Title Page

Associations with baseline Blood Pressure Control in the NURTuRE-CKD

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Keywords:

hypertension, chronic kidney disease, albuminuria, anti-hypertensives, guideline

Introduction

Hypertension is commonly associated with chronic kidney disease (CKD) and is a key mediator of progressive kidney damage and the associated increase in cardiovascular mortality[1].The importance of blood pressure (BP) control as a therapeutic intervention in CKD, both for reduction in mortality and progression of kidney disease, is well established [2,3] but many patients do not achieve their BP targets[4]. The optimum BP target is debated, especially following the cardiovascular benefit shown by targeting a lower systolic BP of <120mmHg in the Systolic Blood Pressure Intervention Trial (SPRINT)[S1].

The National Unified Renal Translational Renal Enterprise (NURTuRE) CKD is a prospective cohort study of participants from secondary care nephrology centres in the UK which aims to study risk factors for adverse outcomes associated with CKD[5]. In this analysis we assessed BP control at baseline against targets recommended by three different guidelines[S2-S4] and investigated factors associated with BP control to identify subgroups who may benefit from additional clinical input.

Results

Study Population

2683/2996 participants with available baseline eGFR, UACR, BP readings and medication history were included in this analysis (see Supplementary Methods). Of these participants 59.3% were male, 86.6% were of white ethnicity, and 30.3% had diabetes. Mean±SD eGFR was 37±18 ml/min/1.73m^2 and median (IQR) uACR was 211 (33 to 938) mg/g. Median age (interquartile range) was 65 (53-73) years. For those with available data (2624/2683) median (IQR) time registered in secondary care nephrology was 4 (3-6) years.

Blood Pressure control

Mean baseline systolic BP for the cohort was 140±20 mmHg and diastolic 80±12 mmHg. Analysis of BP in clinically important subgroups is shown in Table S1. A higher mean systolic BP was observed with age over 65 years compared to those under 65 years, whilst mean diastolic BP was lower in those over 65 years. Mean systolic BP was also higher in males versus females, and in black ethnicity compared with white, Asian and other ethnicities. Lower eGFR categories, participants with diabetes and those in higher albuminuria categories or higher body mass index (BMI) category also had higher mean systolic BP. For those prescribed renin angiotensin system inhibitors, diastolic BP was significantly higher. Current smokers had a significantly higher diastolic BP compared with ex-smokers and non-smokers.

Figure S1. shows median (IQR) BP by Kidney Disease Improving Global Outcomes (KDIGO) heat map category. For those in the high risk (red) KDIGO categories mean systolic BP was 142±21 mmHg versus 134±18 mmHg in lower risk categories (green, yellow and amber); p <0.001. For the lowest risk category (green) mean systolic was 133±18 mmHg, for low risk (yellow) 134±18 mmHg and for medium risk (orange) 135±19 mmHg (Figure S4).

BP control by guideline target is shown in Table 1. For the 2014 National Institute for Health and Care Excellence (NICE) guideline 37.8% of participants achieved target BP. For KIDGO 2012 and 2021, 30.3% and 15.2% achieved BP control, respectively. The proportion of participants achieving target was lower in higher albuminuria categories. Target achievement by KDIGO category is shown in Figures S5 to S7 .

Antihypertensives

The median number of antihypertensive agents prescribed was 2 (IQR 1-3) with 2408 (89.8%) participants prescribed at least one anti-hypertensive or diuretic agent; 679 (25.3%) participants were prescribed a single agent, 699 (26.1%) two agents and 1030 (38.4%) prescribed 3 or more agents. Of those prescribed antihypertensives, 1830 participants

(68.2%) were prescribed either an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEi). In the highest albuminuria category 914 (77.4%) were prescribed an ACEi or ARB. For participants in the high risk (red) KDIGO categories (n=2058), 847 (41.2%) of participants were prescribed three or more agents, whilst 159 (18.8%) were prescribed none. The second most common class of antihypertensive was calcium channel blockers (n=1233, 46%) followed by beta-blockers (n=882, 32.9%). Thiazide diuretics were prescribed in 334 (12.4%) of those prescribed antihypertensives and alpha blockers in 23.0%. The distribution of antihypertensive combinations is illustrated in Figure S3.

Those aged 65 years and over were prescribed on average 2.3±1.4 antihypertensives compared with 2.0±1.4 in the younger age group (p<0.001 for difference). In the older age group, the mean BP for those prescribed three or more antihypertensives was 146±21 mmHg systolic and 75±12 mmHg diastolic.

