Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population

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Objective **To investigate whether baseline systolic blood pressure variability was a risk factor for stroke, cardiovascular mortality or cardiac events during the Syst-Eur trial.**

Design **The Syst-Eur study was a randomized, double-blind, placebo-controlled trial, powered to detect differences in stroke rate between participants on active antihypertensive treatment and placebo. Systolic blood pressure variability measurements were made on 744 participants at the start of the trial. Systolic blood pressure variability was calculated over three time frames: 24 h, daytime and night-time. The placebo and active treatment subgroups were analysed separately using an intention-to-treat principle, adjusting for confounding factors using a multiple Cox regression model.**

Participants **An elderly hypertensive European population.**

Main outcome measures **Stroke, cardiac events (fatal and non-fatal heart failure, fatal and non-fatal myocardial infarction and sudden death) and cardiovascular mortality (death attributed to stroke, heart failure, myocardial infarction, sudden death, pulmonary embolus, peripheral vascular disease and aortic dissection).**

Results **The risk of stroke increased by 80% (95% confidence interval: 17–176%) for every 5 mmHg increase in night-time systolic blood pressure variability in the placebo group. Risk of cardiovascular mortality and cardiac events was not significantly altered. Daytime variability readings did not predict outcome. Antihypertensive treatment did not affect systolic blood pressure variability over the median 4.4-year follow-up.**

Conclusion **In the placebo group, but not the active treatment group, increased night-time systolic blood pressure variability on admission to the Syst-Eur trial was an independent risk factor for stroke during the trial.**
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Introduction

High systolic blood pressure has been correlated with end-organ damage, particularly stroke, in many studies [1–3]. Trials on treatment of isolated systolic hypertension in the elderly have shown that a reduction in blood pressure is accompanied by a reduction in the incidence of stroke [4,5]. Early studies of blood pressure variability (BPV), using invasive intra-arterial methods, found correlations between BPV and end-organ damage [6,7].

Ambulatory blood pressure monitoring (ABPM) has enabled a non-invasive estimate of blood pressure variability to be obtained. ABPM has already been shown to give a more reproducible estimate of blood pressure level than clinic blood pressures [8], and to be

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of prognostic value [9–12]. Analysis of BPV using ABPM can be performed in different time frames (e.g. night, day or 24-hour) and for different components of blood pressure (e.g. systolic, diastolic or mean pressures).

We have analysed the ambulatory blood pressure measurements from the Syst-Eur study to see whether systolic BPV is independently associated with the subsequent risk of stroke, cardiovascular mortality and cardiac events.

Methods

Population and study design

The multicentre Syst-Eur trial investigated the efficacy of antihypertensive therapy in elderly patients with isolated systolic hypertension, according to a randomized, double-blind, placebo-controlled protocol [13]. Patients were randomized to either nitrendipine (10–40 mg/day) with the possible addition of enalapril (5–20 mg/day) and/or hydrochlorothiazide (12.5–25 mg/day), or to identical placebos employed similarly. Prior to randomization, all participants were monitored for 3 months while taking a single-blind placebo, this is known as the 'run-in period', with three clinic visits, to ensure entry requirements were met.

Participants were eligible if, during this run-in phase, the sitting clinic systolic blood pressure was in the range 160–219 mmHg with a diastolic measurement less than 95 mmHg, and their standing blood pressure was 140 mmHg or greater. Participants gave informed consent and long-term follow-up was possible. Participants were excluded if hypertension was secondary to a disorder that required treatment. The other exclusion criteria were: presence of retinal haemorrhages, papilloedema, congestive cardiac failure, dissecting aortic aneurysm, serum creatinine greater than 180 μmol/l (2 mg/dl), a history of severe nose bleeds, a stroke or myocardial infarction within the year before the study, dementia, substance abuse, any condition preventing sitting or standing, and severe concomitant disease.

The primary endpoint, stroke, was defined as a neurological deficit with symptoms continuing for more than 24 h, or leading to death with no apparent cause other than vascular. Secondary endpoints included cardiac events (fatal and non-fatal heart failure, fatal and non-fatal myocardial infarction and sudden death) and cardiovascular mortality (death attributed to stroke, heart failure, myocardial infarction, sudden death, pulmonary embolus, peripheral vascular disease and aortic dissection). An endpoint committee, blind to patient treatment status, identified all major endpoints (by reviewing local patient files or requesting detailed written information from the investigators, or by both approaches).

