Response to Antihypertensive Therapy in Older Patients With Sustained and Nonsustained Systolic Hypertension

Robert H. Fagard, MD; Jan A. Staessen, MD; Lutgarde Thijs, BSc; Jerzy Gasowski, MD; Christopher J. Bulpitt, MD; Denis Clement, MD; Peter W. de Leeuw, MD; Jurij Dobovisek, MD; Matti Jääskivi, MD; Gastone Leonetti, MD; Eoin O'Brien, MD; Paolo Palatini, MD; Gianfranco Parati, MD; José L. Rodicio, MD; Hannu Vanhanen, MD; John Webster, MD; for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators

Background—The goal of the present study was to assess the effect of antihypertensive therapy on clinic (CBP) and ambulatory (ABP) blood pressures, on ECG voltages, and on the incidence of stroke and cardiovascular events in older patients with sustained and nonsustained systolic hypertension.

Methods and Results—Patients who were ≥60 years old, with systolic CBP of 160 to 219 mm Hg and diastolic CBP of <95 mm Hg, were randomized into the double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) Trial. Treatment consisted of nitrendipine, with the possible addition of enalapril, hydrochlorothiazide, or both. Patients enrolled in the Ambulatory Blood Pressure Monitoring Side Project were classified according to daytime systolic ABP into 1 of 3 subgroups: nonsustained hypertension (<140 mm Hg), mild sustained hypertension (140 to 159 mm Hg), and moderate sustained hypertension (≥160 mm Hg). At baseline, patients with nonsustained hypertension had smaller ECG voltages ($P<0.001$) and, during follow-up, a lower incidence of stroke ($P<0.05$) and of cardiovascular complications ($P=0.01$) than other groups. Active treatment reduced ABP and CBP in patients with sustained hypertension but only CBP in patients with nonsustained hypertension ($P<0.001$). The influence of active treatment on ECG voltages ($P<0.05$) and on the incidence of stroke ($P<0.05$) and cardiovascular events ($P=0.06$) was more favorable than that of placebo only in patients with moderate sustained hypertension.

Conclusions—Patients with sustained hypertension had higher ECG voltages and rates of cardiovascular complications than did patients with nonsustained hypertension. The favorable effects of active treatment on these outcomes were only statistically significant in patients with moderate sustained hypertension. **(*Circulation*. 2000;102:1139-1144.)**

Key Words: blood pressure monitoring ■ aging ■ hypertrophy, left ventricular ■ prognosis ■ hypertension, white coat ■ trials

Ambulatory blood pressure (ABP) may be normal in patients with elevated clinic pressure (CBP). This subgroup of so-called white coat, isolated clinic or nonsustained hypertensives composes ≈25% of the hypertensive population.[1–3] This phenomenon has been extensively studied in hypertensives in general but not in isolated systolic hypertension (ISH), which is present in ≈10% of the elderly in the seventh decade of life and in even 25% of octogenarians.[4] With regard to target organ damage, left ventricular mass appeared to be lower in white coat hypertensives than in patients with sustained hypertension,[5–9] and prognostic studies in hypertensives in general[8,10] and in patients with refractory hypertension[11] revealed that the morbidity or mortality risk was less in patients with low ABP than in patients in whom hypertension was sustained during ambulatory monitoring. On the other hand, when the initiation[12,13] or intensification[14] of antihypertensive therapy was based on CBP measurements in patients with elevated CBP and low ABP, CBP was significantly reduced, whereas ABP hardly changed. The latter finding together with the contention of

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From the Hypertension and Cardiovascular Rehabilitation Unit (R.H.F., J.A.S., L.T., J.G.), Catholic University of Leuven, Leuven, Belgium; Imperial College (C.J.B.), Hammersmith Hospital, London, UK; Department of Cardiology (D.C.), University of Gent, Gent, Belgium; Department of Internal Medicine (P.W.d.L.), University of Maastricht, Maastricht, the Netherlands; Hypertension Division (J.D.), University Medical Center, Ljubljana, Slovenia; Department of Epidemiology and Health Promotion (M.J.), National Public Health Institute, Helsinki, Finland; Istituto Auxologico Italiano (G.L., G.P.), Ospedale San Luca, Milano, Italy; Beaumont Hospital (E.O.), Dublin, Ireland; Clinica Medica IV (P.P.), Universitá di Padova, Padova, Italy; Hospital "12de Octubre" (J.L.R.), Madrid, Spain; Department of Medicine (H.V.), Helsinki University Central Hospital, Helsinki, Finland; and Department of Medicine and Therapeutics (J.W.), University of Aberdeen, Aberdeen, UK.