Mean systolic BP was higher in those prescribed a greater number of antihypertensives (Figure S2.): 144±21 for those prescribed three or more antihypertensives vs 133±19 for those prescribed none (p=<0.001). Of those prescribed at least 3 agents, 109 participants (10.5%) achieved control by KDIGO 2021 target, 236 (23%) by KDIGO 2012 and 288 for NICE (28%).

Factors associated with blood pressure control

In univariable analysis (Table S2.) diabetes, BMI >30m/kg^2, taking three or more antihypertensives, lower eGFR and higher albuminuria category were all associated with a lower odds ratio of achieving BP target across all three guidelines. In the KDIG0 2012 and NICE guidelines, male sex and a history of atherosclerotic cardiovascular disease were also associated with a lower odds ratio of achieving target. For KDIGO 2021 and NICE, age ≥65 years was associated with lower odds ratio of BP control.

In multivariable analysis being aged 65 years or older, having a BMI >30m/kg^{2,} prescribed three or more antihypertensives and albuminuria category A3 were associated with lower odds ratio of achieving target across all three guidelines (Table 2.). A2 category albuminuria was significantly associated with lower odds ratio of control for KIDGO 2012 and NICE 2014. In contrast there were no significant associations with sex, ethnicity or educational status. A history of diabetes was only significantly associated with lower odds of BP control for the NICE 2014 where <130/80 mmHg was the target for those with diabetes. A history of cardiovascular disease and being in the lowest index of multiple deprivation was associated with increased odds of achieving the lower KDIGO 2021 target.

Discussion

This analysis demonstrates suboptimal BP control among people with CKD when compared to all three major guidelines with only a minority (15.2-37.8%) of participants within target. In multivariable analyses age ≥65 years, BMI >30 kg/m^2, taking three or more antihypertensives and higher albuminuria category were associated with poorer BP control across all guidelines. Proteinuria and higher age have previously been associated with poorer control, as has male sex which was not significant in our analysis[S5-S6].

We also observed that those in the highest risk categories demonstrated poorer control. The reasons for this are not clear but may include treatment resistant hypertension in CKD, medication non-adherence or fear of polypharmacy [-S12]. Given the higher risk of CKD progression and cardiovascular mortality in this group [1,6,7] addressing the disparity between target and achieved BP is paramount.

Strengths of this analysis include a large study population from across the UK with varying causes of CKD and a large proportion in high risk KDIGO categories. BP measurements were taken according to a standardised operating procedure, similar to the technique recommended in international guidelines and consensus documents [8,9]. Nevertheless, our findings should be considered in the context of some limitations. Importantly BP was only

measured at a single baseline visit. More robust observation would likely be obtained with repeated measurements, home BP measurements or 24 hour ambulatory measurements. Medication data was collected from electronic health records and self-reported by participants at baseline visits and no measure of medication concordance was recorded. However, the study design reflects the “real world” situation and has identified high risk subgroups that will inform focused interventions for improving BP control. Finally, the study was performed in secondary care with volunteers in the UK and may not be representative of other populations.

Given the importance of BP control as the fundamental intervention to improve outcomes in CKD, further research is warranted to understand the reasons for poor BP control and to develop strategies for improvement with initial focus on those with age ≥65 years, obesity or more severe albuminuria.

Disclosure

M.W.T. reports consulting fees from Boehringer Ingelheim, honoraria from Bayer and support to attend conferences from Bayer and a leadership role in the International Society of Nephrology; B.J.L. reports grant funding from the National Institute for Health Research; P.C. reports a leadership position in the UK Kidney Association; D.C.W. reports grant funding from Kidney Research UK, consultancy fees from Astellas, AstraZenca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Janssen, ProKidney and Tricida, honoraria from Amgen, Mundipharma, Merck Sharp and Dohme and Zydus; support for attending meetings from Astellas and AstraZeneca; participation in the data safety monitoring board for the following studies: ProKidney; Galderma; Eledon and a leadership role in the International Society of Nephrology; S.D.S.F. reports grant funding from Kidney Research UK; P.A.K. reports grant funding from Vifor and Astellas, consulting fees from Astra Zeneca, Vifor, Unicyte and UCB, hon- oraria from Vifor, Astra Zeneca and Pfizer, support for attending meetings from Pharmacosmos and Vifor. The other authors declare that they have no competing interests.

