ORIGINAL RESEARCH

# Relationship of Inter-Individual Blood Pressure Variability and the Risk for Recurrent Stroke

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***Background*—**Evidence suggests that patients with higher blood pressure variability (BPV) have a higher risk for stroke, but any link between BPV and stroke recurrence is unknown among those who had a stroke or transient ischemic attack (TIA).

***Methods and Results*—**Data for patients with a history of stroke or TIA at enrollment were extracted from the ASCOT (Anglo Scandinavian Cardiac Outcomes Trial) and the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). BPV was defined as the within-subject standard deviation or coefficient of variation of systolic blood pressure across visits from 12 weeks poststroke or TIA onward. BPV was significantly higher in patients with a history of stroke or TIA than those without. BPV was a predictor of recurrent stroke in the pooled analysis. In the ASCOT study, 252 patients (12.3%) had a recurrent stroke among 2046 with a history of stroke. Incidence of recurrent stroke was significantly higher in the highest BPV quartile (17.8%) compared with the lowest quartile (10.5%); by treatment arm, this reached significance for the amlodipine-arm only (high-BPV: 18.7% versus low-BPV: 12.9%; $P$=0.029). Of the 2173 patients from the ALLHAT with a history of stroke or TIA, patients with the highest quartile of BPV had a higher incidence of recurrent stroke (9.6%) compared with the lowest quartile BPV (5.5%); by treatment arm, this reached significance for the chlorthalidone-arm only (high-BPV: 12.1% versus low-BPV: 5.4%; $P$=0.007).

***Conclusions*—**Visit-to-visit BPV is a predictor of recurrent stroke in patients with a history of stroke or TIA on antihypertensive treatment. Considering BPV following a stroke may be important to reduce the risk for a recurrent stroke. **(*J Am Heart Assoc*. 2018;7:e009480. DOI: 10.1161/JAHA.118.009480.)**

**Key Words:** blood pressure • calcium channel blocker • secondary prevention • stroke • blood pressure variability

Fluctuations in blood pressure (BP) are attributed physiologically to complex interactions of the autonomic nervous system, which ultimately ensure that physical demands are met.[1] However, autonomic and cardiac dysfunction may occur after vascular brain injury, which affects BP control.[2] Alteration of BP control is evident in the acute stage and sustains for several months after stroke.[3] However, there are no data demonstrating the effect of previous stroke on long-term alteration of BP control, to our knowledge.

Variablility in blood pressure (BPV) is becoming increasingly recognized as an important predictor for future cardiovascular events.[4–8] High BPV is also predictive of stroke independent from high mean BP.[5,9–13] Observations linking BPV to stroke have been supported by analyses in previous clinical trials and a cohort study.[8,14] However, the specific relationship between BPV and risk for patients having a recurrent (secondary) stroke is less clear. Stroke patients have various angiopathies in their cerebrovascular structures, such as atherosclerosis, arteriolosclerosis, and microangiopathy.[15,16] High BPV may affect diseased vessels, which may be more or less significant following, compared with preceding, a stroke. How these pathological changes influence a recurrent stroke is unknown. Knowing whether or not BPV is of importance in the risk of recurrent stroke would help physicians to select the most appropriate antihypertensive(s) for these high-risk individuals.

This post hoc analysis of 2, large-scale cardiovascular end point studies sought to determine whether there are differences in BPV between patients who have a history of previous stroke or transient ischemic attack (TIA) compared with

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## Clinical Perspective

### What Is New?

- Long-term visit-to-visit blood pressure variability was higher in patients with a previous stroke or transient ischemic attack than those without.
- In hypertensive patients with a history of previous stroke or transient ischemic attack, visit-to-visit blood pressure variability whilst on antihypertensive treatment is a predictor of future recurrent stroke.

### What Are the Clinical Implications?

- Considering blood pressure variability following a stroke may be important to reduce the risk for a recurrent stroke.

patients who do not. We also aimed to evaluate the association between BPV and recurrence of stroke, using a cohort of patients with a history of previous stroke or TIA.

# Methods

## Study Design and Subjects

Data were extracted from the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) and the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) databases. The full study design and patient characteristics of the ASCOT and ALLHAT have been described elsewhere.[17,18] All patients provided written, informed consent before randomization.

Briefly, the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) randomized 19 257 hypertensive participants aged 40 to 79 years, with systolic BP (SBP) ≥160 and/or diastolic BP ≥100 mm Hg, in untreated patients or SBP ≥140 and/or diastolic BP ≥90 mm Hg, in treated patients and with at least 3 additional cardiovascular risk factors, to an amlodipine-based regimen or an atenolol-based regimen. Participants were followed up for an average of 5.5 years.[18,19] BP was measured 3 times (after a 5-minute rest) using a semiautomated device. Follow-up visits took place at 6 weeks, 3 months, 6 months, and then 6-monthly. At each visit, BP was monitored and treatment titrated to achieve BP target.[18,19]