Ambulatory blood pressure monitoring side project

This was an optional project organized prospectively to determine whether 24-hour ambulatory blood pressure (ABP) monitoring is able to add prognostic information over and above that of clinic measurements [14]. Of the 198 Syst-Eur centres, 46 opted to enrol their participants in the present study. Of the 837 randomized patients with at least one 24-hour ABP recording at baseline, 93 (11%) were excluded from analysis because more than 20% of the readings were missing ($n = 29$) or because blood pressure readings were not available during more than 2 consecutive hours ($n = 64$). The baseline ambulatory blood pressure recording of the remaining 744 patients was taken during the placebo run-in period in 635 patients, or shortly after randomization in 109 patients. On the 14 February 1997 the Syst-Eur trial stopped early because of a 42% decrease in the risk of stroke in the active treatment group, by which time 495 of the remaining 744 participants had undergone at least one follow-up 24-hour ABP recording of sufficient quality.

The procedures for ABP recording have been published previously [15]. Validated monitors [8] were programmed to obtain measurements at intervals no longer than 30 min. The cuff was secured to the non-dominant arm. However, if, on conventional sphygmomanometry, the difference in systolic pressure between both arms was 10 mmHg or more, the arm giving the highest reading was chosen for all blood pressure measurements. If arm circumference exceeded 31 cm, larger cuffs with 35 × 15 cm bladder were used.

Blood pressure variability

The within-subject standard deviation of the systolic ambulatory blood pressure level was used as a measure of BPV. The standard deviation was calculated from unedited recordings for the whole 24-hour period, daytime (from 10.00 to 20.00 hours) and night-time (from midnight to 06.00 hours), and was weighted for the time interval between consecutive readings. Clinic BPV was also calculated from the standard deviation of the six clinic systolic blood pressure levels obtained during the placebo run-in period in the same group of patients.

Statistical analysis

The statistical analyses were based on the intention-to-treat principle and two-sided tests, using SAS software version 8 (Cary, North Carolina, USA). The association between blood pressure variability and outcome was assessed using multiple Cox regression analysis adjusted for sex, cardiovascular complications at baseline [defined as symptoms or signs suggestive of coronary heart disease (angina, history of myocardial infarction), symptoms or signs suggestive of cerebrovascular disease (history of transient ischaemic attack or stroke), electro-

cardiographic changes compatible with left ventricular hypertrophy (Sokolow index > 3.5 mV), retinal lesions or renal lesions], age, smoking status and ambulatory systolic pressure level for the index period (24 h, daytime, night-time). Previously published analyses had demonstrated that these variables were significant predictors of one or more endpoints [15].

To determine whether BPV at baseline responded to antihypertensive treatment independent of the level of pressure, the BPV was adjusted for differences in systolic blood pressure, using the coefficient of variance. The net changes in BP and in BPV were calculated by subtracting the changes from baseline in the placebo group from the corresponding changes in the active treatment group. The significance of the mean differences was determined using the normal z-distribution.

Results

Patient characteristics at randomization

At randomization, patients in the placebo ($n = 360$) and active treatment ($n = 384$) groups had similar characteristics. The median age was 69.5 years (60–92 years) and mean body mass index 26.7 (SD 3.9); 61% (454 participants) were female, 26.7% (199 participants) had a history of cardiovascular complications, and 8.6% (64 participants) were smokers. Blood pressure and blood pressure variability were similar in the two treatment groups (Table 1). Pulse rate averaged 73.4 (9.2) beats/min on clinic measurement and 69.8 (8.9) beats/min on 24-hour ambulatory measurement.

Factors affecting blood pressure variability

Baseline systolic BPV on ambulatory blood pressure monitoring, as estimated by the within-subject standard deviation, was positively correlated with systolic blood pressure level for daytime ($r = 0.30$, $P < 0.001$), night-time ($r = 0.20$, $P < 0.001$), and 24-hour periods ($r = 0.25$, $P \leqslant 0.001$). At baseline, women had a higher unadjusted systolic BPV than men for the daytime ($P = 0.005$), night-time ($P = 0.04$), and 24-hour periods ($P = 0.001$) (Table 2). In addition, both daytime ($r = 0.09$, $P = 0.01$) and night-time ($r = 0.08$, $P = 0.02$) but not 24-hour ($r = 0.01$, $P = 0.70$) systolic BPVs were positively correlated with age. Increased ambulatory pulse rate was associated with higher daytime ($r = 0.14$, $P < 0.001$) but not night-time ($r = 0.06$, $P = 0.11$) systolic BPV. No relationships were found between systolic BPV and body mass index (BMI), history of cardiovascular complications, smoking status, or clinic pulse rate.