Acknowledgements

Bethany Lucas (Doctoral Fellowship NIHR302626) is funded by the National Institute for Health Research (NIHR) for this research project. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS or the UK Department of Health and Social Care.

Supplementary Material(PDF)

Supplementary methods

Supplementary Table S1. Blood Pressure by baseline demographics

Supplementary Figure S1. Blood pressure in the NURTuRE-CKD cohort according KDIGO CKD risk categories

Supplementary Figure S2. Mean systolic and diastolic BP by number of antihypertensives

Supplementary Figure S3. Pattern of use of anti-hypertensives at baseline in the NURTuRE-CKD cohort

Supplementary Table S2. Univariate associations with BP control by guideline

Supplementary Figure S4. Mean ± standard deviation BP at baseline by KDIGO CKD risk

Categories

Supplementary Figure S5. Proportion of participants meeting KDIG0 2021 BP guideline by KDIGO GFR category

Supplementary Figure S6. Proportion of participants meeting KDIGO 2012 BP target

Supplementary Figure S7. Proportion of participants meeting NICE BP target

Supplementary references

STROBE statement

Supplementary information is available at KI Report's website.

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	Diabetes, n=812 n (column%) unless otherwise stated			No Diabetes n=1871 n (column%) unless otherwise stated			Total n (%)
Albuminuria status	A1 n=140	A2 n=248	A3 n=424	A1 n=485	A2 n=629	A3 n=757	n=2683
Mean Systolic BP (mmHg)	134±18	140±21	149±21	134±19	137±20	141±20	140±20
Mean Diastolic BP (mmHg)	72±11	75±11	79±13	79±11	81±12	84±12	80±12
Albuminuria status	A1 n=140	A2 n=248	A3 n=424	ACR<70mg/mmol n=1323		ACR≥70mg/mmol n=548	n=2683
BP controlled (NICE 2014 target)[a]	55 (39.3)	63 (25.4)	58 (13.7)	748 (56.5)		89 (16.2)	1013 **(37.8)**
BP Controlled (KDIGO 2021 target)[b]	31 (22.1)	38 (15.2)	26 (6.1)	107 (22.0)	116 (18.4)	91 (12.0)	409 **(15.2)**
BP controlled (KDIGO 2012)[c]	89 (63)	63 (25.4)	58 (13.7)	300 (61.9)	164 (26.1)	138 (18.2)	812 **(30.3)**

Table 1. Mean blood pressure and proportion of participants in different categories achieving BP control according to different guideline targets in NURTuRE-CKD.

a NICE 2014 <140/90mmHg without diabetes, <130/80mmHg with diabetes or ACR ≥70mg/mmol

