Predicting Cardiovascular Risk Using Conventional vs Ambulatory Blood Pressure in Older Patients With Systolic Hypertension

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Context The clinical use of ambulatory blood pressure (BP) monitoring requires further validation in prospective outcome studies.

Objective To compare the prognostic significance of conventional and ambulatory BP measurement in older patients with isolated systolic hypertension.

Design Substudy to the double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) Trial, started in October 1988 with follow up to February 1999. The conventional BP at randomization was the mean of 6 readings (2 measurements in the sitting position at 3 visits 1 month apart). The baseline ambulatory BP was recorded with a noninvasive intermittent technique.

Setting Family practices and outpatient clinics at primary and secondary referral hospitals.

Participants A total of 808 older (aged ≥60 years) patients whose untreated BP level on conventional measurement at baseline was 160 to 219 mm Hg systolic and less than 95 mm Hg diastolic.

Interventions For the overall study, patients were randomized to nitrendipine (n = 415; 10-40 mg/d) with the possible addition of enalapril (5-20 mg/d) and/or hydrochlorothiazide (12.5-25.0 mg/d) or to matching placebos (n = 393).

Main Outcome Measures Total and cardiovascular mortality, all cardiovascular end points, fatal and nonfatal stroke, and fatal and nonfatal cardiac end points.

Results After adjusting for sex, age, previous cardiovascular complications, smoking, and residence in western Europe, a 10-mm Hg higher conventional systolic BP at randomization was not associated with a worse prognosis, whereas in the placebo group, a 10-mm Hg higher 24-hour BP was associated with an increased relative hazard rate (HR) of most outcome measures (eg, HR, 1.23 [95% confidence interval {CI}, 1.00-1.50] for total mortality and 1.34 [95% CI, 1.03-1.75] for cardiovascular mortality). In the placebo group, the nighttime systolic BP (12 AM-6 AM) more accurately predicted end points than the daytime level. Cardiovascular risk increased with a higher night-to-day ratio of systolic BP independent of the 24-hour BP (10% increase in night-to-day ratio; HR for all cardiovascular end points, 1.41; 95% CI, 1.03-1.94). At randomization, the cardiovascular risk conferred by a conventional systolic BP of 160 mm Hg was similar to that associated with a 24-hour daytime or nighttime systolic BP of 142 mm Hg (95% CI, 128-156 mm Hg), 145 mm Hg (95% CI, 126-164 mm Hg) or 132 mm Hg (95% CI, 120-145 mm Hg), respectively. In the active treatment group, systolic BP at randomization did not significantly predict cardiovascular risk, regardless of the technique of BP measurement.

Conclusions In untreated older patients with isolated systolic hypertension, ambulatory systolic BP was a significant predictor of cardiovascular risk over and above conventional BP.

JAMA. 1999;282:539-546 www.jama.com

AMBULATORY MONITORING makes it possible to record blood pressure (BP) throughout the day while subjects engage in their routine activities. In comparison with conventional BP measurements, automated recordings are devoid of digit preference and observer bias and minimize the white-coat effect.[1] As a consequence of these advantages and the large number of measurements, a single ambulatory BP recording provides a reliable estimate of a person's BP. To gain equivalent information, conventional BP readings must be standardized and repeated at frequent intervals.[2] Furthermore, several studies support the hypothesis that ambulatory BP, in comparison with conventional BP, is better correlated with hypertensive target organ damage, such as left ventricular hypertrophy,[3-5] or with

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other cardiovascular complications.[5-10] In the framework of the Systolic Hypertension in Europe (Syst-Eur) Trial,[11,12] we compared the prognostic accuracy of conventional and ambulatory BP measurements.[13,14] We also validated diagnostic thresholds[15,16] for BP monitoring through follow-up of morbidity and mortality of the placebo group.