In multiple regression analyses, daytime systolic BPV was 1.1 mmHg ($P = 0.004$) higher in women than in men, and increased by 0.9 mmHg ($P < 0.001$) for each 10 mmHg increment in daytime systolic pressure, and by 0.5 mmHg ($P = 0.003$) for every 10 beats/min incre-

Table 1 Changes in systolic blood pressure level and variability at follow-up

	Placebo mmHg (SD)	Active treatment mmHg (SD)	Difference between placebo and active treatment groups mmHg (95% CI)	*P* value
Baseline measurements				
Number of patients	360	384		
Clinic mean*	173.1 (10.6)	173.7 (11.3)	0.60 (−0.98,2.18)	0.46
Clinic SD	7.7 (4.8)	7.4 (4.8)	−0.27 (−0.96,0.43)	0.45
24-hour mean	145.7 (15.5)	145.4 (15.3)	−0.31 (−2.53,1.91)	0.79
Daytime mean	151.4 (16.2)	150.9 (15.7)	−0.54 (−2.84,1.76)	0.64
Night-time mean	133.6 (17.4)	133.9 (19.3)	0.28 (−2.37,2.93)	0.83
24-hour SD	17.7 (4.3)	17.8 (5.0)	0.06 (−0.61,0.74)	0.86
Daytime SD	15.7 (5.1)	15.6 (5.1)	−0.05 (−0.79,0.69)	0.89
Night-time SD	11.4 (4.5)	11.7 (4.9)	0.27 (−0.41,0.95)	0.43
24-hour CV	12.2 (3.0)	12.3 (3.3)	0.06 (−0.40,0.52)	0.79
Daytime CV	10.4 (3.4)	10.3 (3.1)	−0.04 (−0.51,0.43)	0.86
Night-time CV	8.6 (3.4)	8.8 (3.6)	0.20 (−0.30,0.71)	0.43
Changes at follow-up				
Number of patients	245	250		
Clinic	−14.3 (17.2)	−25.4 (16.3)	−11.1 (−14.1,−8.1)	< 0.001
24-hour mean	−2.2 (13.7)	−10.3 (13.3)	−8.1 (−10.5,−5.7)	< 0.001
Daytime mean	−3.5 (16.8)	−10.6 (14.7)	−7.1 (−9.8,−4.3)	< 0.001
Night-time mean	−0.2 (14.2)	−9.4 (16.9)	−9.2 (−11.9,−6.4)	< 0.001
24-hour SD	−0.77 (5.3)	−1.70 (5.0)	−0.94 (−1.84,−0.03)	0.04
Daytime SD	−0.38 (6.3)	−1.90 (5.6)	−1.52 (−2.57,−0.47)	0.005
Night-time SD	0.08 (5.5)	−0.99 (5.8)	−1.07 (−2.07,−0.07)	0.04
24-hour CV	−0.35 (3.5)	−0.36 (3.6)	−0.01 (−0.63,−0.61)	0.97
Daytime CV	0.00 (4.2)	−0.63 (3.8)	−0.63 (−1.33,0.07)	0.08
Night-time CV	0.06 (3.9)	−0.22 (4.5)	−0.28 (−1.03,0.46)	0.46

95% CI, 95% confidence interval; SD, standard deviation; CV, coefficient of variation.
*Mean of six readings, i.e. two at each of three baseline visits 1 month apart.

Table 2 Systolic blood pressure and blood pressure variability at baseline

	Women mmHg (SD)	Men mmHg (SD)	$P^{\dagger}$
Clinic BP in sitting position*			
Mean	173.9 (11.3)	172.5 (10.4)	0.09
SD	7.7 (4.8)	7.3 (4.9)	0.25
Ambulatory monitoring			
24-hour mean	144.8 (15.9)	146.7 (14.5)	0.11
Daytime mean	150.4 (16.4)	152.3 (15.2)	0.11
Night-time mean	132.7 (18.8)	135.5 (17.6)	0.04
24-hour SD	18.2 (4.9)	17.1 (4.2)	0.001
Daytime SD	16.0 (5.1)	15.0 (5.1)	0.005
Night-time SD	11.8 (4.7)	11.1 (4.7)	0.04

SD, standard deviation.
$^{\dagger}P$ value according to unpaired *t*-test.
*Mean of six readings, i.e. two at each of three baseline visits 1 month apart.

ment in daytime pulse rate. In addition, daytime systolic BPV tended to increase by 0.5 mmHg ($P = 0.06$) for each 10 years increase in age. Night-time systolic BPV was 0.9 mmHg ($P = 0.01$) higher in women than in men, and increased by 0.5 mmHg ($P = 0.03$) per 10 mmHg increment in night-time systolic blood pressure.