The ALLHAT randomized 33 357 participants aged 55 years or older with stage 1 or 2 hypertension, and at least 1 additional cardiovascular risk factor, to chlorthalidone, amlodipine, or lisinopril. Patients were followed up for a mean of 4.9 years.[17] Follow-up visits took place after 1 month; 3, 6, 9, and 12 months; and 4 monthly thereafter. BP was monitored and titrated according to the predefined protocol to achieve BP goal.[17] Patients with known renal insufficiency or previous myocardial infarction (within the past 6 months) were excluded from the ALLHAT.[20]

The ASCOT and ALLHAT were both approved by the ethics committee at each site. This study—a post hoc analysis of the ASCOT and ALLHAT—was approved by the local ethics committee for analyzing the combined data. Patients from either study who had experienced a stroke or TIA were identified from the patient history forms and medical history captured during enrollment. The data that support the findings of this study are available from the sponsor upon reasonable request.

## Statistical Analyses

A pooled analysis was performed for the ASCOT and ALLHAT, but because significant differences were observed between studies, the data were also analyzed and presented separately. The BPV evaluable population comprised all patients who received at least 1 dose of antihypertensive study drug and had at least 2 postbaseline BP assessments. BPV was defined as the within-subject standard deviation (BPV-SD) or coefficient of variation (BPV-CoV) of SBP measurements across visits from 12 weeks (3 months/84 days) onward.

Three separate analyses were conducted, all using SAS (version 9.3 or above; SAS Institute Inc, Cary, NC).

1. To examine BPV distribution in the subset of patients who had a history of stroke or TIA before entry into the respective study (ASCOT or ALLHAT) compared with patients who did not have a history of stroke, a linear model was used with terms for treatment group, previous history of stroke, and interaction between treatment group and previous history of stroke, and mean baseline sitting SBP at rest. Comparisons between treatment groups, and comparison between subjects with a history of stroke versus those without a history of stroke, with regard to BPV distribution, were made. BPV was analyzed both as BPV-SD and BPV-CoV.
2. In the subset of patients who had a history of stroke or TIA (Prior Stroke BPV Evaluable cohort) within each study, patients were separated into 4 BPV quartiles, based on ordered BPV values. Incidence of recurrent stroke in patients who fell in the highest BPV-SD quartile (fourth quartile) was compared with the incidence of recurrent stroke in patients who fell in the lowest BPV-SD quartile (first quartile) using a chi-square test. This analysis was carried out by treatment arm within study, and also for the overall pooled cohort (ASCOT+ALLHAT). Similar analyses were conducted for BPV-CoV. Recurrent stroke was defined as a stroke occurring during follow-up among patients with a previous history of stroke or TIA at enrollment.

**Table 1.** BPV Among Patients Who Did Versus Those Who Did Not Have a History of Stroke or TIA Before Entry Into ASCOT

| | Amlodipine (n=9453) | | Atenolol (n=9399) | |
|---|---|---|---|---|
| | Previous Stroke or TIA (n=1014) | No Previous Stroke or TIA (n=8439) | Previous Stroke or TIA (n=1032) | No Previous Stroke or TIA (n=8367) |
| BPV-SD, mm Hg | | | | |
| Mean±SD | 11.86±4.99 | 11.36±4.71 | 15.06±6.11 | 13.92±5.75 |
| LS mean (SE) | 12.08 (0.16) | 11.59 (0.05) | 14.61 (0.15) | 13.73 (0.05) |
| Difference stroke history vs no stroke history,* LS mean [95% CI]; *P* value | 0.49 [0.17, 0.82]; *P*=0.003 | | 0.88 [0.56, 1.20]; *P*<0.001 | |
| Treatment difference vs amlodipine,* LS mean [95% CI]; *P* value | | | 2.53 [2.10, 2.96]; *P*<0.001 | 2.14 [1.99, 2.29]; *P*<0.001 |
| BPV-CoV, mm Hg | | | | |
| Mean±SD | 8.47±3.39 | 8.10±3.16 | 10.41±3.96 | 9.72±3.73 |
| LS mean (SE) | 8.53 (0.11) | 8.16 (0.04) | 10.29 (0.11) | 9.67 (0.04) |
| Treatment difference vs amlodipine,* LS mean [95% CI]; *P* value | | | 1.76 [1.46, 2.06]; *P*<0.001 | 1.50 [1.40, 1.61]; *P*<0.001 |

ASCOT indicates Anglo Scandinavian Cardiac Outcomes Trial; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; BPV, blood pressure variability; CoV, coefficient of variation; LS mean, least squares mean; TIA, transient ischemic attack.
*All estimates are based on a linear regression model with terms for treatment group, previous history of stroke, mean systolic blood pressure, and the interaction between treatment group and previous history of stroke (*P*=0.095); therefore, individual comparisons are presented.