METHODS

The protocol of the Syst-Eur Trial was approved by the ethics committees of the University of Leuven and participating centers. Inclusion and exclusion criteria, the definition of end points, and procedures for recruitment and randomization were previously published.[11] The study was started in October 1988 with follow up to February 1999. Eligible patients were aged 60 years or older. On conventional measurement, they had to have a sitting systolic BP of 160 to 219 mm Hg, with a diastolic BP of less than 95 mm Hg. Standing systolic BP had to be at least 140 mm Hg. These entry criteria were based on the means of 6 BP readings obtained during the placebo run-in period (2 readings in each position at 3 visits 1 month apart). Eligible patients were randomized to double-blind treatment with active medication or placebo.[11] The study medications were stepwise titrated and combined to reduce the sitting systolic BP (mean of 2 readings at each follow-up visit) by 20 mm Hg or more to less than 150 mm Hg.[11] Active treatment was initiated with nitrendipine (10-40 mg/d). If necessary, the dihydropyridine was combined with or replaced by enalapril (5-20 mg/d), hydrochlorothiazide (12.5-25.0 mg/d), or both drugs. In the control group, identical placebos were used in the same way.

Ambulatory BP was recorded at entry and approximately 1 year later[13] with properly validated[17,18] and calibrated monitors programmed to obtain measurements at intervals no longer than 30 minutes. Editing criteria encoded in the monitor were disabled or set at limits as wide as possible. The cuff was secured to the nondominant arm. However, if on conventional sphygmomanometry the difference in systolic BP between both arms was 10 mm Hg or more, the arm giving the highest reading was chosen. If arm circumference exceeded 31 cm, larger cuffs with a 35 × 15 cm bladder were used.

Of 198 Syst-Eur centers, 46 opted to enroll their patients in the current study. Of 837 randomized patients with a 24-hour BP recording at entry, 29 (3.5%) were excluded because less than 80% of the required readings were available. Because the Syst-Eur Trial stopped early,[11] only 536 of the remaining 808 patients underwent a follow-up recording. Most recordings were obtained with SpaceLabs (Redmond, Wash) 90202 (n = 258; 19.2%) or 90207 (n = 838; 62.4%) devices.

The blinded end-point committee ascertained all major end points by reviewing the local patient files and other source documents, requesting detailed written information from the investigators, or both approaches. Cardiac end points included fatal and nonfatal heart failure, fatal and nonfatal myocardial infarction, and sudden death. Patients without any report within the year before the trial stopped were considered to be lost to follow-up. This occurred in only 2.6% of all randomized patients.[12]

We based the statistical analysis on an intention-to-treat principle and 2-sided tests. We used SAS software, Version 6.12 (SAS Institute Inc, Cary, NC). The BP changes during follow-up were analyzed using the difference between baseline and the last available measurements.[19] Ambulatory recordings were not edited. Means of ambulatory measurements were weighted by the interval between consecutive readings. Awake and sleeping periods were determined from diary cards.[13,14] Daytime and nighttime BP, nocturnal BP decrease, and the night-to-day BP ratio were calculated from short, fixed clock time[20] periods ranging from 10 AM to 8 PM and from 12 AM to 6 AM. The morning increase in BP was computed by fitting a regression line through each person's BP readings between 4 AM and 10 AM.

We determined the significance of mean differences and Pearson correlation coefficients using the normal z distribution. We calculated relative hazard rates by multiple Cox regression stratified for treatment group and adjusted for significant covariates.[21] We modeled the probability of the 2-year incidence of end points assuming the Weibull distribution for failure time. We estimated that from 2500 to 5000 patient-years of follow-up would be necessary to test the hypothesis of an association between the incidence of cardiovascular complications and the ambulatory BP.[13]

RESULTS

Patients Characteristics at Randomization

At randomization, patients in the placebo (n = 393) and active treatment (n = 415) groups had similar characteristics. The 808 patients had a mean (SD) age of 69.6 (6.2) years. Body mass index averaged 26.1 (3.2) kg/m^2 in 311 men and 27.0 (4.4) kg/m^2 in 497 women. Previous cardiovascular complications were present in 215 patients, 119 of whom had a Sokolow-Lyon voltage index[22] compatible with left ventricular hypertrophy. Of the 808 patients, 93 (11.5%) had been recruited in eastern Europe, 344 (42.6%) had been treated with antihypertensive drugs before enrollment, 218 (27.0%) were past smokers, 69 (8.5%) were current smokers, and 124 (15.3%) consumed more than 1 glass of beer, wine, or liquor per day.

