Original Paper

Relationship Between Visit-to-Visit Blood Pressure Variability (BPV) and Kidney Function in Patients with Hypertension

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Key Words

Blood pressure variability (BPV) • Hypertension • Estimated glomerular filtration rate (eGFR) • Amlodipine • Post hoc analysis

Abstract

Background/Aims: To investigate the impact of kidney function (using estimated glomerular filtration rate, [eGFR]) on blood pressure variability (BPV) via a retrospective *post hoc* analysis of patients with hypertension enrolled in two large clinical trials. **Methods:** Subject-level data were extracted from ASCOT (N=18,852) and ALLHAT (N=26,441) databases; both were randomized, active controlled studies, with treatment duration for hypertension ≥ 4 years. Visit-to-visit BPV was assessed using the square root of the coefficient of variation of systolic blood pressure (SBP) across visits from 12 weeks onwards. Baseline GFR, estimated by the simplified Modification of Diet in Renal Disease equation, was stratified into ≤ 60 , 61-90, and > 90 mL/min/1.73 m². The relationship between baseline eGFR and systolic BPV was analyzed using an analysis of covariance, with baseline factors considered as covariates. Studies were pooled and analyzed individually. **Results:** Patient characteristics were largely consistent between studies. In the pooled population (n=38,133) there were 19.1%, 62.9%, and 18.0% patients, with eGFR ≤ 60 , 61-90, and > 90 mL/min/1.73 m², respectively. Patients with lower baseline eGFR had higher systolic BPV, in the pooled population and the individual analyses. Other baseline predictors of high systolic BPV included high SBP and age, being male, and a smoker. An amlodipine-based regimen was a negative predictor of high systolic BPV, vs. other antihypertensives, regardless of eGFR. **Conclusions:** Patients with declining renal function tended to have higher systolic BPV vs. those without, even after adjusting for risk factors. Amlodipine-based therapy reduced BPV more than other antihypertensive agents, regardless of level of eGFR.

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Introduction

Declining renal function and chronic kidney disease (CKD) are important public health concerns, as they are associated with high healthcare costs and poor therapeutic outcomes [1, 2]. Hypertension is an important risk marker for decline in renal function, as high blood pressure (BP) is linked to both initiation and progression of CKD, alongside other risk factors such as diabetes, hyperlipidemia, obesity, and smoking [1, 3, 4]. However, the underlying mechanism by which hypertension influences renal function, and vice versa, is not fully understood. Clinical trial data have demonstrated that antihypertensive therapy can slow renal decline, with different types of antihypertensive reported to have different abilities to stabilize renal function in patients with and without coexisting diabetes [5-8]. Some evidence suggests that a lower BP goal does not provide additional benefit to slow progression of hypertensive nephrosclerosis [8], suggesting that management of BP alone is not sufficient to reduce the impact hypertension has on renal function.

Evidence suggests blood pressure variability (BPV), independently of mean BP or medication adherence, is an important risk factor for cardiovascular disease (CVD) [9-13]. In patients with hypertension, the amplitude of BPV is greater than that seen in patients with normal BP, and the increased amplitude of BPV progressively increases with increasing BP [14]. As such, high BPV is associated with a higher risk of cardiovascular outcomes in different patient populations [15-19]. Evidence also suggests that in patients with different degrees of renal impairment, fluctuations in BP may contribute towards the progression and severity of vascular and renal damage [20], independently of elevated mean BP [21-25]. For example, in non-diabetic patients with Stage 3-4 CKD, visit-to-visit systolic BPV over at least 12 consecutive visits was an independent determinant of renal function deterioration estimated using glomerular filtration rate (eGFR) [24]. In diabetic individuals with nephropathy, visit-to-visit systolic BPV was associated independently with kidney disease outcomes, such as increased overall mortality and cardiovascular mortality [25]. However, in a study of diabetic patients with Stage 3-4 CKD, no association between BPV and renal decline was seen [26]. Furthermore, in a population of elderly CKD patients without CVD, an association between BPV and risk for mortality was found, but no link between BPV and CKD progression to dialysis was seen [27]. Therefore, the relationship between BPV and renal decline cannot be inferred from different patient populations, and should be explored for those with different basal levels of renal function and cardiovascular risk status, including with only mild renal impairment. Given the need to fully understand the relationship between renal function and BP, the objective of this analysis was to evaluate the relationship between kidney function (using eGFR) and BPV, in patients with hypertension and additional cardiovascular risk factors. Whether or not renal function influences how antihypertensives affect BPV, will also be investigated.