b KDIGO 2021 - <120mmHg systolic

c KDIGO 2012 <140/90mmHg, unless high risk ACR >30mg/g then <130/80mmHg

Table 2. Multivariable associations with BP control by guideline

		Multivariable Odds ratio of achieving KDIDO 2012 OR (95% CI)	*P*	Multivariable Odds ratio of achieving KDIGO 2021 OR (95% CI)	*P*	Multivariable Odds ratio of achieving NICE OR (95% CI)	*P*
Age years	≥65	0.61 (0.44,0.84)	0.002	0.46 (0.31,0.68)	< 0.001	0.60 (0.44,0.81)	< 0.001
	<65	Reference		Reference		Reference	
Sex	Male	0.95 (0.78,1.16	0.625	1.07 (0.84,1.35)	0.602	0.96 (0.79,1.15)	0.633
	Female	Reference		Reference		Reference	
Ethnicity	Non-white ethnicity	1.02 (0.76,1.38)	0.875	1.13 (0.79,1.60)	0.506	1.07 (0.81,1.42)	0.630
	White ethnicity	Reference		Reference		Reference	
Diabetes	Diabetes	1.18 (0.94, 1.48)	0.163	0.98 (0.74,1.30)	0.886	0.482 (0.39, 0.60)	< 0.001
	No diabetes	Reference		Reference		Reference	
BMI (m/kg²)	>30	0.63 (0.48,0.81)	< 0.001	0.52 (0.39, 0.70)	< 0.001	0.67 (0.52,0.85)	< 0.001
	25-30	0.65 (0.51,0.84)	< 0.001	0.62 (0.46,0.82)	< 0.001	0.72 (0.57,0.91)	0.006
	<25	Reference		Reference		Reference	
Smoking Status	Ever smoked	1.06 (0.87,1.29)	0.543	1.11 (0.88,1.40)	0.395	1.12 (0.94,1.35)	0.210
	Never smoked	Reference		Reference		Reference	
History of CVD disease	Yes	1.22 (0.931,1.59)	0.151	1.43 (1.03, 1.98)	0.031	1.214 (0.94, 1.57))	0.137
	No	Reference		Reference		Reference	
Employment	Working	Reference		Reference		Reference	
	Retired	1.16 (0.85,1.59)	0.355	1.14 (0.78,1.67)	0.504	1.00 (0.74,1.35)	0.998
	Unemployed	1.38 (0.73, 2.59)	0.318	1.40 (0.71, 2.75)	0.336	0.95 (0.51, 1.76)	0.860
	Student	2.57 (0.61,10.91)	0.200	1.81 (0.41, 7.91)	0.430	4.22 (0.80,22.13)	0.089
	Other	0.62 (0.43,0.90)	0.013	0.78 (0.52,1.18)	0.242	0.714 (0.510,1.000)	0.037
Education status	No qualifications	Reference		Reference		Reference	
	GCSE	1.08 (0.82,1.43)	0.590	0.94 (0.67,1.32)	0.703	1.11 (0.85,1.44)	0.450
	A Levels	0.96 (0.64,1.46)	0.860	1.035 (0.64,1.68)	0.890	1.07 (0.73,1.56)	0.741
	NVQ	0.98 (0.6.1.37)	0.905	1.01 (0.74,1.62)	0.638	0.96 (0.71,1.32)	0.815
	First degree	1.23 (0.89,1.68)	0.206	0.98 (0.66-1.43)	0.900	1.13 (0.84,1.52	0.408
	Higher degree	1.38 (0.97,1.96)	0.078	0.95 (0.61,1.49)	0.836	1.41 (1.01,1.97)_	0.044
	Other	0.94 (0.26, 3.42)	0.921	0.46 (0.06,3.67)	0.462	1.09 (0.33,3.57)	0.885
IMD Quintiles	1 (Most deprived)	0.84 (0.62,1.15)	0.283	0.56 (0.38, 0.82)	0.003	0.94 (0.70,1.26)	0.681
	2	0.98 (0.72,1.34)	0.920	0.74 (0.51, 1.06)	0.103	0.94 (0.70, 1.25)	0.668
	3	0.92 (0.68, 1.26)	0.612	1.024 (0.72,1.46)	0.894	0.94 (0.70,1.27)	0.697
	4	1.06 (0.78,1.4)	0.715	0.9 (0.63, 1.28)	0.560	1.08 (0.81, 1.44)	0.606
	5 (least deprived)	Reference		Reference		Reference	

Number of anti-hypertensives	None	Reference		Reference		Reference	
	One	0.90 (0.62,1.32)	0.600	0.93 (0.60, 1.43)	0.742	0.93 (0.65,1.33)	0.684
	Two	0.90 (0.61,1.34)	0.610	0.75 (0.47,1.18)	0.215	0.95 (0.66,1.38)	0.791
	Three or more	0.61 (0.41,0.93	0.020	0.55 (0.34,0.90)	0.017	0.66 (0.45,0.97)	0.032
RAASi	No	Reference		Reference		Reference	
	Yes	1.15 (0.90,1.48)	0.256	1.21 (0.89,1.64)	0.225	1.22 (0.97,1.54)	0.094
ACR mg/g	A1	Reference		Reference		Reference	
	A2	0.20 (0.16,0.25)	< 0.001	0.76 (0.58,1.01)	0.054	0.67 (0.54, 0.84)	< 0.001
	A3	0.11 (0.09,1.4)	< 0.001	0.34 (0.25, 0.46)	< 0.001	0.19 (0.15, 0.24)	< 0.001
eGFR ml/min/1.73m²	Per 1ml/min/1.73m²	1.00 (0.99,1.00)	0.225	1.00 (0.99,1.01)	0.991	1.00 (0.99,1.00)	0.120

BMI- body mass index, CVD – cardiovascular disease, eGFR – estimated glomerular filtration rate, GCSE – general certificate of secondary education, IMD- index of multiple deprivation, NVQ- national vocational qualification, RAASi - renin angiotensin system inhibition, UACR – urinary albumin creatinine ratio