3. Time to recurrent stroke in the subset of patients who had a history of stroke or TIA was analyzed using time-to-event techniques. For each study, Kaplan–Meier curves were generated for patients with BPV above (>) versus below or equal to (≤) median BPV level, by treatment group. Log-rank tests compared the Kaplan–Meier curves among

**Table 2.** BPV Among Patients Who Did Versus Those Who Did Not Have a History of Stroke or TIA Before Entry Into ALLHAT

| | Amlodipine (n=7194) | | Chlorthalidone (n=12 210) | | Lisinopril (n=7037) | |
|---|---|---|---|---|---|---|
| | Previous Stroke or TIA (n=604) | No Previous Stroke or TIA (n=6590) | Previous Stroke or TIA (n= 990) | No Previous Stroke or TIA (n=11 220) | Previous Stroke or TIA (n=579) | No Previous Stroke or TIA (n=6458) |
| BPV-SD, mm Hg | | | | | | |
| Mean±SD | 11.3±6.93 | 10.75±6.38 | 11.08±6.40 | 10.88±6.51 | 13.05±7.54 | 12.30±7.23 |
| LS mean (SE) | 11.24 (0.26) | 10.74 (0.08) | 11.16 (0.20) | 11.04 (0.06) | 12.80 (0.26) | 12.06 (0.08) |
| Difference stroke history vs no stroke history,* LS mean [95% CI]; *P* value | 0.50 [−0.03, 1.03]; *P*=0.063 | | 0.12 [−0.29, 0.54]; *P*=0.557 | | 0.75 [0.21, 1.28]; *P*=0.007 | |
| Treatment difference vs amlodipine,* LS mean [95% CI]; *P* value | | | −0.07 [−0.72, 0.57]; *P*=0.821 | 0.30 [0.11, 0.50]; *P*=0.002 | 1.56 [0.84, 2.29]; *P*<0.001 | 1.32 [1.10, 1.54]; *P*<0.001 |
| BPV-CoV, mm Hg | | | | | | |
| Mean±SD | 8.24±4.79 | 7.82±4.40 | 8.11±4.51 | 7.98±4.53 | 9.42±5.17 | 8.87±4.96 |
| LS mean (SE) | 8.21 (0.19) | 7.82 (0.06) | 8.14 (0.15) | 8.03 (0.04) | 9.33 (0.19) | 8.78 (0.06) |
| Treatment difference vs amlodipine,* LS mean [95% CI]; *P* value | | | −0.07 [−0.53, 0.39]; *P*=0.758 | 0.22 [0.08, 0.35]; *P*=0.002 | 1.12 [0.60, 1.64]; *P*<0.001 | 0.97 [0.81, 1.12]; *P*<0.001 |

ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; BPV, blood pressure variability; CoV, coefficient of variation; LS mean, least squares mean; TIA, transient ischemic attack.
*All estimates are based on a linear regression model with terms for treatment group, previous history of stroke, mean systolic blood pressure, and the interaction between treatment group and previous history of stroke (*P*=0.179); therefore, individual comparisons are presented.

**Table 3.** Demographic and Baseline Characteristics of Patients Who Had a History of Stroke or TIA Prior to Entry Into the ASCOT or ALLHAT Studies (Previous Stroke or TIA and BPV Evaluable Patients)

| | ASCOT (N=2046) | | ALLHAT (N=2173) | | |
|---|---|---|---|---|---|
| | Amlodipine (n=1014) | Atenolol (n=1032) | Amlodipine (n=604) | Chlorthalidone (n=990) | Lisinopril (n=579) |
| Male, n (%) | 721 (71.1) | 714 (69.2) | 332 (55.0) | 550 (55.6) | 346 (59.8) |
| Age, y | 66.3±7.69 | 66.1±7.97 | 67.8±7.78 | 68.1±7.76 | 67.9±7.85 |
| Race, n (%) | | | | | |
| White | 976 (96.3) | 1005 (97.4) | 360 (59.6) | 561 (56.7) | 336 (58.0) |
| Black/African | 21 (2.1) | 16 (1.6) | 221 (36.6) | 366 (37.0) | 215 (37.1) |
| Other | 17 (1.7) | 11 (1.1) | 23 (3.8) | 63 (6.4) | 28 (4.8) |
| Weight, kg | 81.0±14.4 | 80.9±15.0 | 83.1±28.3 | 81.5±21.2 | 82.6±23.7 |
| SBP, mm Hg | 164.5±17.9 | 163.8±18.7 | 145.5±15.9 | 146.0±15.8 | 145.4±15.8 |
| eGFR,* mL/min/1.73 $m^2$ | 66.0±12.3 | 65.5±12.5 | 77.1±20.4 | 75.3±19.1 | 75.8±19.9 |
| Diabetes mellitus | 217 (21.4) | 223 (21.6) | 179 (29.6) | 289 (29.2) | 181 (31.3) |
| Current smoker | 250 (24.7) | 261 (25.3) | 119 (19.7) | 174 (17.6) | 121 (20.9) |
| History of CKD* | 568 (56.0) | 596 (57.8) | 119 (21.1) | 204 (21.6) | 114 (20.9) |

Data are shown as mean±SD or n (%), unless otherwise specified. ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo Scandinavian Cardiac Outcomes Trial; BPV, blood pressure variability; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; TIA, transient ischemic attack.

