Relationship between ambulatory blood pressure and follow-up clinic blood pressure in elderly patients with systolic hypertension

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Background **Patients with elevated clinic blood pressure and normal ambulatory blood pressure have a better prognosis than patients with sustained ambulatory hypertension, and may not have to be treated with antihypertensive drugs. On the contrary, current guidelines emphasize repeated clinic blood pressure measurements for the initiation of antihypertensive therapy.**

Objective **To examine the relationship between ambulatory blood pressure at baseline and clinic blood pressure after 6 months of follow-up in untreated hypertensive patients, and the relationships of these pressures with the subsequent incidence of cardiovascular events.**

Methods **Patients who were ⩾ 60 years old, with systolic clinic blood pressure of 160–219 mmHg and diastolic pressure < 95 mmHg, participated in the Systolic Hypertension in Europe trial. The relationship between ambulatory blood pressure at baseline and clinic blood pressure after 6 months of follow-up was examined in 295 patients enrolled in the Ambulatory Blood Pressure Monitoring substudy and randomized to the placebo arm, and who were still on double-blind treatment and not taking other antihypertensive drugs after 6 months follow-up.**

Results **Age averaged 70 ± 6 years, 41% were men, and baseline daytime ambulatory blood pressure was 152 ± 16/84 ± 10 mmHg; clinic blood pressure decreased from 173 ± 10/86 ± 6 mmHg at baseline to 163 ± 20/85 ± 9 mmHg at month 6. Systolic daytime ambulatory blood pressure at baseline and systolic clinic blood pressure at month 6 were considered normal if < 140 mmHg. Of the 74 patients with normal systolic daytime ambulatory blood pressure at baseline, only seven (9.5%) had a normal systolic clinic blood pressure during follow-up. Conversely, of the 24 patients with normal follow-up clinic blood pressure, only seven (29%) had a normal systolic daytime ambulatory blood pressure at baseline. The incidence of cardiovascular events beyond the 6-month visit was significantly related to baseline ambulatory blood pressure but not to follow-up clinic pressure.**

Conclusions **Baseline daytime ambulatory blood pressure and follow-up clinic blood pressure do not identify the same patients for antihypertensive treatment. Baseline ambulatory pressure is a better predictor of cardiovascular events than follow-up clinic pressure.** ***J Hypertens*** **22:81–87 © 2004 Lippincott Williams & Wilkins.**

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A list of all Systolic Hypertension in Europe trial participants is available at www.kuleuven.ac.be/hypertension/systeur/index.htm

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Introduction

Approximately 25% of patients with high blood pressure (BP) in the clinic (CBP) have a normal BP on ambulatory blood pressure monitoring (ABP) [1–3]. There is growing evidence that patients with so-called white-coat hypertension (isolated clinic hypertension)

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have a better outcome than patients with sustained hypertension during ABP monitoring, and may not have to be treated with antihypertensive drugs [4–9]. Whereas current guidelines [10–12] consider ABP monitoring for selected patients, the decision to initiate antihypertensive drug treatment is mainly based on repeated CBP measurements, apart from the presence of other risk factors, target organ damage and concomitant clinical conditions such as diabetes and cardiovascular or renal disease. Whereas drug treatment is recommended without much delay in patients at high risk, patients at lower risk should be monitored for several weeks or months, with initiation of drug treatment in cases of persistent CBP elevation in spite of the initiation of lifestyle measures. As far as BP is concerned, guidelines emphasize follow-up CBP, rather than baseline ABP, for the initiation of antihypertensive treatment. The question therefore arises whether patients found hypertensive with high CBP but with normal ABP will develop a normal CBP during follow-up. Conversely, it is not known whether patients whose CBP normalizes during follow-up are the same as those with white-coat hypertension at baseline. Whereas cross-sectional relationships between CBP and ABP have been studied repeatedly [13–15], much less is known on the relationships between baseline ABP and follow-up CBP. Data from the Ambulatory Blood Pressure Monitoring side project of the Systolic Hypertension in Europe (Syst-Eur) trial [16] allow us to address this question. In the Syst-Eur trial [17], 4695 older patients with isolated systolic hypertension were randomized to active treatment or matching placebo and, after termination of the double-blind part of the trial, patients were followed-up on active treatment for another 5 years [18]. ABP was monitored during the single-blind placebo run-in period in 717 participants in the ABP monitoring side project. In the current analysis, we examine the relationships between baseline ABP and CBP after 6 months of follow-up in patients randomized to the placebo group. In addition, we report on the incidence of cardiovascular events after the 6-month visit in relation to these blood pressures.

