya S, Gill J, Levin A, Kiberd B. Cardiac risk factors and the use of cardioprotective medications in patients with chronic renal insufficiency. Am J Kidney Dis. 2001 Mar;37(3):484-9.

7. De Nicola L, Minutolo R, Chiodini P, Zoccali C, Castellino P, Donadio C, et al. Global approach to cardiovascular risk in chronic kidney disease: reality and opportunities for intervention. Kidney Int. 2006 Feb;69(3):538-45.

8. Banegas JR, Segura J, Ruilope LM, Luque M, Garcia-Robles R, Campo C, et al. Blood pressure control and physician management of hypertension in hospital hypertension units in Spain. Hypertension. 2004 Jun;43(6):1338-44.

9. Oliveria SA, Lapuerta P, McCarthy BD, L'Italien GJ, Berlowitz DR, Asch SM. Physician-Related Barriers to the Effective Management of Uncontrolled Hypertension. Arch Intern Med. 2002 Feb 25;162(4):413-20.

10. He J, Muntner P, Chen J, Roccella EJ, Streiffer RH, Whelton PK. Factors Associated With Hypertension Control in the General Population of the United States. Arch Intern Med. 2002 May 13;162(9):1051-8.

11. Van Zuilen AD, Blankestijn PJ, van Buren M, Ten Dam MA, Kaasjager KA, Ligtenberg G, et al. Quality of care in patients with chronic kidney disease is determined by hospital specific factors. Nephrol Dial Transplant. 2010 Nov;25(11):3647-54.

12. Van Zuilen AD, Wetzels JF, Blankestijn PJ, Bots ML, Van Buren M, Ten Dam MA, et al. Rationale and design of the MASTERPLAN study: Multifactorial approach and superior treatment efficacy in renal patients with the aid of nurse practitioners. J Nephrol. 2005 Jan;18(1):30-4.

13. Van Zuilen AD, Van der Tweel I, Blankestijn PJ, Bots ML, Van Buren M, Ten Dam MA, et al. Multifactorial approach and superior treatment efficacy in renal patients with the aid of nurse practitioners. Design of The MASTERPLAN Study [ISRCTN73187232]. Trials. 2006;7:8.

14. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004 May 1;43(5 Suppl 1):S1-290.

15. Mancia G, Sega R, Bravi C, De Vito G, Valagussa F, Cesana G, et al. Ambulatory blood pressure normality: results from the PAMELA study. J Hypertens. 1995 Dec;13(12 Pt 1):1377-90.

16. Wendel-Vos GCW, Schuit AJ, Saris WHM, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003 Dec;56(12):1163-9.

17. Levey AS, Greene T, Kusek JW, Beck GL, MDRD Study Group. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol. 2000 Sep 9;11:a0828.

18. Kenward MG, Carpenter J. Multiple imputation: current perspectives. Stat Methods Med Res. 2007 Jun;16(3):199-218.

19. Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology-A practical guide. Cambridge: Cambridge University Press; 2003.

20. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA. 2003 May 14;289(18):2363-9.

21. Becker GJ, Wheeler DC. Blood pressure control in CKD patients: why do we fail to implement the guidelines? Am J Kidney Dis. 2010 Mar;55(3):415-8.

22. Agyemang C, Ujcic-Voortman J, Uitenbroek D, Foets M, Droomers M. Prevalence and management of hypertension among Turkish, Moroccan and native Dutch ethnic groups in Amsterdam, the Netherlands: The Amsterdam Health Monitor Survey. J Hypertens. 2006 Nov;24(11):2169-76.

23. Agyemang C, van Hooijdonk C, Wendel-Vos W, Ujcic-Voortman JK, Lindeman E, Stronks K, et al. Ethnic differences in the effect of environmental stressors on blood pressure and hypertension in the Netherlands. BMC Public Health. 2007;7:118.

24. Krousel-Wood MA, Muntner P, Islam T, Morisky DE, Webber LS. Barriers to and Determinants of Medication Adherence in Hypertension Management: Perspective of the Cohort Study of Medication Adherence Among Older Adults. Med Clin North Am. 2009 May;93(3):753-69.

25. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008 May 17;336(7653):1114-7.

26. Ter Wee PM, Jorna AT. [Treatment of patients with chronic renal insufficiency; a guideline for internists]. Ned Tijdschr Geneeskd. 2004 Apr 10;148(15):719-24.