Clinic BPV from clinic measurements did correlate significantly with 24-hour ambulatory BPV, but the relationship was weak ($r = 0.16$; $P < 0.001$).

Treatment and blood pressure variability during follow-up

The median follow-up in the 744 patients was 4.4 years. The patients had been recruited over 8 years and, because the trial stopped early, follow-up of the individual patients ranged from 1 to 109 months. The number of patient-years in the placebo and active-treatment groups amounted to 1528 and 1620, respectively.

Of the 744 participants, 250 in the active treatment group and 245 in the placebo group underwent a follow-up 24-hour ABP recording. At the last follow-up visit, 199 (81.2%) of the participants randomized to placebo and 225 (90.0%) of the participants randomized to active treatment were still taking double-blind treatment, while the others were in open follow-up. Of the actively treated patients, 194 (86.2%) were taking nitrendipine (mean daily dose, 27.8 mg), 69 (31.4%) were on enalapril (13.9 mg) and 38 (16.9%) on hydrochlorothiazide (22.7 mg).

At the last follow-up visit, the net reduction in 24-hour systolic blood pressure level was 8.1 mmHg ($P < 0.001$) with similar reductions seen when day- and night-time readings were analysed separately. The net effect of antihypertensive treatment on systolic BPV was a 1.5 mmHg reduction ($P = 0.005$) for daytime BPV measurements and a 1.1 mmHg reduction ($P = 0.04$) for night-time BPV measurements. However, after adjustments for the systolic blood pressure level, by expressing the BPV as the coefficient of variation, antihypertensive treatment did not effect 24-hour, daytime or night-time BPV (Table 1).

Blood pressure variability as a predictor of outcome

Stroke (primary endpoint)

After adjustment for age, sex, smoking, history of cardiovascular complications and the 24-hour mean systolic blood pressure level, the baseline 24-hour systolic BPV was significantly predictive of the incidence of stroke in the placebo group, and this appeared to be due largely to the night-time variability (Table 3). The risk of stroke increased by 80% (95% CI 17–176%, $P = 0.007$) for each 5 mmHg increment in night-time systolic BPV. In Figure 1, the 2-year stroke rate is plotted against the night-time systolic blood pressure level and night-time systolic BPV, and it is seen that for any level of systolic blood pressure, the risk of stroke increased with higher night-time systolic BPV. Daytime BPV and clinic BPV at baseline were not predictors of stroke.

Cardiovascular mortality and cardiac events (secondary endpoints)

Cardiovascular mortality was a heterogeneous group. In the placebo group the 18 cardiovascular deaths comprised 6 myocardial infarctions, 4 cases of heart failure, 4 sudden deaths, 2 strokes, 1 aortic dissection, and 1 acutely ischaemic necrotic leg. In the active treatment group, the 13 cardiovascular deaths comprised of 8 sudden deaths, 2 strokes, 1 myocardial infarction, 1 case of heart failure and 1 fatal pulmonary embolism.

Although there was a tendency to increased cardiovascular mortality with increasing night-time BPV in the placebo group, this relationship was not significant ($P = 0.07$). Daytime BPV and clinic BPV were not predictive of cardiovascular mortality.

Night-time, daytime and clinic BPV were not predictive of cardiac event rate.

Discussion

In this substudy of the Syst-Eur trial, we found that increased night-time systolic blood pressure variability was a risk factor for stroke, even after adjusting for blood pressure level and other confounding variables. This is the first longitudinal study to report an association between night-time systolic BPV and stroke in an elderly hypertensive population. There have been three other longitudinal studies of BPV and outcome [7,16,17].