Materials and Methods

Study populations

This retrospective, *post hoc* analysis of clinical trial data identified studies with individual subject-level data, at least one active antihypertensive therapy comparator arm, and a study duration of at least 4 years. Two studies, the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) [28] and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [29], fulfilled these selection criteria and were used to evaluate the relationship between renal function (based on eGFR) and BPV. Studies were analyzed separately and data were pooled.

ASCOT was a multicenter, prospective, randomized controlled trial of 19,257 subjects aged 40-79 years with hypertension (SBP $\geq$ 140 and/or DBP $\geq$ 100 mmHg) and at least three additional risk factors for CVD [28]. Eligible subjects were randomized to an amlodipine-based regimen (amlodipine 5-10 mg, adding perindopril 4-8 mg as required) or an atenolol-based antihypertensive regimen (atenolol 50-100 mg, adding bendroflumethiazide 1.25-2.5 mg and potassium as required). Median follow-up was 5.5 years.

BP was measured three times (after 5 minutes of rest) at each visit using a semi-automated device, and the mean of the last two readings was used. Follow-up visits took place at 6 weeks, 3 months, 6 months, and then every 6 months thereafter. At each visit BP was monitored and treatment titrated to achieve BP target (< 140/90 mmHg [$< 130/80$ mmHg for patients with diabetes]) [28].

ALLHAT was a randomized, double-blind, active-controlled clinical trial enrolling 33,357 subjects aged 55 years or older with hypertension (e.g., untreated patients: SBP of > 140 but ≤ 180 mmHg, and/or DBP > 90 but ≤ 110 mmHg; on-treatment SBP ≤ 160 mmHg and DBP ≤ 100 mmHg), and with at least one additional risk factor for coronary heart disease [29]. Patients were randomly assigned to chlorthalidone (12.5-25 mg/day), amlodipine (2.5-10 mg/day), or lisinopril (10-40 mg/day). Mean follow-up was 4.9 years. Follow-up appointments took place after 1, 3, 6, 9, and 12 months; and every 4 months thereafter. Trained observers used standardized techniques to measure BP, calculated as the average of two measurements. BP was monitored throughout follow-up, with antihypertensive therapy titrated at each visit to achieve BP goal (< 140/90 mmHg) [29, 30].

For both studies, where SBP measurements from sitting or standing positions were available, measurements from the sitting position were used in preference. The simplified Modification of Diet in Renal Disease (MDRD) equation was used to estimate GFR (in ml/min per 1.73 m^2) [31] using creatinine analyzed from blood samples drawn from patients at baseline [28, 32], where $\text{GFR (ml/min/1.73m}^2\text{)} = 186 \times (\text{creatinine}/88.4)^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times 1.21 \text{ if black}$.

Data analysis

To study the relationship between eGFR and systolic BPV, the following scenarios are evaluated: firstly, BPV was used as a dependent variable and baseline eGFR as a covariate; secondly, post-baseline change in eGFR is used as a dependent variable and BPV as a covariate. BPV was defined as the within-subject coefficient of variation (CoV) of SBP measurements across visits from 12 weeks (or 3 months [84 days]) onwards to the end of follow-up, and this formed the BPV evaluable population.

For the first analysis, an ANCOVA analysis was carried out using the square root of coefficient of variation for SBP from 3 months (CV3 of SBP) as the outcome, and study, treatment, baseline eGFR, age, baseline SBP, baseline glucose, gender, treatment, and smoking history as covariates. Patients were categorized by baseline eGFR: ≤ 60 , 61-90, and $> 90 \text{ mL/min/1.73 m}^2$.

For the second analysis, a repeated measured analysis was used for ASCOT only, including age, baseline eGFR, categorized BPV (CV3 of SBP), baseline glucose, gender, treatment, smoking history, visit, and antihypertensive treatment by visit interaction as independent variables, and post-baseline change in eGFR at years 2, 4, 5, 6, and 10 as dependent variables. The category of BPV (CV3 of SBP) was defined using 25th, 50th, and 75th percentiles as the cut-offs.