A list of all Syst-Eur Trial participants is given in the Appendix, which may be found Online at www.circulationaha.org

Correspondence to R. Fagard, MD, PhD, Department of Medicine, U.Z. Gasthuisberg–Hypertensie, Herestraat 49 B-3000, Leuven, Belgium. E-mail robert.fagard@uz.kuleuven.ac.be

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some investigators that white coat hypertension may not be innocuous[9,15] might favor the initiation of drug treatment in these patients. To obtain a better insight into the cardiovascular consequences of nonsustained systolic hypertension in the elderly and the impact of antihypertensive therapy, we analyzed the data from the Ambulatory Blood Pressure Monitoring Side Project[16,17] of the Systolic Hypertension in Europe (Syst-Eur) Trial,[18] an outcome trial of antihypertensive treatment in older patients with ISH. To the best of our knowledge, the Syst-Eur Trial is the only randomized placebo-controlled trial available that included ABP monitoring in its design.[16]

Methods

Trial Design

The protocol of the Syst-Eur Trial[18] was approved by the ethics committees of the University of Leuven and of the participating centers; all subjects gave informed consent. Eligible patients had to be ≥60 years old. During the run-in period on placebo treatment, patients were seen at 3 baseline visits ≥1 month apart. CBP was measured twice in the sitting position at each visit by use of standard sphygmomanometry. Patients could be admitted to the double-blind phase of the trial when they had an average run-in systolic blood pressure (BP) of 160 to 219 mm Hg with diastolic BP of <95 mm Hg. After stratification by center, sex, and previous cardiovascular complications, the patients were randomized to double-blind treatment with active medication or matching placebo. Active treatment consisted of nitrendipine (10 to 40 mg/d), which could be combined with or replaced by enalapril (5 to 20 mg/d), hydrochlorothiazide (12.5 to 25 mg/d), or both drugs, to reduce the sitting systolic BP by ≥20 mm Hg or to <150 mm Hg. At each 3-monthly visit, CBP was measured twice in the sitting position, and the 2 BPs were averaged. ECG was performed yearly. ECG left ventricular mass was estimated as the sum of the S wave in lead V_1 and the R waves in leads aVL and V_5 and is expressed in millivolts.[19] Biochemical measurements included serum cholesterol (mmol/L) and serum creatinine (μmol/L).

ABP Monitoring

Of the 198 Syst-Eur centers, 46 agreed to enroll all of their patients in the substudy on ABP monitoring, which involved recordings at entry, at 6 and 12 months, and annually thereafter with properly validated and calibrated monitors and appropriate cuff size.[16,17] All monitors were programmed to record BP during an entire 24-hour period at intervals of ≤30 minutes. 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. Mean values of ambulatory measurements were weighted by the time interval between consecutive readings. Day and night were defined with short fixed clock time periods that ranged from 10 AM to 8 PM and from midnight to 6 AM.[20]

Because there is no consensus on the cutoff values for ABP in ISH, we arbitrarily defined 3 subgroups on the basis of the average daytime systolic ABP. In accordance with cutoff values for conventional systolic BP,[21,22] patients were classified as having moderate sustained hypertension (MoSH), mild sustained hypertension (MiSH), or nonsustained hypertension (Non-SH) when daytime systolic ABP averaged ≥160 mm Hg, 140 to 159 mm Hg, or <140 mm Hg, respectively.

Follow-Up

The analysis of the changes of BP during follow-up was restricted to patients who had ≥1 repeat ABP monitoring within 2 years after randomization and who were still on double-blind treatment and not taking other antihypertensive drugs. If >1 monitoring was performed within that period, that closest to 12 months after randomization was used for the analysis. The ECG analysis was also based on the recordings closest to the 1-year visit.