Methods

Trial design

The protocol of the Syst-Eur trial [17] was approved by the Ethics Committee of the University of Leuven and of the participating centers; all subjects gave informed consent. Eligible patients had to be at least 60 years old. During the run-in period on placebo treatment they were seen at three baseline visits 1 month apart. CBP was measured twice in the sitting position at each visit, using standard sphygmomanometry. Patients could be admitted to the double-blind phase of the trial when they had an average run-in systolic CBP of 160–219 mmHg with diastolic CBP < 95 mmHg. After stratification by center, sex and previous cardiovascular complications, the patients were randomized to double-blind treatment with active medication or matching placebo. Open label medication was allowed for a maximum of 3 months. At each 3-monthly visit the CBP was measured twice in the sitting position and the two pressures were averaged. Biochemical measurements included serum cholesterol (mmol/l) and serum creatinine (μmol/l). After the end of the double-blind part of the trial [17], the patients of the control group were switched to the active study treatment regimen and followed-up for another 5 years [18].

ABP monitoring

Of the 198 Syst-Eur centers, 46 agreed to enroll all their patients in the substudy on ABP monitoring, using properly validated and calibrated monitors and appropriate cuff size [16]. All monitors were programmed to record the BP over an entire 24-h period at intervals no longer than 30 min. At least 80% of the required recordings had to be available for inclusion in the analysis. Editing criteria encoded in the monitor were disabled or set at limits as wide as possible. No further editing was performed after data acquisition. Means of ambulatory measurements were weighted by the time interval between consecutive readings. Day and night were defined using short fixed clock time periods, ranging from 1000 to 2000 h and from 000 to 0600 h [19].

Classification of subgroups

Patients were classified in subgroups according to the average daytime ABP at baseline, and according to the CBP at the 6-month visit; only systolic BP was considered in these patients with isolated systolic hypertension. In agreement with current guidelines [10–12] 140 and 160 mmHg were used as cut-off values to define three subgroups for follow-up CBP. According to the recommendations of the Working Group on BP Monitoring of the European Society of Hypertension [20], a daytime ABP > 140 mmHg is abnormal and a pressure < 135 mmHg is considered normal. In our primary analysis we used 140 mmHg as the lower cut-off point for daytime ABP. Some relevant results are also given on the smaller number of patients with daytime ABP < 135 mmHg. An ABP level of 160 mmHg was taken as the higher cut-off point for daytime ABP.

Cardiovascular events during follow-up

With regard to outcome we considered cardiovascular events, which occurred after the 6-month follow-up visit, including the extended follow-up part of the Syst-Eur trial [18]. Cardiovascular events comprised cardiovascular death, all stroke, all myocardial infarction and all heart failure, as previously described [17]. The analysis on outcome was performed according to the intention-to-treat principle.

Statistical analysis

Database management and statistical analysis were performed with SAS software, version 6.12 (SAS Institute Inc., Cary, North Carolina, USA). Data are reported as means ± standard deviations. Within-group comparisons were performed by paired Student's *t* test. Comparisons among groups were done by one-way analysis of variance; in case of significance of the overall *P* value, intergroup comparisons were made by Scheffe's multiple means tests. Relationships between variables were studied by use of single regression analysis. Rates of events were calculated as the number of events divided by the total follow-up time and are expressed as events/1000 patient-years. All tests were two-sided. $P < 0.05$ was considered significant.

Results

Patient population

ABP monitoring was performed during the single-blind placebo run-in period in a total of 717 patients, of whom 695 had successful measurements. The current analysis was restricted to patients randomized to the placebo group, who were still on double-blind treatment and not taking other antihypertensive drugs after 6 months of follow-up. Among the 353 patients of the placebo group, 310 were still on double-blind treatment after 6 months. Fifteen patients were taking open-label antihypertensive medication, leaving 295 patients for further analysis. Their age averaged 70.0 ± 6.1 years, the body mass index was 26.8 ± 3.9 kg/m^2, and 41% were men. The mean of six CBPs was 173 ± 10/86 ± 6 mmHg, daytime ABP was 152 ± 16/84 ± 10 mmHg and night-time ABP 133 ± 17/70 ± 10 mmHg. During the run-in period, CBP averaged 174 ± 13/87 ± 7 mmHg at the first visit, and 174 ± 14/87 ± 8 and 171 ± 13/85 ± 7 mmHg, respectively, at the second and third visits. Serum creatinine averaged 89.0 ± 17.4 μmol/l and serum cholesterol 6.02 ± 1.02 mmol/l. Ten percent of the patients were current smokers, 10% had diabetes, 2.0% a history of myocardial infarction and 1.4% a history of stroke. These characteristics were similar in the 58 patients who were excluded from the analysis.