Systolic and diastolic BP were, on average, 21.9 mm Hg and 1.9 mm Hg higher ($P<.001$) on conventional than daytime ambulatory measurement, respectively (TABLE 1). The corresponding mean ±2 SD intervals ranged from −8.3 to 52.3 mm Hg and −17.2 to 21.2 mm Hg, respectively. The difference between conventional and daytime BP did not correlate with age ($P = .16$ and $P = .57$ for systolic and diastolic BP, respectively). Awake and sleeping BP measurements were similar to daytime and nighttime BP measurements, respectively. The results of Cox regression analysis were also comparable regardless of whether the diurnal high and low BP spans were defined by time or

sleep. Because short, fixed clock time intervals[20] are easy to reproduce across studies, only the results for the daytime and nighttime BP are reported herein. The mean (SD) within-subject coefficient of variation was significantly smaller for nighttime than for daytime BP (8.7% [3.6%] vs 10.4% [3.3%]; $P<.001$).

Treatment and BP During Follow-Up

The median follow-up in the 808 patients was 4.4 years. Because the patients had been recruited over 8 years and because the trial stopped early,[11] follow-up of individual patients ranged from 1 to 110 months. The number of patient-years in the placebo and active treatment groups amounted to 1666 and 1742, respectively.

Of the 808 patients, 265 in the placebo group and 271 in the active treatment group underwent a reassessment of their conventional and ambulatory BP after randomization (TABLE 2). At the last follow-up visit, 214 (80.8%) of the patients randomized to placebo and 243 (89.7%) of the active treatment group were still taking double-blind treatment ($P = .004$), while 51 (19.2%) and 28 (10.3%) were in open follow-up. Of the actively treated patients, 213 (87.7%) were taking nitrendipine (mean dosage, 27.7 mg/d), 75 (30.9%) were taking enalapril (14.0 mg/d), and 47 (19.3%) were taking hydrochlorothiazide (22.6 mg/d); for matching placebos in the control group, these numbers were 201 (93.9%), 128 (59.8%), and 74 (34.6%), respectively. For all patients in double-blind or open follow-up (intention-to-treat analysis), the net treatment effect on BP averaged 10.6 mm Hg for systolic and 4.2 mm Hg for diastolic for the conventional levels and 8.5 mm Hg for systolic and 3.8 mm Hg for diastolic for the 24-hour levels (Table 2).

Conventional and Ambulatory BP as Risk Predictors

In exploratory nonparametric analyses, the incidence of all cardiovascular end points was plotted in thirds of the distributions of the conventional and ambulatory BP at entry. For systolic BP in the placebo group, we observed positive associations regardless of the type of BP measurement (FIGURE 1). Diastolic BP was not associated with outcome. The Cox regression analysis was therefore restricted to systolic BP.

In Cox regression we applied cumulative adjustments for sex, age, previous cardiovascular complications, current smoking status, and residence in

Table 1. Conventional and Ambulatory BPs at Entry in 808 Patients*

	Systolic BP, mm Hg	Diastolic BP, mm Hg
Conventional BP in sitting position†	173.3 (10.8)	86.0 (5.8)
Ambulatory BP measurements		
24-Hour	145.8 (15.6)	79.3 (8.9)
Daytime (10 AM-8 PM)	151.4 (16.2)	84.1 (9.8)
Nighttime (12 AM-6 AM)	134.0 (18.6)	70.2 (10.1)
Nocturnal decrease‡	17.4 (14.8)	13.8 (8.8)
Increase from 4 AM to 10 AM	4.7 (4.9)	3.7 (3.5)
Night-to-day ratio§	0.89 (0.09)	0.84 (0.10)
Awake	151.0 (15.8)	83.6 (9.4)
Sleeping	134.7 (18.1)	70.8 (9.9)