A pooled analysis was also conducted, with post baseline change in eGFR at years 2 and 3 as the dependent variables for patients taking amlodipine-based therapy compared with any other antihypertensive regimen, using patients from both ASCOT and ALLHAT. Data were also summarized for each decile of BPV (CV3 of SBP) using descriptive statistics, including mean, standard deviation, median, and 95% CIs of eGFR, for ASCOT, ALLHAT, and the pooled data set.

The 95% CI were estimated using one sample Z-test, $\bar{X} \pm Z_{1-\alpha/2} \frac{SD}{\sqrt{N}}$. Data were analyzed using SAS (version 9.3 or above).

Results

Patient populations

Overall, 18,852 patients were analyzed from ASCOT and 26,441 from ALLHAT, giving an overall population of 45,293 (16,647 patients on an amlodipine-based regimen; 28,646 on an alternative antihypertensive regimen). Patient characteristics were largely consistent between ASCOT and ALLHAT (Table 1), although the majority of subjects in ASCOT were male (76.6% vs. 54.7% of ALLHAT), and patients from ASCOT were younger than patients in ALLHAT (mean age 62.9 years vs. 66.7 years). Mean baseline SBP was 164.0 mmHg in ASCOT patients and 145.9 mmHg for ALLHAT patients. Systolic BPV (CV3 of SBP) was 9.0 for all patients in ASCOT and 8.2 for patients in ALLHAT. For each study analyzed

Table 1. Baseline characteristics and demographics for ASCOT and ALLHAT populations

	ASCOT (N = 18,852)		ALLHAT (N = 26,441)		Pooled (N = 45,293)	
	Amlodipine (n = 9,453)	Atenolol (n = 9,399)	Amlodipine (n = 7,194)	Chlorthalidone (n = 12,210)	Lisinopril (n = 7,037)	
Male, n (%)	7,233 (76.5%)	7,201 (76.6%)	3,899 (54.2%)	6,637 (54.4%)	3,924 (55.8%)	28,894 (63.8%)
Age, mean (±SD) years	62.9 (±8.47)	62.9 (±8.48)	66.7 (±7.49)	66.7 (±7.47)	66.7 (±7.53)	65.1 (±8.14)
Smoker, n (%)	3,099 (32.8%)	3,026 (32.2%)	1,558 (21.7%)	2,601 (21.3%)	1,499 (21.3%)	11,783 (26.0%)
Baseline SBP, mean (±SD), mmHg	164.0 (±18.0)	163.9 (±17.9)	146.0 (±15.7)	145.9 (±15.6)	146.0 (±15.5)	153.4 (±18.9)
[min, max]	[108.0, 251.5]	[110.0, 276.0]	[80.0, 180.0]	[94.0, 184.0]	[90.0, 180.0]	[80.0, 276.0]
BPV (CV3 of SBP), mean (±SD)	8.1 (±3.18)	9.8 (±3.76)	7.9 (±4.43)	8.0 (±4.53)	8.9 (±4.98)	8.5 (±4.25)
[min, max]	[0.0, 33.1]	[0.0, 48.4]	[0.0, 43.0]	[0.0, 50.8]	[0.0, 43.5]	[0.0, 50.8]
Baseline eGFR, mL/min/1.73 m ²	n = 6,419	n = 6,411	n = 6,891	n = 11,704	n = 6,708	n = 38,133
< 60	1,469 (22.9%)	1,455 (22.7%)	1,172 (17.0%)	2,051 (17.5%)	1,133 (16.9%)	7,280 (19.1%)
60- < 90	4,677 (72.9%)	4,667 (72.8%)	3,945 (57.2%)	6,808 (58.2%)	3,880 (57.8%)	23,977 (62.9%)
> 90	273 (4.3%)	289 (4.5%)	1,774 (25.7%)	2,845 (24.3%)	1,695 (25.3%)	6,876 (18.0%)
Glucose, n = 8,573	n = 8,500	n = 8,500	n = 5,333	n = 9,068	n = 5,281	n = 36,755
Mean (±SD), mg/dL	112.1 (±37.6)	112.1 (±37.6)	122.0 (±55.2)	122.4 (±56.6)	122.0 (±53.7)	117.5 (±48.2)
[min, max]	[1.8, 412.2]	[9.0, 430.2]	[38.0, 543.0]	[26.0, 648.0]	[33.0, 521.0]	[1.8, 648.0]