*For calculation of eGFR in the ASCOT, n=689 (amlodipine) and n=707 (atenolol). In the ALLHAT, n=565 (amlodipine), n=946 (chlorthalidone), and n=546 (lisinopril).

treatment groups. In order to evaluate predictors of time to recurrent stroke in the subset of patients who had a history of stroke, a step-wise Cox proportional hazards model was used with the following terms: BPV category, treatment, baseline sitting SBP and heart rate (ASCOT only) at rest, total cholesterol, age, sex, race, smoking habit, diabetes mellitus, and renal dysfunction. These analyses were also performed for pooled cohort (ASCOT+ALLHAT); however, the analysis indicated differences between the ASCOT and ALLHAT, and as such, the time-to-event analyses are only presented for the studies separately.

# Results

## BPV and Patients With a History of Stroke: ASCOT and ALLHAT

For the ASCOT, BPV was significantly higher for patients who did (n=2046) versus those who did not (n=16 806) have a previous history of stroke, for both the amlodipine and atenolol treatment arms (Table 1). BPV was significantly higher with atenolol compared with amlodipine treatment, regardless of whether patients had a history of stroke (SD and CoV analysis; Table 1).

For the ALLHAT, BPV was numerically higher for patients who did (n=2173) versus those who did not (n=24 268) have a history of stroke (Table 2). BPV was higher in patients who had a previous stroke or TIA within all 3 treatment arms; however, statistical significance was only reached within the lisinopril arm (BPV-SD analysis; $P$=0.007; Table 2). For patients with a history of stroke or TIA and for those who did not, BPV was significantly higher with lisinopril versus amlodipine treatment. BPV was higher with chlorthalidone versus amlodipine treatment for patients without a history of previous stroke or TIA (BPV-SD and BPV CoV analysis; Table 2).

## BPV and Risk of Recurrent Stroke: ASCOT

Demographic and baseline characteristics of patients in ASCOT with a history of stroke (n=2046) are given in Table 3. The majority of these patients were male, and the mean age was ≈66 years. Within the cohort of patients with a history of stroke (n=2046), 252 patients (12.3%) had a recurrent stroke (Table 4); 100 patients (9.8%) with BPV-SD ≤median and 152 (14.9%) with BPV-SD >median. Patients who fell in the highest BPV quartile (fourth quartile, BPV-SD >16.64) had a significantly higher risk of recurrent stroke ($P$<0.001) compared with those who fell in the first BPV quartile (BPV-SD ≤9.36). The incidence for recurrent stroke was not significantly higher in the fourth quartile versus first quartile within the atenolol arm, and significance was only reached within the amlodipine-treatment arm ($P$=0.029). Overall, similar results were observed for BPV-SD and BPV-CoV analyses (Figure 1).

**Table 4.** Recurrent Stroke Outcomes by BPV-SD Quartile, in the Cohorts of Patients Who Had a History of Stroke or TIA

| | ASCOT (N=2046) | | ALLHAT (N=2173) | | | |
|---|---|---|---|---|---|---|
| | Amlodipine (n=1014) | Atenolol (n=1032) | Amlodipine (n=604) | Chlorthalidone (n=990) | Lisinopril (n=579) | Pooled (N=4219) |
| First quartile | | | | | | |
| No. of patients | 334 | 178 | 163 | 277 | 104 | 1056 |
| Recurrent stroke/TIA | 31 (9.3%) | 23 (12.9%) | 6 (3.7%) | 15 (5.4%) | 9 (8.7%) | 84 (8.0%) |
| Second quartile | | | | | | |
| No. of patients | 297 | 214 | 165 | 244 | 134 | 1054 |
| Recurrent stroke/TIA | 24 (8.1%) | 22 (10.3%) | 11 (6.7%) | 22 (9.0%) | 11 (8.2%) | 90 (8.5%) |
| Third quartile | | | | | | |
| No. of patients | 220 | 292 | 136 | 246 | 161 | 1055 |
| Recurrent stroke/TIA | 30 (13.6%) | 31 (10.6%) | 10 (7.4%) | 15 (6.1%) | 10 (6.2%) | 96 (9.1%) |
| Fourth quartile | | | | | | |
| No. of patients | 163 | 348 | 140 | 223 | 180 | 1054 |
| Recurrent stroke/TIA | 26 (16.0%) | 65 (18.7%) | 9 (6.4%) | 27 (12.1%) | 16 (8.9%) | 143 (13.6%) |
| Totals | | | | | | |
| No. of patients | 1014 | 1032 | 604 | 990 | 579 | 4219 |
| Recurrent stroke/TIA | 111 (10.9%) | 141 (13.7%) | 36 (6.0%) | 79 (8.0%) | 46 (7.9%) | 413 (9.8%) |
| 1st vs 4th BPV quartile* | $P$=0.029 | $P$=0.094 | $P$=0.272 | $P$=0.007 | $P$=0.946 | $P$<0.001 |

BPV is defined as the within-subject SD of systolic blood pressure measurements across visits from 12 weeks (or 3 months [84 days]) onward. Percentages are based on sample size within each BPV quartile, by treatment arm. Quartiles are calculated from ordered BPV values from all subjects with history of previous stroke, individually for each study. ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo Scandinavian Cardiac Outcomes Trial; BPV, blood pressure variability; TIA, transient ischemic attack.