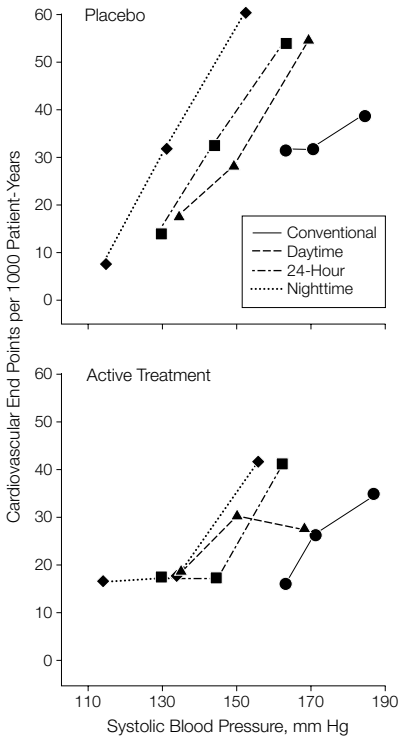
*BP indicates blood pressure. All data are given as mean (SD).
†Mean of 6 readings, ie, 2 at each of 3 baseline visits 1 month apart.
‡Daytime minus nighttime BP.
§Dimensionless ratio of night-to-day BP.

Table 2. Treatment Status and Reduction in BP at Follow-up*

	Placebo Group	Active Treatment Group	Both Treatment Groups
No. of patients with follow-up ambulatory BP recording	265	271	536
Treatment status at last follow-up visit			
Double-blind follow-up†	214	243	457
Nitrendipine only	75	144	219
Nitrendipine‡	201	213	414
Enalapril‡	128	75	203
Hydrochlorothiazide‡	74	47	121
Other antihypertensive drugs‡§	4	2	6
Open follow-up	51	28	79
Taking antihypertensive drugs	45	20	65
Not taking antihypertensive drugs	5	7	12
Unknown	1	1	2
Reduction in BP, mean (SD), mm Hg‖			
Systolic			
Conventional	12.8 (19.6)	23.5 (19.0)	10.6 (7.4-13.9)
24-Hour	2.1 (13.6)	10.7 (13.8)	8.5 (6.2-10.8)
Daytime (10 AM-8 PM)	3.7 (16.6)	11.2 (14.7)	7.5 (4.8-10.1)
Nighttime (12 AM-6 AM)	0.0 (14.2)	9.7 (18.1)	9.7 (6.9-12.4)
Diastolic			
Conventional	3.8 (9.3)	8.0 (9.6)	4.2 (2.6-5.8)
24-Hour	2.6 (8.1)	6.4 (8.5)	3.8 (2.4-5.2)
Daytime (10 AM-8 PM)	3.6 (9.7)	7.0 (10.2)	3.4 (1.8-5.1)
Nighttime (12 AM-6 AM)	1.3 (9.0)	5.4 (10.2)	4.1 (2.5-5.8)

*BP indicates blood pressure.
†In the placebo group, matching placebos were used. In the active treatment group, the mean (SD) dosages of nitrendipine, enalapril, and hydrochlorothiazide were 27.7 (12.5) mg/d, 14.0 (6.7) mg/d, and 22.6 (5.0) mg/d, respectively.
‡Because many patients were taking combined treatment, these numbers are not additive.
§To bridge medical emergencies without having to break the code, antihypertensive drugs could be prescribed during the double-blind period for up to 3 consecutive months.
‖For the 2 treatment groups combined, the net treatment effects, corrected for baseline and placebo, are given with 95% confidence intervals in parentheses.