Follow-up clinic blood pressure

In the 295 patients, systolic CBP decreased from 172.8 ± 10.4 mmHg at baseline to 162.8 ± 19.7 mmHg after 6 months of follow-up ($P < 0.001$), whereas diastolic CBP decreased from 86.2 ± 5.9 to 85.0 ± 9.1 mmHg ($P < 0.05$). A small change in heart rate, from 73.3 ± 9.1 to 72.3 ± 9.7 beats/min, was also observed ($P < 0.05$).

General characteristics according to blood pressure category

Tables 1 and 2 summarize the general characteristics of the patients at baseline, either according to baseline systolic daytime ABP or according to follow-up systolic CBP. Subgroups did not differ with regard to age, gender, body mass index or heart rate. The ABP and CBP, except diastolic CBP, increased with higher levels of systolic daytime ABP. Patients with higher systolic CBP at follow-up had higher systolic BPs at baseline. Serum cholesterol, serum creatinine, current smoking, and prevalence of diabetes and history of myocardial infarction did not differ between the groups. The subgroup with systolic daytime ABP ⩾ 160 mmHg included more patients with a history of stroke than the

Table 1 Baseline characteristics in three subgroups according to systolic daytime ambulatory blood pressure (ABP) at baseline

	Systolic daytime ABP at baseline			
	< 140 mmHg	140–159 mmHg	⩾ 160 mmHg	*P*[a]
Number	74	134	87	–
Age (years)	70.3 ± 5.7	69.7 ± 6.2	70.1 ± 6.2	0.78
Gender (% men)	39	44	39	0.70
Body mass index (kg/m^2)	27.2 ± 3.8	26.4 ± 4.0	27.1 ± 3.7	0.22
Heart rate (beats/min)	71.3 ± 8.0	74.3 ± 9.2	73.6 ± 9.7	0.08
Systolic blood pressure (mmHg)				
Ambulatory				
Daytime	132.6 ± 5.5	149.6 ± 5.5	172.2 ± 9.9	–
Night-time	119.1 ± 11.8	131.5 ± 13.5*	148.8 ± 14.4*,**	< 0.001
Clinic	168.6 ± 6.4	171.5 ± 9.1	178.4 ± 12.6*,**	< 0.001
Diastolic blood pressure (mmHg)				
Ambulatory				
Daytime	78.1 ± 7.6	83.6 ± 8.8*	90.7 ± 10.5*,**	< 0.001
Night-time	66.6 ± 8.2	69.3 ± 8.6	75.3 ± 10.9*,**	< 0.001
Clinic	85.6 ± 5.1	86.2 ± 6.7	86.9 ± 5.4	0.39

Values presented as mean ± standard deviation or percentage of patients. *P* values are from multiple means tests. [a]*P* values from one-way analysis of variance. *$P \leq 0.05$ versus systolic daytime ABP < 140 mmHg. **$P \leq 0.05$ versus systolic daytime ABP of 140–159 mmHg.

Table 2 Baseline characteristics in three subgroups according to systolic clinic blood pressure (CBP) after 6 months of follow-up