*$P$ value for chi-square test.

In a time-to-event analysis, there were no significant differences between treatment arms for patients with BPV above or below median (Figure 2A and 2B). BPV, age, baseline SBP, sex, and smoking were all significant predictors in the time-to-event analysis (all $P$<0.05).

## BPV and Risk of Recurrent Stroke: ALLHAT

Demographic and baseline characteristics of patients with a history of stroke in the ALLHAT (n=2173) are given in Table 3. The majority of these patients were male, and the mean age was ≈68 years. Baseline mean SBP ranged from 145.4 to 146.0 mm Hg. Only 20.1% of patients had a history of chronic kidney disease, in line with patients being excluded from the ALLHAT with a history of renal insufficiency.

Within the cohort of patients with a history of stroke (n=2173), 161 (7.4%) had a recurrent stroke (Table 4); this comprised 74 patients (6.8%) with BPV≤median and 87 patient (8.0%) with BPV>median. When patients with a history of stroke were analyzed by quartile, more patients with high BPV (fourth quartile) versus low BPV (first quartile) had a recurrent stroke (BPV-SD or CoV analysis; Figure 3). When analyzed by treatment arm, incidence of recurrent stroke was higher in patients with high (fourth quartile, BPV-SD >15.029) versus low BPV (first quartile, BPV-SD ≤6.850), although this difference reached statistical significance for the chlorthalidone arm only ($P$=0.007; BPV-SD analysis; Table 4).

In a time-to-event analysis, there was no significant difference between treatment arms for patients with BPV above median or BPV below median (Figure 2C and 2D). BPV alone was not a significant predictor in the time-to-events analysis; however, age and sex were both found to be significant predictors of time to recurrent stroke ($P$<0.05 for both).

## BPV and Risk of Recurrent Stroke: Pooled Cohort

In the pooled data set (ASCOT+ALLHAT), 413 patients (9.8%) had a recurrent stroke (BPV-SD analysis; Table 4). When analyzed by BPV quartile, patients with high versus low BPV were significantly more likely to have a recurrent stroke (BPV in fourth versus first quartile; $P$<0.001). By treatment group, a significant difference between patients with high versus low BPV (fourth versus first quartile) was observed for amlodipine ($P$=0.049) and chlorthalidone ($P$=0.007) treatment arms. The results of the pooled time-to-events analysis indicated differences between the ASCOT and ALLHAT studies, and