Figure 1. Incidence of All Cardiovascular End Points in Thirds of the Distributions of Systolic Blood Pressure at Entry



western Europe.[21] In the placebo group, conventional BP at baseline was only weakly associated with incidence of cardiovascular complications, whereas the 24-hour, daytime, and nighttime systolic BP measurements significantly predicted cardiovascular mortality, all cardiovascular end points, and fatal and nonfatal stroke (TABLE 3). Cardiac end points were predicted only by nighttime BP, which was a significant and consistent predictor of all types of end points. Furthermore, in the placebo group, after additional adjustment for the conventional BP (TABLE 4), the nighttime BP still predicted all types of end points with the exception of stroke, while the 24-hour and daytime BP still predicted the incidence of all cardiovascular end points and total stroke (Table 4).

In treated patients, ambulatory BP at entry was only a weak predictor of end points (Table 3); after additional adjustment for the conventional BP, none of the ambulatory measurements was significantly correlated with outcome (Table 4). Furthermore, in both treatment groups combined, nighttime BP was an independent and consistent predictor of all end points, both before (Table 3) and after (Table 4) adjustment for conventional BP.

In the adjusted[21] Cox models, nighttime BP was a consistently stronger predictor of risk than daytime BP, regardless of whether the patients had been randomized to placebo or active treatment (TABLE 5). The only exception was noted for stroke in the placebo group (Table 5). Excluding the initial 2 hours from each recording did not improve the predictive accuracy of the daytime BP.

Analyses Confined to the Placebo Group

After adjustment for the same potential confounders as already mentioned (Table 5), the 24-hour level and the night-to-day ratio of systolic BP were significantly and independently correlated with the incidence of all cardiovascular end points in the placebo group (FIGURE 2). The relative hazard rates associated with a 10-mm Hg increase in the 24-hour BP and with a 10% higher night-to-day ratio were 1.23

Table 3. Relative Hazard Rates for Systolic BP on Conventional and Ambulatory Measurement at Entry*

	Mortality		Fatal and Nonfatal End Points Combined		
	Total	Cardiovascular	Cardiovascular	Stroke	Cardiac
Placebo group					
End points, No.	39	22	54	20	35
Conventional BP	1.21 (0.94-1.56)	1.29 (0.93-1.79)	1.09 (0.86-1.39)	1.30 (0.91-1.86)	1.05 (0.78-1.42)
24-Hour BP	1.23 (1.00-1.50)‡	1.34 (1.03-1.75)‡	1.26 (1.06-1.49)§	1.47 (1.12-1.93)§	1.14 (0.92-1.41)
Daytime BP	1.18 (0.97-1.44)	1.30 (1.01-1.68)‡	1.19 (1.01-1.41)‡	1.51 (1.17-1.95)§	1.07 (0.86-1.32)
Nighttime BP	1.24 (1.03-1.49)‡	1.42 (1.11-1.82)§	1.31 (1.12-1.52)‖	1.30 (1.01-1.69)‡	1.27 (1.06-1.53)‡
Active treatment group					
End points, No.	29	14	44	10	34
Conventional BP	1.35 (1.00-1.82)‡	1.04 (0.93-1.22)	1.20 (0.94-1.52)	1.33 (0.80-2.22)	1.19 (0.91-1.56)
24-Hour BP	1.04 (0.80-1.34)	1.01 (0.71-1.43)	1.11 (0.91-1.36)	1.25 (0.81-1.92)	1.10 (0.88-1.39)
Daytime BP	0.93 (0.72-1.19)	1.01 (0.72-1.41)	1.01 (0.84-1.22)	0.96 (0.64-1.43)	1.04 (0.84-1.29)
Nighttime BP	1.07 (0.88-1.29)	1.03 (0.79-1.34)	1.14 (0.97-1.33)	1.42 (0.99-2.03)‡	1.09 (0.91-1.31)
Both treatment groups¶					
End points, No.	68	36	98	30	69
Conventional BP	1.24 (1.03-1.49)‡	1.32 (1.03-1.68)‡	1.13 (0.96-1.34)	1.29 (0.98-1.71)‡	1.11 (0.91-1.35)
24-Hour BP	1.16 (0.99-1.35)†	1.20 (0.98-1.49)	1.18 (1.04-1.35)§	1.40 (1.12-1.76)§	1.12 (0.96-1.31)
Daytime BP	1.07 (0.91-1.24)	1.17 (0.96-1.44)	1.11 (0.98-1.25)	1.30 (1.05-1.62)‡	1.06 (0.91-1.23)
Nighttime BP	1.17 (1.03-1.33)‡	1.23 (1.03-1.46)‡	1.21 (1.09-1.35)‖	1.35 (1.11-1.65)§	1.17 (1.03-1.33)‡