The analyses on outcome were performed according to the intention-to-treat principle. Stroke was the primary end point of the Syst-Eur Trial and was defined as a neurological deficit with symptoms that continued for >24 hours or led to death with no apparent cause other than vascular. The incidence of all cardiovascular events was the second end point for the present study and included sudden death and fatal and nonfatal stroke, myocardial infarction, and heart failure, as described previously.[18]

Statistical Analysis

Database management and statistical analysis were performed with SAS software, version 6.12 (SAS Institute Inc). Data are reported as mean±SD or ±SEM values. Analyses of the data were performed by Student's paired and unpaired *t* tests or by ANOVA and ANCOVA. Rates of events were calculated as the number of events divided by the total follow-up time and are expressed as events/1000 patient-y; these rates were compared between the active treatment and placebo groups.[23] All tests were 2-sided.

Results

Patient Characteristics at Baseline

ABP monitoring was performed at baseline in a total of 717 patients, of whom 695 had successful measurements. The mean age was 70.0±6.3 years, the mean body mass index (BMI) was 26.6±4.0 kg/m^2, and 38% were men. The mean of the 6 CBPs was 174±11/86±6 mm Hg, and 24-hour ABP averaged 147±16/80±9 mm Hg. Forty-three percent of the patients had received antihypertensive therapy in the past, and 9% were current smokers. Serum creatinine levels averaged 88.2±17.6 μmol/L, and serum cholesterol levels averaged 6.03±1.13 mmol/L. These baseline characteristics did not differ significantly between the 342 patients randomized to active treatment and the 353 patients randomized to the placebo group and were in general similar to the characteristics of the total Syst-Eur Trial population (n=4695).[18]

Daytime systolic ABP was <140 mm Hg in 167 patients, between 140 and 159 mm Hg in 326 patients, and ≥160 mm Hg in 202 patients. The Table 1 shows the characteristics of the 3 subgroups. Age, sex, and BMI did not differ between these groups. Diastolic daytime and systolic and diastolic nighttime and clinic BPs were higher in sustained than in nonsustained hypertensives, except for diastolic CBP (P=0.36). Within each group, baseline characteristics did not differ according to whether patients were allocated to active or to placebo treatment.

The sum of three ECG voltages averaged 3.23±1.0 mV at baseline and did not differ according to treatment group. However, the voltages increased from Non-SH to MiSH and MoSH (P<0.001) (Table 1). The differences in voltages among the 3 groups remained significant after adjustment for systolic CBP (P=0.005) but not after control for daytime systolic ABP (P=0.91).

Follow-Up

BP and Heart Rate

ABP was available in 465 patients on double-blind treatment after an average of 11.7±3.4 months of follow-up, which was similar in the various subgroups. Seven patients were taking open-label antihypertensive medication, leaving 458 patients

TABLE 1. Baseline Characteristics in 3 Subgroups According to Daytime Systolic BP

	Non-SH	MiSH	MoSH
n	167	326	202
Age, y	69.3±5.6	70.1±6.5	70.5±6.4
Sex, % men	37.1	37.4	38.6
BMI, kg/m^2	26.9±4.3	26.3±3.9	26.8±3.8
Systolic BP, mm Hg			
Daytime	132.3±6.0	149.8±5.6*	172.1±10.3*†
Nighttime	118.8±13.4	133.4±14.2*	149.9±17.9*†
Clinic	168.0±6.5	172.7±9.9*	179.7±13.2*†
Diastolic BP, mm Hg			
Daytime	78.5±7.8	83.4±8.2*	90.5±10.9*†
Nighttime	66.8±8.5	69.5±8.7*	74.9±12.0*†
Clinic	86.0±5.3	85.5±6.3	86.2±5.8
Heart rate, bpm			
Daytime	73.6±9.7	74.7±9.8	75.2±10.5
Nighttime	61.1±8.2	62.3±8.9	63.2±9.1
Clinic	73.1±9.0	73.9±9.0	74.2±9.0
Previous antihypertensive therapy, %	31.1	41.7	54.0*
Current smoking, %	4.2	9.2	12.4*
Serum creatinine, μmol/L	86.0±17.2	88.2±16.9	89.9±18.8
Serum cholesterol, mmol/L	6.02±1.06	5.98±1.13	6.11±1.16
ECG voltages ($RaV_L+SV_1+RV_5$), mV	2.94±0.08	3.22±0.09*	3.50±1.13*†