	Systolic daytime CBP at 6 months			
	<140 mmHg	140–159 mmHg	⩾ 160 mmHg	P^a
Number	24	116	155	
Age (years)	70.7 ± 5.5	69.2 ± 5.6	70.4 ± 6.5	0.26
Gender (% men)	37	44	40	0.75
Body mass index (kg/m^2)	27.5 ± 5.1	26.3 ± 3.6	27.1 ± 3.9	0.22
Heart rate (beats/min)	73.7 ± 9.2	72.8 ± 8.4	73.4 ± 9.7	0.74
Systolic blood pressure (mmHg)				
Ambulatory				
Daytime	146.5 ± 14.3	146.5 ± 15.3	156.9 ± 15.9*,**	< 0.001
Night-time	128.3 ± 15.3	128.3 ± 16.1	138.2 ± 17.3*,**	< 0.001
Clinic	169.8 ± 10.8	167.9 ± 6.1	176.9 ± 11.2*,**	< 0.001
Diastolic blood pressure (mmHg)				
Ambulatory				
Daytime	84.1 ± 9.7	83.6 ± 11.3	84.8 ± 9.3	0.60
Night-time	68.8 ± 11.5	70.1 ± 9.5	70.9 ± 9.8	0.57
Clinic	85.1 ± 5.0	86.1 ± 5.6	86.5 ± 6.3	0.53

Values presented as mean ± standard deviation or percentage of patients. *P* values are from multiple means tests. [a]*P* values from one-way analysis of variance. *$P \leqslant 0.05$ versus systolic daytime ABP < 140 mmHg. **$P \leqslant 0.05$ versus systolic daytime ABP of 140–159 mmHg.

other groups (4.6 versus 0%; $P < 0.01$), but stroke prevalence did not differ according to follow-up CBP.

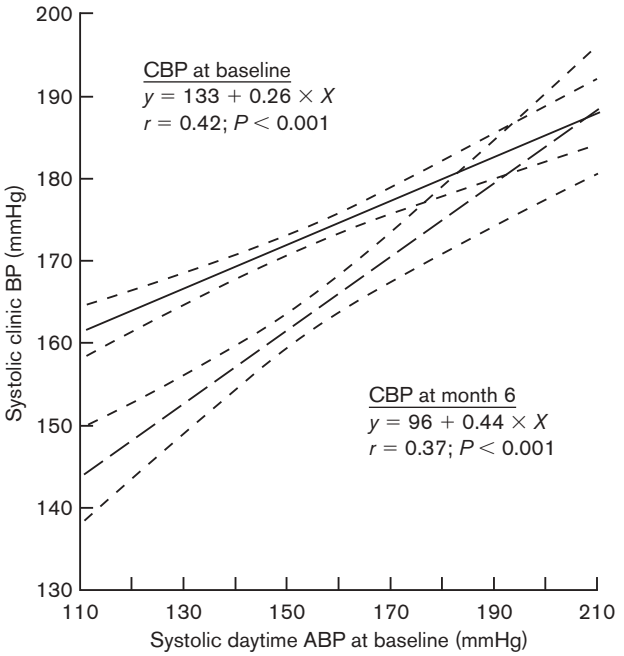
Relationships between ambulatory and clinic blood pressure

Figure 1 illustrates the relationships between systolic daytime ABP at baseline, and, respectively, systolic CBP at baseline and systolic CBP after 6 months of follow-up. Both CBPs were significantly related to ABP at baseline. The relationship was significantly steeper for follow-up CBP than for baseline CBP ($P = 0.002$). The regression equations were similar in men and women. Baseline systolic daytime ABP (X) was a significant predictor of the change in systolic CBP from baseline to month 6 (Y): $Y = -36.8 + 0.18 \times X$ ($r = +0.18$; $P = 0.002$); CBP decreased more when baseline ABP was low.

Table 3 summarizes the number of patients in each of nine subcategories according to the three categories based on systolic daytime ABP at baseline and the three categories based on systolic CBP at month 6. Of the 74 patients with baseline systolic daytime ABP < 140 mmHg, only seven (9.5%) had a normal systolic CBP (< 140 mmHg) during follow-up, whereas systolic CBP remained ⩾ 160 mmHg in 22 (30%) patients. Among 87 patients with systolic daytime ABP ⩾ 160 mmHg at baseline, 62 (71%) also had a systolic CBP ⩾ 160 mmHg at month 6. Systolic CBP normalized in 24 patients during follow-up, of whom seven (29%) had a systolic daytime ABP at baseline of < 140 mmHg.

Systolic daytime ABP at baseline was < 135 mmHg in 45 patients. CBP at month 6 was < 140 mmHg in four of these patients (8.9%), between 140 and 159 mmHg in 30 (67%) patients and ⩾ 160 mmHg in 11 (24%) patients. Among the 24 patients with normal systolic CBP after 6 months, baseline daytime systolic ABP was < 135 mmHg in only four patients (17%).