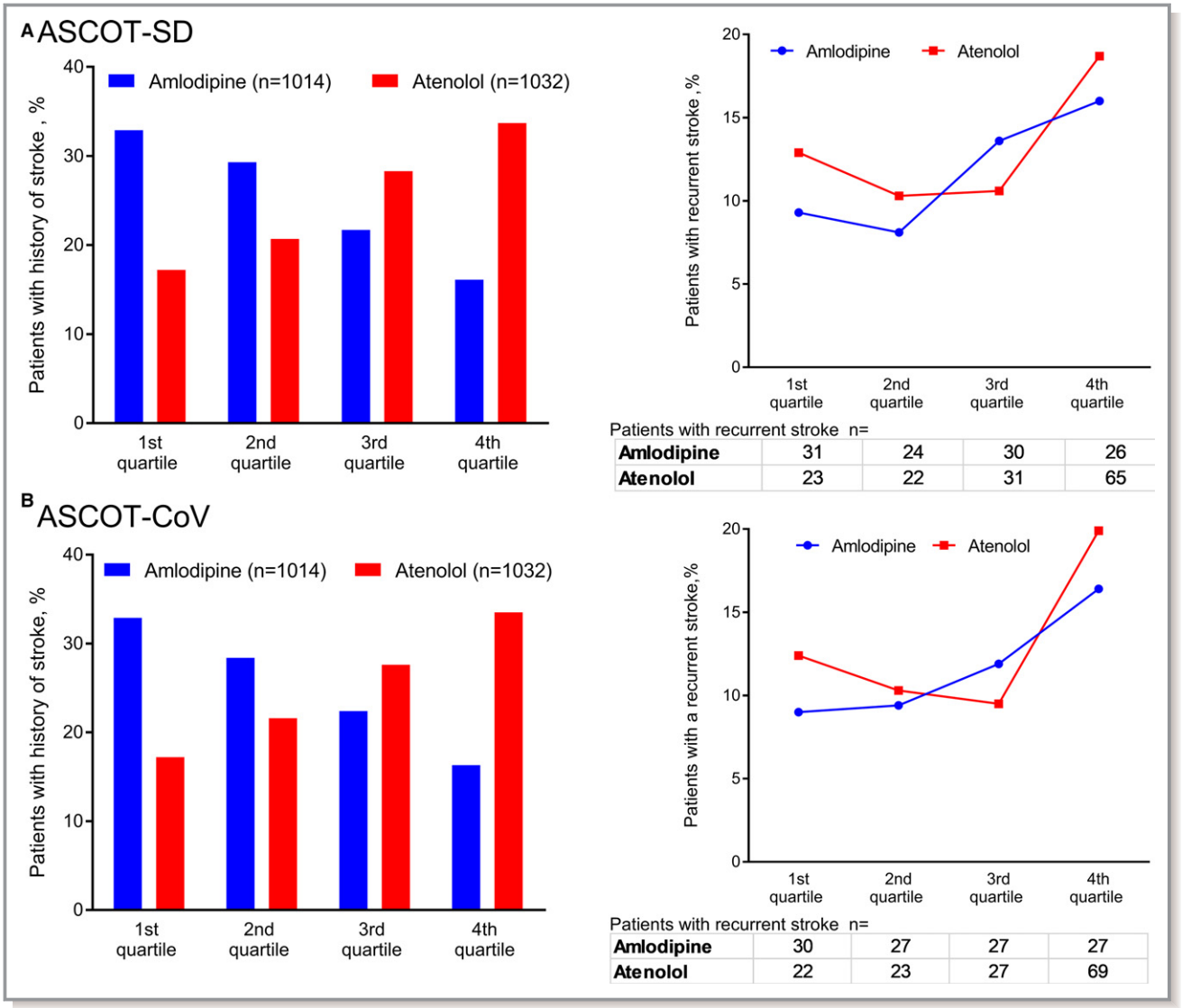


**Figure 1.** ASCOT (Anglo Scandinavian Cardiac Outcomes Trial): distribution of patients with a history of stroke or TIA by BPV quartile and relationship to recurrent stroke outcomes. **A**, Data as BPV-SD. **B**, Data as BPV-CoV. BPV indicates blood pressure variability; CoV, coefficient of variation; Pts., patients.

therefore in this article, the analyses are only presented separately.

## Discussion

This analysis of 2 large cardiovascular end point studies is the first to demonstrate that long-term BPV was significantly higher in patients with a history of stroke or TIA compared with those without. Furthermore, high BPV was strongly associated with the risk of having a recurrent stroke, in patients with a previous stroke. However, whereas the type of antihypertensive agent can make a significant difference to the risk of cardiovascular outcomes for patients with primary stroke,[9,21,22] we found that antihypertensive used in the ASCOT or ALLHAT was not as important as having low BPV on any treatment to lower the risk for recurrent stroke.

Our study was undertaken to investigate how patients who have a recurrent stroke may differ from patients who do not, looking specifically at BPV and treatment response to antihypertensives. We demonstrate that increased BPV is strongly correlated with the risk of recurrent stroke in patients with hypertension and a history of previous stroke or TIA. More specifically, we found that patients who had a recurrent stroke generally had significantly higher BPV compared with patients who did not have a history of previous stroke or TIA, regardless of the study in which patients were enrolled. Studies of long-term BPV in a different high-risk group of patients have