Values are given as mean±SD or percent of patients.
*$P\leq0.05$ vs non-SH.
†$P\leq0.05$ vs MiSH.

for further analysis. Table 2 summarizes the study treatment at the time of the repeat ABP monitoring in the 6 subgroups. More patients progressed to dual and triple antihypertensive therapy in the sustained than in the nonsustained hypertensive groups. Figures 1 and 2 illustrate the changes in systolic and diastolic BPs, respectively. Within the active treatment group, daytime and nighttime ABPs decreased significantly in patients with sustained hypertension but not in patients with nonsustained hypertension; by contrast, CBP was reduced in all 3 subgroups. Active treatment reduced ABP and CPB more than placebo in MiSH and MoSH. In Non-SH, however, there were no significant differences between the treatment groups with regard to the changes in ABP except for daytime systolic BP; the changes in both systolic and diastolic CBPs were more pronounced in the active treatment group than in the placebo group. Changes in daytime, nighttime, and clinic

TABLE 2. Antihypertensive Therapy During Follow-Up

	Placebo Treatment			Active Treatment		
	Non-SH	MiSH	MoSH	Non-SH	MiSH	MoSH
n	48	107	70	51	116	66
Monotherapy, %	63.8	57.6	34.4	80.4	73.9	66.7
N	61.7	51.9	28.6	70.6	67.8	59.1
E	0.0	3.8	2.9	2.0	3.5	6.1
HCT	2.1	1.9	2.9	7.8	2.6	1.5
Dual therapy, %	25.5	24.5	32.9	19.7	22.6	27.3
N+E	21.3	20.8	27.1	15.7	18.3	16.7
N+HCT	2.1	2.8	2.9	2.0	2.6	3.0
E+HCT	2.1	0.9	2.9	2.0	1.7	7.6
Triple therapy, %						
N+E+HCT	10.6	17.9	32.9	0.0	3.5	6.1

Values are given as number or percent of patients.
N indicates nitrendipine; E, enalapril; and HCT, hydrochlorothiazide.

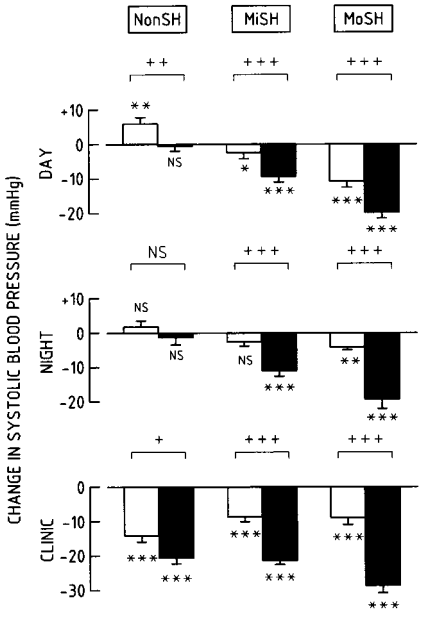

Figure 1. Mean±SEM changes in daytime, nighttime, and conventional clinic systolic BP (mm Hg) in patients with Non-SH, MiSH, and MoSH, divided according to treatment group (open columns, placebo treatment; filled columns, active treatment). Analysis is based on data obtained closest to 1 year after randomization. *$P\leq0.05$, **$P\leq0.01$, ***$P\leq0.001$ for within-group comparison between baseline and follow-up. +$P\leq0.05$, ++$P\leq0.01$, +++$P\leq0.001$ for comparison of changes between active and placebo treatment.

heart rate from baseline to follow-up averaged 0.1±8.5, −0.4±6.7, and −0.3±9.6 bpm, respectively, in all patients combined (NS) and did not differ between the various subgroups.