Fig. 1



Relationship of systolic daytime ambulatory blood pressure (ABP) at baseline with, respectively, systolic clinic blood pressure (CBP) at baseline, and systolic CBP after 6 months of follow-up. The figure shows the regression lines and the 95% confidence limits. The slopes are significantly different ($P = 0.002$).

Table 3 Distribution of patients according to systolic daytime ambulatory blood pressure (ABP) at baseline and systolic clinic blood pressure (CBP) after 6 months of follow-up

	Systolic daytime ABP at baseline			
Systolic CBP at month 6	< 140 mmHg	140–159 mmHg	⩾ 160 mmHg	All
< 140 mmHg	7	12	5	24
140–159 mmHg	45	51	20	116
⩾ 160 mmHg	22	71	62	155
All	74	134	87	295

Data presented as numbers of patients.

Cardiovascular events

The median follow-up time after the 6-month visit was 7.5 years, ranging from 0.5 to 13 years. During this period, 58 of the 295 patients suffered a cardiovascular event, which corresponds to a rate of 28.1 events per 1000 patient years. Table 4 presents the results in the nine subgroups. In the three groups according to systolic daytime ABP, the event rate increased with increasing levels of ABP; the event rate was significantly ($P = 0.02$) higher in patients with ABP ⩾ 160 mmHg (40.5) than in patients with ABP < 140 mmHg (18.9). There were no significant differences among the three groups based on follow-up CBP. It is unlikely that these results have been confounded by other risk factors such as age, gender, relative weight, serum cholesterol, smoking, diabetes and heart rate because they did not differ among the subgroups. Finally, six of the 45 patients with daytime systolic ABP < 135 mmHg suffered a cardiovascular event (event rate, 19.3 events per 1000 patient-years).

Discussion

The major findings of the present study in older patients with systolic hypertension randomized to the placebo arm of the Syst-Eur trial are: (1) that there is a poor relationship between ABP at baseline and follow-up CBP, (2) that patients with normal ABP at baseline do not necessarily develop a normal CBP during follow-up, and (3) that patients with normal CBP during follow-up did not necessarily have a normal ABP at baseline. In addition, baseline ABP predicted the incidence of cardiovascular events, which was not the case for follow-up CBP.

These findings have consequences for patient management. It has indeed been shown that white-coat hypertension is associated with a better prognosis than sustained ambulatory hypertension [4–9]. Verdecchia *et al.* [4] even observed that cardiovascular outcome was similar in patients with white-coat hypertension and in true normotensive subjects with normal CBP and normal ABP. The better outcome in white-coat hypertension than in sustained hypertension was also observed in the double-blind part of the Syst-Eur trial [7]. The incidence of stroke was 7.3 per 1000 patient-years in patients with systolic daytime ABP < 140 mmHg and this figure amounted to 27.8 when this pressure was ⩾ 160 mmHg ($P = 0.03$). The rates of cardiovascular events were, respectively, 22.1 and 59.5 events per 1000 patient-years ($P = 0.01$). In addition, antihypertensive drug treatment did not significantly affect the incidence of stroke and of cardiovascular complications when the systolic daytime ABP was low. These findings suggest that patients with white-coat hypertension may not have to be treated with antihypertensive drugs, but that careful monitoring and appropriate non-pharmacological measures may suffice. However, if one accepts that patients whose CBP does not normalize after 6 months of follow-up require antihypertensive treatment, drugs should be instituted in 90% of these patients, despite the normal ABP at baseline. Systolic CBP was normal in only 24 of the 295 patients after

Table 4 Incidence of cardiovascular events, beyond the 6-month visit, according to systolic daytime ambulatory blood pressure (ABP) at baseline and systolic clinic blood pressure (CBP) after 6 months of follow-up

	Systolic daytime ABP at baseline			
Systolic CBP at month 6	< 140 mmHg	140–159 mmHg	⩾ 160 mmHg	All
< 140 mmHg	2/7 (–)	2/12 (–)	2/5 (–)	6/24 (34.7)
140–159 mmHg	5/45 (16.2)	8/51 (24.9)	6/20 (45.9)	19/116 (25.0)
⩾ 160 mmHg	3/22 (–)	13/71 (25.4)	17/62 (37.5)	33/155 (29.1)
All	10/74 (18.9)	23/134 (24.9)	25/87 (40.5)*	58/295 (28.1)

Data presented as number of events/number of patients (rate of events per 1000 patient-years). Rates in subgroups are only given when ⩾ 5 cardiovascular events occurred. *$P = 0.02$ versus ABP < 140 mmHg.