Data are shown as mean ± SD or n (%) unless otherwise specified. BPV, blood pressure variability; SD, standard deviation; SBP, systolic blood pressure. BPV was calculated as square root of the within-subject coefficient of variation for SBP from 3 months across visits from 12 weeks (or 3 months [84 days]) onwards (CV3 of SBP).

Table 2. Relationship between blood pressure variability (BPV), kidney function, and baseline risk factors and characteristics in the ASCOT population

Effect	Estimate	SD	t-value	P-value	Lower	Upper
(A) ASCOT						
Amlodipine vs. atenolol	-0.2732	0.0083	-32.80	< 0.0001	-0.2895	-0.2569
Baseline eGFR (mL/min/1.73 m ²)						
< 60-90 vs. ≤ 60	-0.1089	0.0124	-8.78	< 0.0001	-0.1332	-0.0846
> 90 vs. ≤ 60	-0.1296	0.0270	-4.81	< 0.0001	-0.1825	-0.0768
90 vs. > 60-90	-0.0207	0.0254	-0.81	0.4155	-0.0706	0.0291
Age	0.1213	0.0050	24.39	< 0.0001	0.1116	0.1311
SBP	0.0691	0.0023	29.67	< 0.0001	0.0645	0.0736
Glucose	0.8099	0.1196	6.77	< 0.0001	0.5754	1.0444
Male (vs. female)	0.1596	0.0100	15.89	< 0.0001	0.1399	0.1793
Smoker (vs. non-smoker)	-0.0252	0.0091	-2.76	0.0058	-0.0431	-0.0073

ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; eGFR, estimated glomerular filtration rate (at baseline); SBP, systolic blood pressure. BPV was calculated as square root of the within-subject coefficient of variation for SBP from 3 months across visits from 12 weeks (or 3 months [84 days]) onwards (CV3 of SBP). The units for continuous covariates in the analysis model are: 10 years for age, 10 mmHg for SBP, and 1,000 mg/dL for glucose.

separately, and when the data were pooled, systolic BPV was lower for patients treated with amlodipine compared with other treatments (pooled data amlodipine-based 8.0 vs. other antihypertensive 8.8).

eGFR data were available from 38,133 participants overall (12,830 from ASCOT; 25,303 ALLHAT), with 19.1%, 62.9%, and 18.0% of patients from the overall population classified with baseline eGFR ≤ 60, 61-90, and > 90 mL/min/1.73 m², respectively. The majority of patients from either study were classified with eGFR between 61-90 mL/min/1.73 m² (Stage 2 CKD according to Kidney Disease Outcomes Quality Initiative classification) [1].

Predictors of renal decline, by study and by treatment

Lower baseline eGFR (< 60-90 vs. ≤ 60 or > 90 vs. ≤ 60 mL/min/1.73 m²) was a predictor of high systolic BPV, in ASCOT, ALLHAT when analyzed separately, and in the pooled population (Table 2). Other baseline predictors of higher systolic BPV included higher SBP and age and being male, in both studies analyzed separately and in the pooled population (Table 2). Being on an amlodipine-based regimen was a negative predictor of systolic BPV vs. other antihypertensive treatment in the overall analysis (Table 2). For the ALLHAT population, amlodipine or chlorthalidone treatment was a negative predictor of high systolic BPV when compared with lisinopril. There was no significant difference found between amlodipine and chlorthalidone treatment arms (Table 3).