The Ohasama study [16] followed 1542 participants for an average of 8.5 years in a rural Japanese community. The population was more diverse in terms of age and

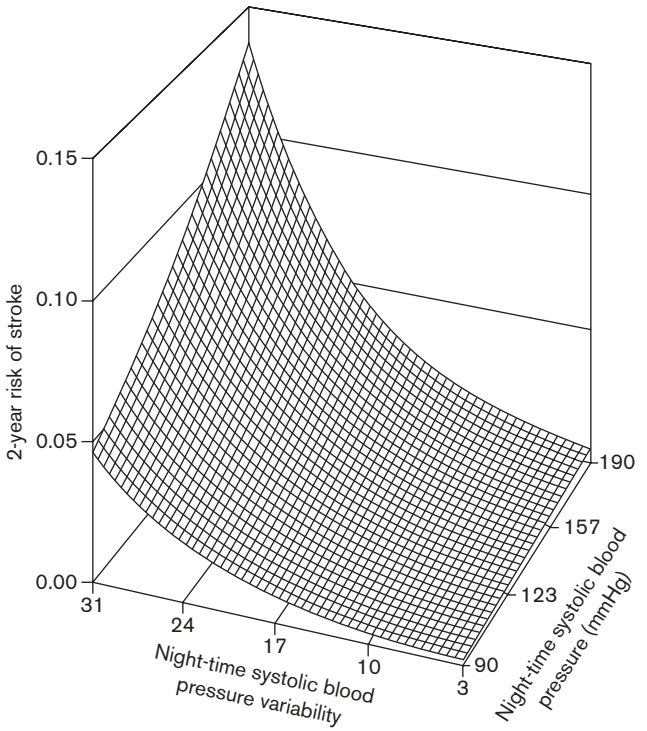
Table 3 Relative hazard rates associated with a 5 mmHg increase in systolic blood pressure variability

	Cardiovascular mortality	Fatal and non-fatal stroke	Cardiac events
Placebo group			
Number of endpoints	18	18	31
Clinic BPV	0.82 (0.49–1.38)	0.84 (0.50–1.39)	1.04 (0.74–1.47)
24-hour BPV	1.17 (0.64–2.13)	1.82 (1.14–2.93)**	0.93 (0.58–1.50)
Daytime BPV	1.11 (0.70–1.78)	1.03 (0.66–1.61)	1.24 (0.89–1.73)
Night-time BPV	1.54 (0.96–2.47)*	1.80 (1.17–2.76)**	0.99 (0.66–1.48)
Active-treatment group			
Number of endpoints	13	10	32
Clinic BPV	1.15 (0.76–1.74)	1.50 (0.93–2.41)	0.88 (0.64–1.20)
24-hour BPV	0.78 (0.41–1.47)	1.04 (0.59–1.84)	1.08 (0.77–1.51)
Daytime BPV	1.08 (0.65–1.80)	1.51 (0.88–2.58)	1.10 (0.81–1.50)
Night-time BPV	0.61 (0.29–1.31)	1.08 (0.59–1.97)	0.77 (0.51–1.16)

BPV, Blood pressure variability, determined by the weighted standard deviation of consecutive systolic blood pressure measurements

Relative hazard rates (95% confidence interval) reflect the risk associated with a 5 mmHg increase in blood pressure variability. The hazard rates were adjusted for the level of the ambulatory pressure and for other characteristics at baseline, including sex, age, previous cardiovascular complications and current smoking status. Significance levels are indicated: $^{*}P = 0.07$, $^{**}P < 0.01$.

Fig. 1



Night-time systolic blood pressure variability and night-time systolic blood pressure level at baseline as independent predictors of the 2-year incidence of stroke in the placebo group. The event rate was standardized to female sex, 70.4 years (mean age), no previous cardiovascular complications and non-smoking. Incidence is given as a fraction (i.e. 0.01 is an incidence of 1 event per 100 participants).

blood pressure level, but the only outcome examined was mortality related to the circulatory system (as defined by the ICD-10 code 'I'). Rather than treating BPV as a continuous variable as here, BPV was divided into quintiles of severity. They found that the highest quintile of night-time systolic BPV (greater than 14.4 mmHg) was significantly associated with a 121% increase in mortality when compared to the quintile with lowest mortality (night-time systolic BPV: 11.8–14.4 mmHg) after adjusting for blood pressure level. However, no clear trend of increasing mortality with increasing severity of night-time systolic BPV was demonstrated.

The Cornell study [17] analysed data from 729 mildly hypertensive patients (average follow-up 5 years), using a Cox regression model to predict risk of cardiovascular morbidity (cardiovascular death, myocardial infarction, completed stroke, coronary bypass or angioplasty). Unfortunately, a substantial number of subjects did not have acceptable night-time recordings, for technical reasons. Only daytime diastolic BPV was a risk for morbidity. In concordance with our study, daytime systolic BPV was not of prognostic value.