*BP indicates blood pressure. Relative hazard rates (95% confidence intervals) reflect the risk associated with a 10-mm Hg increase in systolic BP level. Hazard rates were adjusted for sex, age, cardiovascular complications at entry, current smoking status, and residence in western Europe.[21]
†$P \leq .07$.
‡$P \leq .05$.
§$P \leq .01$.
‖$P \leq .001$.
¶Adjusted for active treatment as well.

(95% confidence interval [CI], 1.03-1.46; $P = .02$) and 1.41 (95% CI, 1.03-1.94; $P = .03$), respectively. Furthermore, after adjustment for daytime BP, the early morning increase in systolic BP was a significant and independent predictor of all cardiovascular end points in the placebo group. In the latter model, a 10-mm Hg increase in the daytime systolic BP and a 1-mm Hg/h steeper increase in the morning systolic BP were associated with relative hazard rates of 1.22 (95% CI, 1.03-1.44; $P = .02$) and 0.92 (95% CI, 0.87-0.97; $P = .003$), respectively.

If systolic BP on conventional measurement at randomization to placebo was 160 mm Hg, the Cox model, adjusted for sex, age, previous cardiovascular complications, current smoking status, and residence in western Europe,[21] predicted a 2-year incidence of cardiovascular end points of 3.4 per 100 patients (95% CI, 1.3-5.5 per 100 patients, FIGURE 3). The predicted rate of cardiovascular complications was similar if, at randomization, the 24-hour BP level was 142 mm Hg (95% CI, 128-156 mm Hg), if the daytime BP level was 145 mm Hg (95% CI, 126-164 mm Hg), or if the nighttime BP level was 132 mm Hg (95% CI, 126-145 mm Hg).

COMMENT

We found that in untreated older patients with isolated systolic hypertension, the ambulatory systolic BP, over and above the conventional BP, predicted cardiovascular risk. Active treatment weakened this relationship to a nonsignificant level. In the placebo group, at any given level of conventional systolic BP, each 10-mm Hg increment in the daytime systolic BP was accompanied by a 20% higher cardiovascular risk. Thus, in

Table 4. Adjusted Relative Hazard Rates for Ambulatory Systolic BP After Adjustment for Conventional Systolic BP and Entry Characteristics From Table 3*