Table 3. Relationship between blood pressure variability (BPV), kidney function, and baseline risk factors and characteristics in the ALLHAT population

Effect	Estimate	SD	t-value	P-value	Lower	Upper
Amlodipine vs. lisinopril	-0.1743	0.0138	-12.63	< 0.0001	-0.2014	-0.1473
Chlorthalidone vs. lisinopril	-0.1533	0.0123	-12.44	< 0.0001	-0.1774	-0.1291
Amlodipine vs. chlorthalidone	-0.0211	0.0122	-1.72	0.0854	-0.0450	0.0029
Baseline eGFR (mL/min/1.73 m ²)						
< 60-90 vs. ≤ 60	-0.1054	0.0142	-7.42	< 0.0001	-0.1333	-0.0776
> 90 vs. ≤ 60	-0.1111	0.0162	-6.85	< 0.0001	-0.1429	-0.0793
90 vs. > 60-90	-0.0057	0.0124	-0.46	0.6476	-0.0300	0.0186
Age	0.0618	0.0068	9.12	< 0.0001	0.0485	0.0750
SBP	0.0262	0.0033	8.05	< 0.0001	0.0198	0.0326
Glucose	0.0828	0.1042	0.80	0.4268	-0.1210	0.2870
Male (vs. female)	0.0220	0.0102	2.16	0.0311	0.0020	0.0420
Smoker (vs. non-smoker)	0.0110	0.0124	0.88	0.3769	-0.0133	0.0352

ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; eGFR, estimated glomerular filtration rate (at baseline); SBP, systolic blood pressure. BPV was calculated as square root of the within-subject coefficient of variation for SBP from 3 months across visits from 12 weeks (or 3 months [84 days]) onwards (CV3 of SBP). The units for continuous covariates in the analysis model are: 10 years for age, 10 mmHg for SBP, and 1,000 mg/dL for glucose.

Table 4. Relationship between blood pressure variability (BPV), kidney function, and baseline risk factors and characteristics in the Pooled population

Effect	Estimate	SD	t-value	P-value	Lower	Upper
ALLHAT vs. ASCOT	-0.1949	0.0070	-27.76	< 0.0001	-0.209	-0.1812
Amlodipine vs. other antihypertensive	-0.1139	0.0072	-15.78	< 0.0001	-0.128	-0.0998
Baseline eGFR (mL/min/1.73 m ²)						
< 60-90 vs. ≤ 60	-0.1092	0.0101	-10.78	< 0.0001	-0.1290	-0.0893
> 90 vs. ≤ 60	-0.1764	0.0127	-13.86	< 0.0001	-0.2013	-0.1510
90 vs. > 60-90	-0.0672	0.0104	-6.49	< 0.0001	-0.0875	-0.0469
Age	0.0579	0.0043	13.53	< 0.0001	0.0495	0.0663
SBP	0.0606	0.0018	33.14	< 0.0001	0.0570	0.0642
Glucose	0.0733	0.0780	0.94	0.3480	-0.0798	0.2264
Male (vs. female)	0.0205	0.0073	2.83	0.0047	0.0063	0.0348
Smoker (vs. non-smoker)	-0.0337	0.0080	-4.23	< 0.0001	-0.0493	-0.0181

ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm; eGFR, estimated glomerular filtration rate (at baseline); SBP, systolic blood pressure. BPV was calculated as square root of the within-subject coefficient of variation for SBP from 3 months across visits from 12 weeks (or 3 months [84 days]) onwards (CV3 of SBP). The units for continuous covariates in the analysis model are: 10 years for age, 10 mmHg for SBP, and 1,000 mg/dL for glucose.

Effect of antihypertensive treatment on BPV and renal function

Regardless of level of renal function, systolic BPV was consistently lower in patients on an amlodipine-based regimen compared with an atenolol-based regimen in ASCOT (Table 4). More specifically, systolic BPV was 0.3-units lower with amlodipine compared with atenolol for those with the highest degree of renal insufficiency (eGFR ≤ 60 mL/min/1.73 m²) (2.9 vs. 3.2 respectively; Table 4). Similar observations were noted for ALLHAT patients with the highest degree of renal insufficiency (Table 5), although the differences with amlodipine vs. chlorthalidone were less than amlodipine vs. lisinopril (Table 6).