6 months of follow-up. However, baseline systolic daytime ABP was ⩾ 140 mmHg in 71% of these patients (⩾ 135 mmHg in 83%), so that drug treatment would have been indicated according to ABP after the baseline observations, but not according to follow-up CBP.

It is difficult to compare our results with those from previous studies because of different study populations and study design. Nevertheless, our results are in keeping with the general conclusion that baseline ABP and follow-up CBP do not identify the same patients for the initiation of antihypertensive treatment or as having sustained hypertension. Chatellier *et al.* [21] studied the predictive value of one baseline daytime ABP monitoring for the initiation of antihypertensive treatment according to the 1989 World Health Organization/International Society of Hypertension guidelines for the management of mild hypertension. Patients with diastolic CBP of 90–104 mmHg at the second clinic visit were followed up over 6 months. The authors concluded that the predictive value of ABP, that is a diastolic ABP of two standard deviations above age-specific values in normotensive volunteers, was too low to detect with confidence those patients who need treatment according to the 1989 World Health Orgnization/International Society of Hypertension guidelines. Stergiou *et al.* [22] investigated whether BP measurement by ABP monitoring is a reliable alternative to the traditional strategy for the diagnosis of hypertension based on BP measurement on repeated clinic visits over 3 months. They enrolled patients with a diastolic CBP of 90–115 mmHg and systolic CBP < 180 mmHg on the initial visit. The same BP threshold of at least 140 mmHg systolic, of at least 90 mmHg diastolic, or both, was used for the diagnosis of hypertension using each method, i.e. at the last clinic visit, or the average awake ABP of two recordings. Disagreement between CBP and ABP was observed in 27% of the patients. Finally, Palatini [23] observed that ABP was not a good predictor of the systolic CBP fall during the following 6 months of observation in 66 elderly subjects with mild hypertension.

The question arises whether the decision to initiate antihypertensive therapy should be based on baseline ABP or on follow-up CBP. Our data on outcome could favor the baseline ABP because ABP significantly predicted subsequent cardiovascular events, whereas CBP after 6 months of follow-up did not.

The present study confirms the substantial difference between systolic CBP and systolic daytime ABP at baseline in older patients with systolic hypertension [15]. In addition, CBP decreased further during follow-up on placebo, despite the fact that in these patients baseline CBP was the mean of three duplicate measurements over a 3-month period. The drop in CBP appeared to be most pronounced in patients with low systolic daytime ABP at baseline.

A number of limitations have to be considered with regard to the present findings. The analysis was performed in older patients with systolic hypertension defined as systolic CBP ⩾ 160 mmHg and diastolic CBP < 95 mmHg. Furthermore, the baseline CBP was the average of two CBPs at each of three visits 1 month apart. Results are likely to differ in other patient populations and with less frequent or standardized CBP measurements. Nevertheless, Chatellier *et al.* [21] and Stergiou *et al.* [22] reached similar conclusions from differently designed studies. Whereas the definitions of hypertension and of grades of severity of hypertension are well established [10–12], there is as yet no definitive definition of white-coat hypertension, and particularly isolated systolic white-coat hypertension. We used 140 mmHg as the cut-off point for systolic daytime ABP in our primary analysis, but also presented data for the lower level of 135 mmHg [20]. We have based our analysis on the CBP after 6 months of follow-up. It could be argued that the CBP would normalize in more patients after a longer follow-up period. However, the average CBP remained stable beyond 6 months in the placebo group of the Syst-Eur trial [17]. The classification of patients in subgroups according to ABP might have been different if more than one 24-h recording was taken due to regression-to-the-mean [24]. In addition, ABP monitoring was not systematically performed at month 6. However, recordings after 1 year showed that the average ABP differed only slightly from the baseline values [25]. With regard to outcome, the present analysis is based on a small subgroup of patients from the Syst-Eur trial, so the number of events is relatively small. Larger studies are therefore warranted to assess the relationship between, respectively, baseline ABP and follow-up CBP, and the incidence of cardiovascular events.

In conclusion, the selection of older patients with isolated systolic hypertension for antihypertensive treatment differs according to whether the decision is based on baseline ABP or on follow-up CBP. Data on outcome may favor baseline ABP.

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