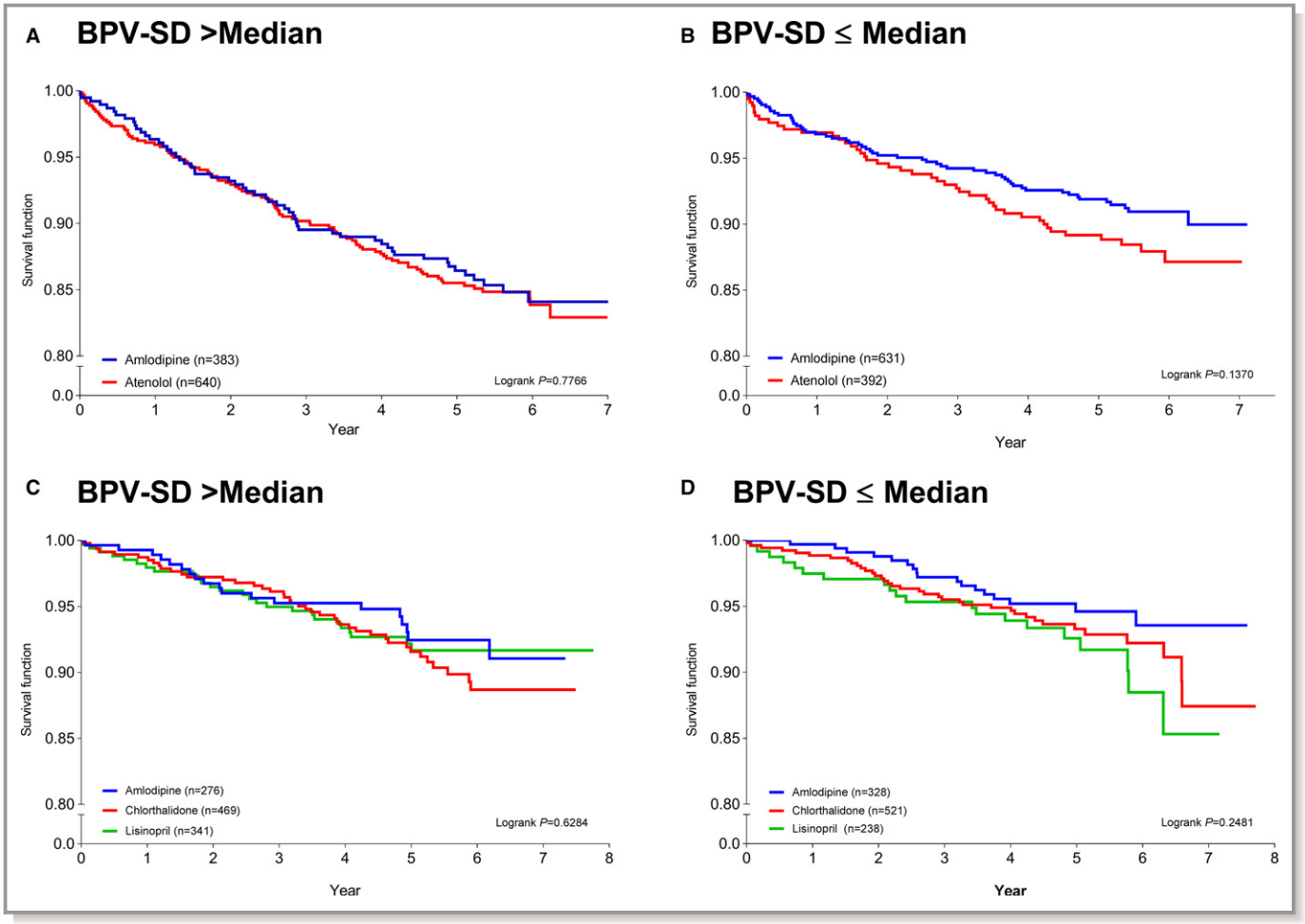


**Figure 2.** Kaplan–Meier analysis of the ASCOT (Anglo Scandinavian Cardiac Outcomes Trial; **A** and **B**) and the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; **C** and **D**) for time to recurrent stroke or TIA by treatment arms. **A** and **C**, Subjects with BPV above median; **B** and **D**, Subject with BPV below or equal to median. BPV indicates blood pressure variability.

demonstrated that BPV is an important marker for risk of stroke and other cardiovascular outcomes.[4,10–12,19,23,24] Our study demonstrates that BPV is an important predictor for recurrent stroke, filling this gap in the literature of BPV in high-risk patients with a previous history of stroke.

Controlling mean BP with antihypertensive treatment has been the cornerstone of hypertension management for decades. Major cerebrovascular changes may occur following a stroke, which will influence the body's response to BP fluctuations.[25,26] However, these pathological changes may also influence how the body reacts to different types of antihypertensive. Our study of the ASCOT and ALLHAT enabled us to investigate the impact of different types of antihypertensive on BPV within a large cohort of high-risk patients, including a calcium channel blocker–(amlodipine), beta-blocker– (atenolol), diuretic- (chlorthalidone), or angiotensin-converting enzyme inhibitor-based (lisinopril). Both studies in our analysis had an amlodipine-based treatment arm, and we found regardless of study that recurrent stroke patients who received amlodipine had lower BPV, in line with previous data from these studies in different subsets of patients.[21,25]

However, we found evidence to suggest that BPV matters more than the type of antihypertensive treatment, given that higher BPV led to a higher risk of recurrent stroke, even after adjusting for treatments. Similarly, in a time-to-events analysis, there was no difference in risk of recurrent stroke by treatment arm for patients with high or low BPV (using median BPV), in either the ASCOT or ALLHAT. This suggests that for these high-risk individuals, being on any antihypertensive regimen is more important than the type of antihypertensive used to manage BP and BPV, in order to lower the risk for recurrent stroke. Although BPV may be considered during selection of antihypertensive treatment, BPV itself is not the focus of management. This is at least partly attributed to the methodology used for BPV assessment not being standardized or widely used within the medical community. Indeed, when these studies were designed and conducted, BP management would have been different from standards used