In the pooled population, in line with the individual study analyses, systolic BPV was consistently lower for patients on amlodipine-based regimen compared with other antihypertensives, regardless of level of renal function (Table 6). The difference with amlodipine-based therapy was largest for patients with the highest degree of renal insufficiency. More specifically, being on an amlodipine-based regimen reduced systolic BPV by +0.2 units in those with baseline eGFR ≤ 60 mL/min/1.73 m² when compared with any other antihypertensive regimen (Table 7). Overall, patients with the highest degree of renal insufficiency at baseline (eGFR ≤ 60 mL/min/1.73 m²) had marginally higher systolic BPV

Table 5. Relationship between blood pressure variability (BPV) and baseline eGFR categories in patients by treatment arm (amlodipine-treated patients compared with other antihypertensive treatments) in the ASCOT population

Baseline eGFR	Amlodipine (n = 6,419)	Atenolol (n = 6,411)	Total (N = 12,830)
≤ 60 mL/min/1.73 m ²			
n	1,469	1,455	2,924 (22.8%†)
Mean (SD)	2.9 (0.57)	3.2 (0.60)	3.0 (0.61)
Median	2.9	3.1	3.0
Min, max	0.5, 5.8	0.4, 7.0	0.4, 7.0
P25, P75	2.5, 3.3	2.8, 3.5	2.6, 3.4
> 60-90 mL/min/1.73 m ²			
N	4,677	4,667	9,344 (72.8%†)
Mean (SD)	2.8 (0.54)	3.0 (0.59)	2.9 (0.58)
Median	2.7	3.0	2.9
Min, max	0.0, 5.7	0.0, 6.2	0.0, 6.2
P25, P75	2.4, 3.1	2.6, 3.4	2.5, 3.3
> 90 mL/min/1.73 m ²			
n	273	289	562 (4.4%†)
Mean (SD)	2.8 (0.51)	3.0 (0.59)	2.9 (0.56)
Median	2.8	3.0	2.9
Min, max	1.7, 4.6	1.0, 5.1	1.0, 5.1
P25, P75	2.4, 3.1	2.6, 3.3	2.5, 3.2

†Proportion of total population. P25, 25th percentile; P75, 75th percentile

Table 6. Relationship between blood pressure variability (BPV) and baseline eGFR categories in all patients by treatment arm (amlodipine-treated patients compared with other antihypertensive treatments) in the ALL-HAT population

Baseline eGFR	Amlodipine (n = 6,891)	Chlorthalidone (n = 11,704)	Lisinopril (n = 6,708)	Total (N = 25,303)
≤ 60 mL/min/1.73 m ²				
n	1,172	2,015	1,133	4,356 (17.2%†)
Mean (SD)	2.7 (0.85)	2.8 (0.86)	3.0 (0.91)	2.8 (0.87)
Median	2.7	2.8	3.0	2.8
Min, Max	0.0, 6.6	0.0, 6.1	0.0, 6.4	0.0, 6.6
P25, P75	2.2, 3.3	2.2, 3.3	2.4, 3.5	2.3, 3.4
> 60-90 mL/min/1.73 m ²				
n	3,945	6,808	3,880	14,633 (57.8%†)
Mean (SD)	2.7 (0.79)	2.7 (0.80)	2.8 (0.84)	2.7 (0.81)
Median	2.7	2.7	2.8	2.7
Min, max	0.0, 5.9	0.0, 7.1	0.0, 6.6	0.0, 7.1
P25, P75	2.2, 3.2	2.2, 3.2	2.3, 3.4	2.2, 3.2
> 90 mL/min/1.73 m ²				
N	1,774	2,845	1,695	6,314 (25.0%†)
Mean (SD)	2.6 (0.78)	2.7 (0.81)	2.8 (0.84)	2.7 (0.81)
Median	2.6	2.7	2.9	2.7
Min, max	0.0, 5.9	0.0, 6.3	0.0, 5.5	0.0, 6.3
P25, P75	2.2, 3.1	2.2, 3.2	2.3, 3.4	2.2, 3.2

†Proportion of total population. P25, 25th percentile; P75, 75th percentile

compared to those with the lowest degree of renal insufficiency (eGFR > 90 mL/min/1.73 m²) (Table 7). When analyzed by decile of BPV, a clear trend was seen whereby patients in the pooled population with lower baseline eGFR had higher systolic BPV at follow-up (Figure 1).