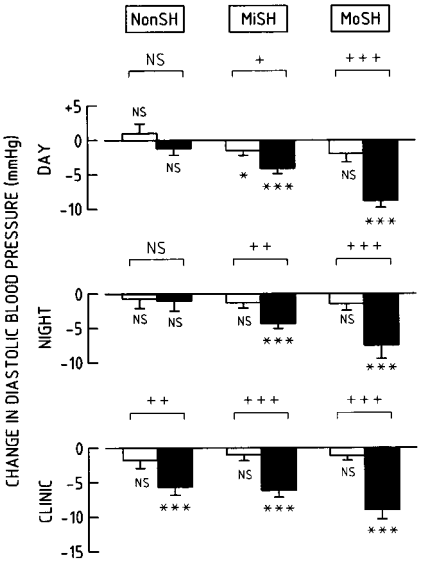

Figure 2. Mean±SEM changes in daytime, nighttime, and conventional clinic diastolic BP (mm Hg) in patients with Non-SH, MiSH, and MoSH, divided according to treatment group (open columns, placebo treatment; filled columns, active treatment). Analysis is based on data obtained closest to 1 year after randomization. *$P\leq0.05$, ***$P\leq0.001$ for within-group comparison between baseline and follow-up. +$P\leq0.05$, ++$P\leq0.01$, +++$P\leq0.001$ for comparison of changes between active and placebo treatment.

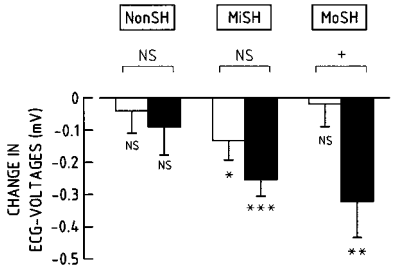

Figure 3. Mean±SEM changes in ECG voltages ($RaV_L+SV_1+RV_5$; mV) in patients with Non-SH, MiSH, and MoSH, divided according to treatment group (open columns, placebo treatment; filled columns, active treatment). Analysis is based on data obtained closest to 1 year after randomization. *$P\leq0.05$, **$P\leq0.01$, ***$P\leq0.001$ for within-group comparison between baseline and follow-up. +$P\leq0.05$ for comparison of changes between active and placebo treatment.

Electrocardiography

Figure 3 shows that active antihypertensive therapy significantly reduced the ECG voltages in patients with sustained hypertension but not in those with Non-SH. The difference between active treatment and placebo was significant only in the group with MoSH.

Cardiovascular Complications

In the placebo group, stroke incidence ($P=0.03$) and the rate of cardiovascular events ($P=0.01$) were significantly higher in patients with MoSH than in nonsustained hypertensives, with intermediate results for those with MiSH. Active treatment significantly reduced the rate of stroke ($P=0.03$) and of all cardiovascular events ($P=0.06$) only in patients with MoSH (Figure 4).

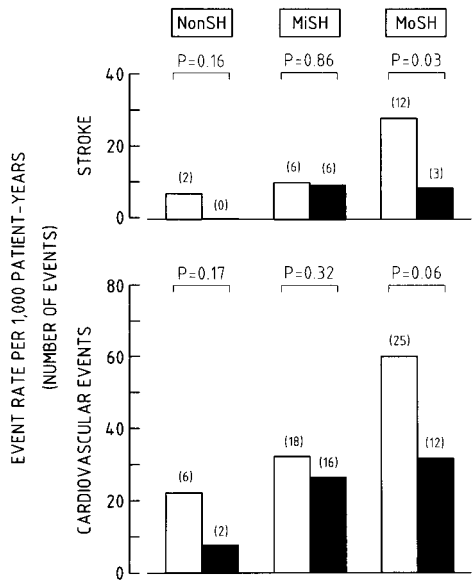

Figure 4. Number of strokes and cardiovascular events per 1000 patient-years and absolute number of events (within parentheses) during follow-up in patients with Non-SH, MiSH, and MoSH, divided according to treatment group (open columns, placebo treatment; filled columns, active treatment). Results are from intention-to-treat analysis. *P* value refers to comparison of rates between 2 treatment groups within each subgroup according to daytime systolic BP.