Frattola *et al.* [7], used invasive intra-arterial monitoring to calculate BPV in a longitudinal study of 73 patients from Milan (average follow-up of 7.4 years). Baseline 24-hour mean arterial BPV was calculated during a period of hospitalization and was predictive of end-organ damage at baseline and follow-up (measured by chest radiograph, ECG, ocular fundoscopic appearance, and echocardiogram).

In our study daytime systolic BPV was not a predictor of the primary endpoint, stroke, or the secondary endpoints, cardiovascular mortality and cardiac events. It has been suggested that night-time blood pressure measurements are a more consistent predictor of cardiovascular outcomes than daytime, as the influence of daytime physical and psychoemotional stress loosens the association between blood pressure parameters and outcome [9]. Leary *et al.* [18] observed that up to 62%

of the daytime BPV may be due to physical activity. In our study, the greater susceptibility of daytime blood readings to physical and psychoemotional stressors may explain the loss of predictive value of daytime systolic BPV for stroke.

Two small cross-sectional studies [19,20] have reported a correlation between daytime systolic BPV and intensity of cerebrovascular disease measured by magnetic resonance imaging (MRI) or computed tomography (CT) imaging techniques. However, in both these studies the outcome was the number of radiological brain lesions, rather than clinical stroke, as used in the current study.

We found that systolic BPV was higher in women and increased with higher systolic blood pressure level, for both night-time and daytime periods. Additionally, for daytime systolic BPV, there was a significant positive correlation with ambulatory pulse rate and a weaker positive correlation with age. There were no associations found, for daytime or night-time BPV, with BMI, smoking status, or history of cardiovascular complications. An earlier analysis of 823 participants in the Ohasama study [21] found similar associations for daytime systolic BPV with blood pressure level, sex, and age (pulse rate was not reported). Night-time BPV was anecdotally reported as 'showing similar results'. The Ohasama study also reported that raised BMI was associated with increased daytime BPV (smoking status and history of cardiovascular complications were not discussed). However, Schartz *et al.* [22] did not find age or body size to be associated with daytime or night-time BPV in a study of 143 healthy adults from Minnesota.

When we compared BPV between the placebo and active treatment groups after an average of 4.4 years follow-up there were no differences in BPV, after adjusting for blood pressure level. This is in agreement with a study [23] of 266 patients who had baseline ABPM and were then treated with either an angiotensin converting enzyme (ACE) inhibitor or calcium-channel blocker for 4–8 weeks before repeating ABPM. They found no significant differences between pre-treatment and treatment systolic BPV for the 24-hour period, daytime or night-time, after adjusting for blood pressure level.

There was a tendency for daytime systolic BPV to be reduced while on active treatment, although this did not reach statistical significance ($P = 0.08$). Given the lack of treatment effect on 24-hour systolic BPV and night-time systolic BPV, it may be that this anomalous tendency to reduced daytime systolic BPV on antihypertensive treatment reflects the multiple factors involved in daytime blood pressure measurements, some of which are diminished during night-time measurements.

The difference in the predictive value of systolic BPV for stroke between the active and placebo groups, is not the effect of treatment on BPV (because after adjusting for blood pressure level the systolic BPV was unaffected by treatment). This difference between the active and placebo groups is most likely to be the result of lower incidence of stroke in the active treatment group (due to the lowering of systolic blood pressure level with antihypertensive medications). BPV was not predictive for the secondary endpoints, cardiac events and cardiovascular mortality. The individual contribution that BPV makes to outcomes such as stroke, myocardial infarction, sudden death and peripheral vascular disease will vary with each of these pathologies. It is likely that the combination of low event rates and outcome heterogeneity led to the lack of predictive value for BPV and the secondary endpoints.

The mechanisms controlling BPV have not been elucidated precisely. There is a growing body of evidence to suggest that BPV is influenced by a number of neural, humoral, behavioural and structural factors [24]. In particular, an age-related degeneration of the arterial baroreflex has been correlated with increasing systolic BPV [25]. Further, increasing arterial stiffness (measured by pulse pressure) was associated with increasing systolic BPV in the Ohasama study.

In this current study, increased night-time systolic BPV was a risk factor for stroke, and was unchanged by antihypertensive treatment when adjusted for blood pressure level. Could night-time systolic BPV, at the pathological level, indicate the extent of the atherosclerotic process and baroreflex degeneration that is currently irreversible?

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The investigators who took part in the Study on Ambulatory Blood Pressure Monitoring are listed in Emelianov *et al*. [8].