Discussion

In patients with hypertension managed on different antihypertensive regimens, our study of two large cardiovascular studies demonstrates that baseline eGFR is a predictor of high systolic BPV. We also report that being on an amlodipine-based treatment regimen was consistently shown to lower systolic BPV, regardless of level of renal function. These observations indicated that the impact of BPV on renal function should be carefully considered, even in patients with managed hypertension and/or only mild renal impairment. Although our study does not link systolic BPV directly to renal outcomes, our study adds to existing evidence demonstrating that hypertensive patients may benefit from the selection of antihypertensive agents that can manage BPV over the long term [9, 12, 18, 33].

Table 7. Relationship between blood pressure variability (BPV) and baseline eGFR categories in all patients by treatment arm (amlodipine-treated patients compared with other antihypertensive treatments) in the pooled population

Baseline eGFR	Amlodipine (n = 13,310)	Other (n = 24,823)	Total (N = 38,133)
≤ 60 mL/min/1.73 m ²			
n (%)	n = 2,641 (36.3%)	n = 4,639 (63.7%)	n = 7,280 (19.1%†)
Mean (SD)	2.8 (0.71)	3.0 (0.81)	2.9 (0.78)
Median	2.8	3.0	2.9
Min, max	0.0, 6.6	0.0, 7.0	0.0, 7.0
P25, P75	2.4, 3.3	2.5, 3.5	2.4, 3.4
> 60-90 mL/min/1.73 m ²			
n (%)	8,622 (36.0%)	15,355 (55.7%)	23,977 (62.9%†)
Mean (SD)	2.7 (0.67)	2.8 (0.77)	2.8 (0.74)
Median	2.7	2.8	2.8
Min, max	0.0	0.0, 7.1	0.0, 7.1
P25, P75	2.3	2.4, 3.3	2.3, 3.3
> 90 mL/min/1.73 m ²			
n (%)	2,047 (29.8%)	4,829 (70.2%)	6,876 (18.0%†)
Mean (SD)	2.7 (0.75)	2.8 (0.81)	2.7 (0.80)
Median	2.7	2.8	2.7
Min, max	0.0, 5.9	0.0, 6.3	0.0, 6.3
P25, P75	2.2, 3.1	2.2, 3.3	2.2, 3.2

†Proportion of total population. P25, 25th percentile; P75, 75th percentile

Fig. 1. Baseline eGFR by BPV decile (D) for the overall population (pooled from ASCOT and ALLHAT). ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; eGFR, estimated glomerular filtration rate (at baseline); SBP, systolic blood pressure; SD, standard deviation.

BPV was calculated as square root of the within-subject coefficient of variation for SBP from 3 months across visits from 12 weeks (or 3 months [84 days]) onwards (CV3 of SBP).

Previous studies have demonstrated that management of BP is critical for lowering the risk for renal decline, as hypertension is a major risk factor for CKD [4]. Evidence to support the potential importance of BPV in long-term cardiovascular risk is growing, including in certain patient populations with renal dysfunction [21-27, 34, 35]. For example high BPV has been associated with macro- and microvascular outcomes and organ damage [24, 25, 36]. However, not all evidence demonstrates a clear link between high BPV and change in renal function or cardiovascular outcomes, particularly for high risk patients such as those with comorbid diabetes and nephropathy, or with more severe renal decline [25-27]. Therefore, further evidence was needed to corroborate findings from studies in patients with hypertension across a range of renal functions.

We demonstrate that patients with lower baseline eGFR had higher systolic BPV, when data were analyzed individually by study and in the pooled population of more than 38, 000 patients. Additional predictors of higher systolic BPV over the ≥ 4-year follow-up period included higher baseline SBP and age and being male or a smoker. These predictors are all well-known risk factors for CVD and in line with other studies of renal decline and BPV [11, 24, 26, 37]. In a *post hoc* analysis of ALLHAT data alone, higher BPV was associated with

a higher risk of renal outcomes, independently from mean BP [33]. This study specifically linked visit-to-visit BPV with renal outcomes, after 3.5-years follow-up demonstrating that higher BPV quintile was associated with cardiovascular outcomes, including ESRD and 50% decline in eGFR. These observations from Whittle et al., [33] therefore support our study pooling ALLHAT data with ASCOT, by suggesting a link between BPV and change in renal function. Our observations therefore support the importance of baseline eGFR as a predictor of high systolic BPV, in population of patients with hypertension and additional risk factors. Whether baseline eGFR could be used by physicians to identify patients at risk for high systolic BPV would need further study.