	Mortality		Fatal and Nonfatal End Points Combined		
	Total	Cardiovascular	Cardiovascular	Stroke	Cardiac
Placebo group					
24-Hour	1.19 (0.95-1.49)	1.29 (0.95-1.75)	1.27 (1.05-1.54)‡	1.51 (1.06-2.15)‡	1.14 (0.90-1.43)
Daytime	1.14 (0.91-1.42)	1.25 (0.92-1.69)	1.20 (1.00-1.45)‡	1.61 (1.14-2.28)§	1.06 (0.85-1.33)
Nighttime	1.21 (1.00-1.47)‡	1.39 (1.07-1.79)‡	1.31 (1.12-1.53)‖	1.25 (0.94-1.66)	1.22 (1.06-1.54)‡
Active treatment group					
24-Hour	0.95 (0.72-1.24)	0.89 (0.61-1.30)	1.05 (0.84-1.31)	1.15 (0.69-1.90)	1.05 (0.81-1.35)
Daytime	0.81 (0.62-1.06)	0.86 (0.60-1.25)	0.94 (0.77-1.16)	0.82 (0.52-1.29)	0.97 (0.77-1.24)
Nighttime	1.05 (0.86-1.27)	1.00 (0.77-1.30)	1.12 (0.95-1.32)	1.38 (0.96-2.00)	1.07 (0.89-1.29)
Both treatment groups¶					
24-Hour	1.09 (0.92-1.29)	1.11 (0.88-1.40)	1.17 (1.01-1.35)‡	1.36 (1.04-1.79)§	1.11 (0.93-1.31)
Daytime	0.98 (0.83-1.17)	1.07 (0.85-1.34)	1.08 (0.94-1.24)	1.25 (0.97-1.61)	1.03 (0.87-1.21)
Nighttime	1.14 (1.00-1.30)‡	1.18 (0.98-1.42)†	1.20 (1.08-1.35)§	1.31 (1.06-1.62)‡	1.16 (1.02-1.33)‡

*BP indicates blood pressure. Relative hazard rates (95% confidence intervals) reflect the risk associated with a 10-mm Hg increase in systolic BP. Hazard rates were also adjusted for sex, age, cardiovascular complications at entry, current smoking status, and residence in western Europe.[21]
†$P \leq .07$.
‡$P \leq .05$.
§$P \leq .01$.
‖$P \leq .001$.
¶Adjusted for active treatment as well.

Table 5. Adjusted Relative Hazard Rates Independently Associated With Daytime and Nighttime Systolic BP*

	Mortality		Fatal and Nonfatal End Points Combined		
	Total	Cardiovascular	Cardiovascular	Stroke	Cardiac
Placebo group					
Daytime	1.03 (0.79-1.33)	1.03 (0.73-1.45)	0.95 (0.76-1.20)	1.52 (1.06-2.17)§	0.80 (0.60-1.06)
Nighttime	1.22 (0.95-1.56)	1.40 (1.00-1.95)‡	1.35 (1.10-1.66)§	0.99 (0.69-1.43)	1.47 (1.14-1.90)§
Active treatment group					
Daytime	0.85 (0.63-1.15)	0.99 (0.67-1.47)	0.90 (0.71-1.14)	0.68 (0.38-1.20)	0.98 (0.75-1.27)
Nighttime	1.13 (0.91-1.42)	1.03 (0.76-1.40)	1.20 (0.99-1.45)†	1.69 (1.07-2.68)‡	1.10 (0.89-1.37)
Both treatment groups‖					
Daytime	0.93 (0.77-1.13)	1.03 (0.79-1.33)	0.94 (0.80-1.10)	1.11 (0.84-1.46)	0.91 (0.75-1.10)
Nighttime	1.21 (1.03-1.42)‡	1.21 (0.96-1.51)	1.26 (1.10-1.45)§	1.28 (0.99-1.65)†	1.23 (1.05-1.45)‡