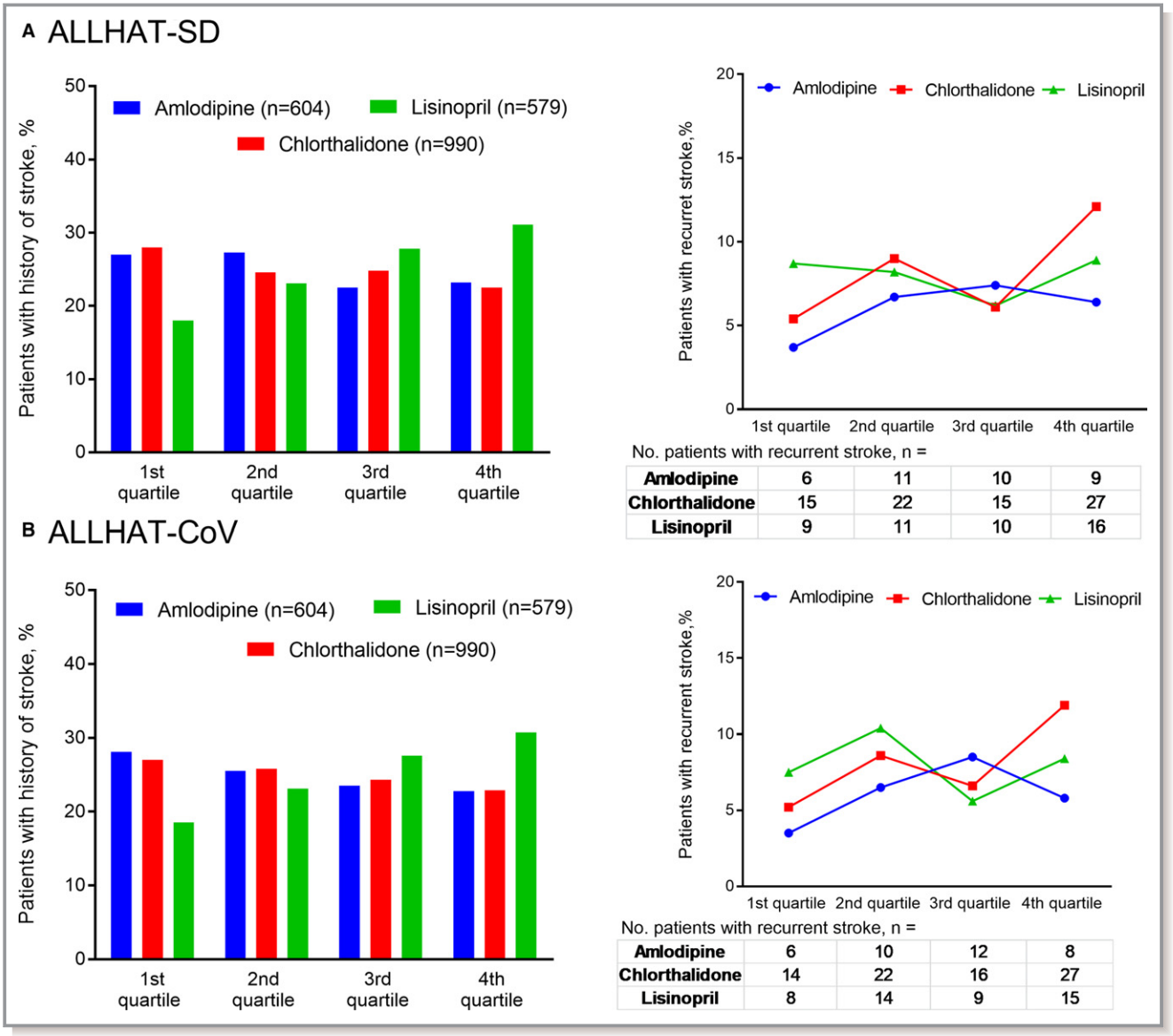


**Figure 3.** ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial): distribution of patients with a history of stroke or TIA by BPV quartile and relationship to recurrent stroke outcomes. **A**, Data as BPV-SD. **B**, Data as BPV-CoV. BPV indicates blood pressure variability; CoV, coefficient of variation; Pts., patients.

today,[17,18] and BPV likely dismissed as "noise" within the BP assessment and considered random in nature, and thus not a consideration for treatment. Although a previous study suggested that BPV-SD >10 mm Hg may predict an increased risk of cardiovascular event,[26] still the level at which high BPV becomes clinically relevant is not clearly verified. Collective evidence is needed to determine the threshold at which BPV becomes of clinical importance in different patient groups.

Although we analyzed 2 large groups of patients with hypertension and additional cardiovascular risk factors, our study should be interpreted in light of its limitations. We do not have direct evidence that controlling or managing BPV will lower the risk of stroke/recurrent stroke. Furthermore, without studies demonstrating the normal range of BPV, the clinical relevance of differences in BPV cannot be inferred. As mentioned above, the method to measure BPV is not standardized. However, we have used both BPV-SD and –CoV, which are the most widely used parameters describing BPV. The patients included in the ASCOT and ALLHAT are largely of white race and Western ethnicity,[17,18] and therefore observations may not be replicated in other ethnicities. Although the sample size within the ASCOT and ALLHAT was large, the relative number of recurrent strokes within each study was low, and therefore evaluating the treatment effect on BPV among patients with a recurrent stroke should be interpreted accordingly. Indeed, the sample size may contribute to the lack of significance observed

by treatment arm in our time-to-event analysis. Finally, we were able to compare different classes of antihypertensive-based therapy. The protocol of each study allowed concomitant medications when a patient failed to achieve predefined BP goals.[17,18] Therefore, the influence of concomitant medications needs to be considered when reviewing our by-treatment results. Given that we selectively included those with previous stroke or TIA from the main randomized trials, imbalance in the unmeasurable factors (ie physical activity, disability, and diet/sodium intake) between treatment groups may have influenced the recurrence of stroke.

## Conclusion

Visit-to-visit BPV in SBP was higher in hypertensive patients with a history of stroke or TIA than those without. Furthermore, visit-to-visit BPV in SBP after antihypertensive treatment is a predictor of recurrent stroke in hypertensive patients with a history of stroke or TIA. Further evidence is needed to determine whether controlling or managing BPV with different antihypertensives will lower the risk of recurrent stroke.

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