Discussion

The Syst-Eur Trial included patients ≥60 years old whose CBP averaged ≥160 mm Hg for systolic BP and <95 mm Hg for diastolic BP at 3 run-in visits while on placebo.[18] Of the patients enrolled in the Ambulatory Blood Pressure Monitoring Side Project of the trial,[16,17] daytime systolic ABP was ≥160 mm Hg in 29% of the patients and between 140 and 159 mm Hg in 47%. Although normal values for ABP have not been definitely established, it appears that about one fourth of the Syst-Eur Trial patients had nonsustained, white coat or isolated clinic systolic hypertension. In hypertensive populations in general, echocardiographic left ventricular mass is larger in patients with sustained hypertension than in white coat hypertensives.[5–9] The present study confirms with the use of ECG voltages that the same holds true in older patients with systolic hypertension; moreover, voltage differences among the 3 subgroups clearly depended on ABP. The incidences of stroke and of cardiovascular events were, respectively, primary and secondary end points in the Syst-Eur Trial. In the placebo group, the rate of both end points was low in nonsustained hypertensives and was 3 to 4 times higher in patients with MoSH. These data fit with findings in hypertensives in general,[8,10,24] in refractory hypertensives,[11] or in the general population[25] that white coat hypertension is associated with a better outcome[8,10,11] or that the predictive value of ABP persists after control for clinic or casual BP.[24,25] When the latter approach was applied to the Syst-Eur Trial data,[26] it was found that systolic ABP was a significant predictor of cardiovascular complications over and above CBP; diastolic CBP and ABP were not associated with outcome in that analysis. The results on surrogate and hard end points from the Syst-Eur Trial therefore allow us to conclude that sustained systolic hypertension is more harmful than white coat systolic hypertension in the elderly, particularly when daytime systolic BP averages ≥160 mm Hg. It is unlikely that our results have been confounded by other risk factors such as age, sex, relative weight, serum cholesterol, and heart rate because they did not differ among the 3 ABP subgroups, and the overall prevalence of smoking was low in the study population. The Syst-Eur Trial data do not provide information, however, on whether nonsustained systolic hypertension is innocuous compared with true normotension, as suggested by some,[5,7] but not other,[9,15] data on left ventricular mass and by the results for morbidity and mortality rates by Verdecchia et al[10] in hypertensive patients in general.

According to current guidelines,[21,22] the management of hypertension is mainly based on CBP. Before concluding that patients with low or normal ABP should not be treated, it is of paramount importance to assess the influence of antihypertensive therapy on BP, surrogate end points, and cardiovascular complications in such patients. The present placebo-controlled study confirms previous uncontrolled observations[12–14] that CBP decreases and ABP hardly changes when treatment is guided by CBP in patients with Non-SH. CBP also decreased in the placebo-treated Syst-Eur Trial patients, probably due to further habituation to the measurement conditions after the run-in period and to regression-to-the-mean. However, both systolic and diastolic CBPs were reduced more in the active treatment group than in the placebo group, which suggests that part of the active treatment effect on CBP can be ascribed to the treatment per se. This could lend support to the initiation of antihypertensive therapy in patients with white coat hypertension. However, a recent study showed that antihypertensive therapy based on ABP led to similar BP control, general well-being, and left ventricular mass as treatment guided by CBP, and these results were achieved with a lesser intake of drugs.[27] Whereas the duration of that study was limited to 6 months, the Syst-Eur Trial data show that the 1-year changes in ECG voltages were not different between active treatment and placebo in patients with Non-SH. By contrast, active treatment induced a significant decrease in ECG left ventricular mass in patients with MoSH. These results are compatible with the observation that the treatment-induced changes in echocardiographic left ventricular mass appear to be more closely related to changes in ABP than to the changes in CBP.[28] With regard to outcome, active treatment reduced the incidence of cardiovascular events and of stroke with statistical significance only in the patients with MoSH. These findings on surrogate and hard end points indicate that most of the benefit of antihypertensive therapy in elderly patients with systolic hypertension is seen in patients whose daytime systolic ABP is ≥160 mm Hg and that the benefit is less evident when this BP is below that value.

A number of limitations have to be considered. The present findings are based on subgroups of patients from the Syst-Eur Trial, so the number of events was relatively small, particularly in the patients with Non-SH. Larger studies are therefore warranted to further clarify the effect of antihypertensive therapy on outcome in hypertensive patients with low or normal ABP. The patients of the present analysis were randomized to the active treatment and placebo groups but not within each stratum of ABP; nevertheless, the characteristics at baseline did not differ between the treatment groups. The classification of patients in subgroups according to ABP might have been different if >1 monitoring would have been used due to regression-to-the-mean.[29] Finally, there is as yet no generally accepted definition of white coat hypertension and certainly not for isolated systolic white coat hypertension, so the results might differ if other cutoff values were used for the classification of patients according to ABP; the arbitrary cutoff values used in the present study should not be taken as an indication of what a normal reference ABP value might be.

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