In this *post hoc* analysis, we were able to investigate the effect of different classes of antihypertensive on BPV, in patients with different levels of baseline renal function, by analyzing the calcium-channel blocker (CCB)-based amlodipine regimen compared with that based on a beta-blocker, atenolol in ASCOT, or diuretic, chlorthalidone, or angiotensin-converting enzyme inhibitor, enalapril, in ALLHAT. Being on amlodipine-based therapy was a negative predictor of high systolic BPV in the pooled population and in the individual studies. This is in agreement with previous studies that suggest CCBs, and in particular amlodipine, are superior to other antihypertensive agents at lowering BPV [33, 38-40]. Although the treatment arms in ASCOT and ALLHAT were not based on monotherapy and the influence of concomitant therapies need to be considered, we also demonstrate that amlodipine-based therapy was numerically superior to other antihypertensive treatments at controlling systolic BPV across different levels of renal function, when analyzed individually by drug or vs. all treatments combined. These observations indicate that the efficacy of amlodipine for lowering BPV is not influenced by patients' renal function. Management of hypertension with certain classes of antihypertensive has been found to slow renal decline, lowering the healthcare and patient burden that is incurred as renal dysfunction progresses [1, 2]. BPV may therefore be an important variable for physicians to monitor and manage in these patients. Further study would be needed to investigate the link between systolic BPV, eGFR and renal outcomes in these patients with hypertension and mild-moderate renal decline.

Our *post hoc* analysis of these two large-scale clinical trials should be considered in light of certain limitations. For example, ASCOT and ALLHAT were designed to assess the impact of antihypertensive treatments on average BP, not on renal function or BPV. Although the study sample was large and follow-up over 4 years allowed long-term systolic BPV to be analyzed, the proportion of patients within the lowest eGFR category was < 20% of the pooled population. Furthermore, patients with severe renal impairment were excluded from ALLHAT, and therefore our observations cannot be generalized to the higher stages of baseline eGFR or CKD. Although the bulk of CKD is thought to arise from individuals with Stage 1 hypertension, and even high-normal BP is important in its association with CKD [3], specifically designed studies would be needed to corroborate our observations in patients with higher levels of renal insufficiency. We used eGFR to assess level of renal function; however international consensus now favors using eGFR in association with other measures of renal function, such as actual serum creatinine, albuminuria, or proteinuria [1]. In addition, we could not correlate change in eGFR with BPV. However, a study over 15-years follow-up recently demonstrated that BPV of SBP for each individual was significantly associated with slope of change in eGFR rate, following adjustment for mean SBP and other confounders [31].

Although we were able to study amlodipine-based therapy compared with other antihypertensive agents, patients in ASCOT and ALLHAT could be prescribed concomitant antihypertensive agents, in addition to their primary antihypertensive (amlodipine- or atenolol in ASCOT, amlodipine, lisinopril, or chlorthalidone in ALLHAT) [28, 29]. Therefore, the influence of concomitant medications on BPV needs to be considered. For example, different antihypertensive drug classes have been found to differentially influence BPV, with CCBs showing the lowest variability in BP over the long term [18, 39]. We also cannot account for unmeasured confounders that may have influenced the association between long-term BPV and baseline eGFR. Finally, we should note that clinical practice and clinical guidelines

for BP control have changed significantly in the years since these trials were designed and conducted. Despite these limitations, our *post hoc* analysis of more than 38,000 patients followed up for more than 4 years demonstrates the efficacy of amlodipine for lowering BPV across patients with hypertension and different levels of mild-moderate renal decline. Systolic BPV may therefore be an important variable for physicians to monitor and manage in these high-risk patients.

Conclusion

Patients with mild-moderate hypertension and mild renal dysfunction tended to have higher systolic BPV, even after adjusting for known risk factors or potential risk factors for BPV. Patients treated with amlodipine-based regimen also had lower systolic BPV, across all patients with hypertension and different levels of renal impairment included in this *post hoc* analysis. When treating patients with hypertension, with or without renal impairment, strategies for managing BP should be carefully considered in light of their effect on BPV and the link between BPV and early renal decline.

Disclosure Statement

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