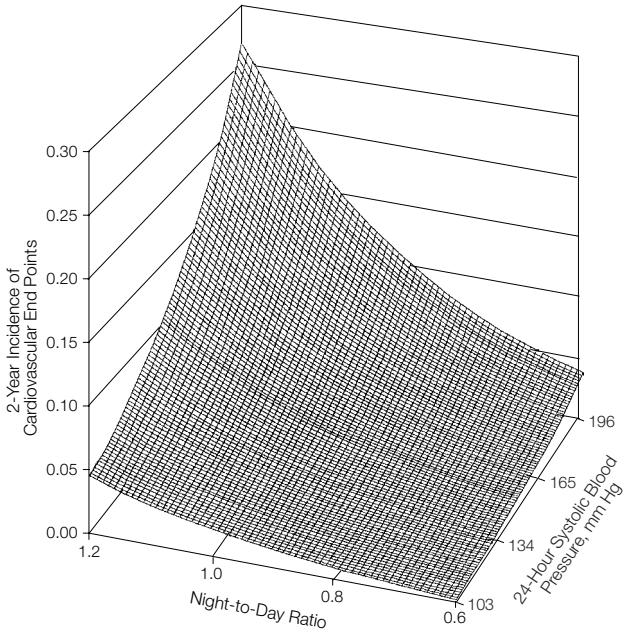
*BP indicates blood pressure. Relative hazard rates (95% confidence intervals) reflect the risk associated with a 10-mm Hg increase in systolic BP level. Because daytime and nighttime BP were forced in the same model, they are automatically adjusted for each other. Hazard rates were also adjusted for sex, age, cardiovascular complications at entry, current smoking status, and residence in western Europe.[21]
†$P \leq .07$.
‡$P \leq .05$.
§$P \leq .01$.
‖Adjusted for active treatment as well.

our untreated patients, the risk conferred by any level of conventional systolic BP at entry declined by nearly one fifth for each 10-mm Hg increase in the white-coat effect, if the latter was defined as the difference between conventional and daytime BP. By introducing both the conventional and ambulatory BP as continuous variables in the same Cox regression model, we avoided the use of arbitrary diagnostic thresholds to classify our patients into those with white-coat hypertension and those with sustained hypertension.

Placebo-controlled trials in isolated systolic hypertension have consistently proven benefit of antihypertensive drug treatment if, on repeated measurement, the conventional systolic BP was 160 mm Hg or higher.[23] The levels of the 24-hour, daytime, and nighttime BP that were, in terms of cardiovascular risk, equivalent to a conventional BP of 160 mm Hg, were 142 mm Hg, 145 mm Hg, and 132 mm Hg, respectively. These thresholds must be cautiously interpreted. In our study, the distribution of the conventional systolic BP level started at 160 mm Hg, whereas in prospective epidemiological studies[24] conventional BP behaved as a continuous risk factor, with a significant proportion of cardiovascular disease already occurring at less than 160 mm Hg for systolic BP. Furthermore, the 95% CIs of the ambulatory BP thresholds with equivalent risk were wide. On the other hand, they included the cutoff values proposed in various national guidelines[16,25] as well as the limits of normality based on the distribution of ambulatory BP in normotensive subjects[15,16] or on the absence of left ventricular hypertrophy in patients with white-coat hypertension.[26]

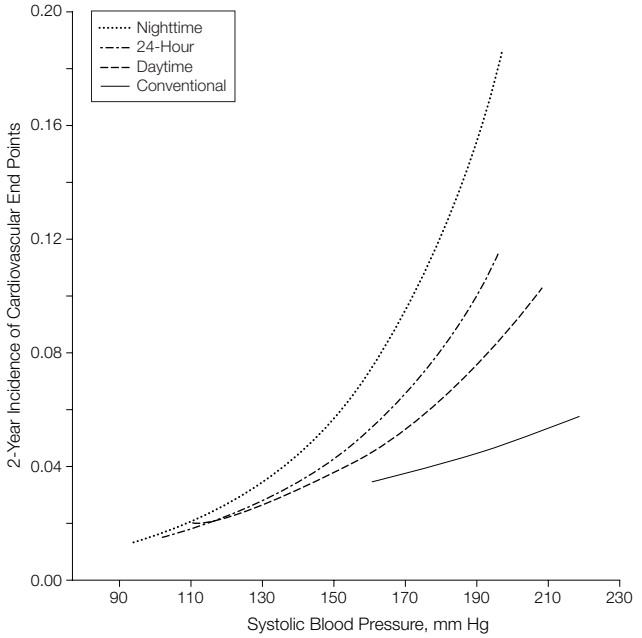
Perloff et al[7] started the validation of ambulatory BP monitoring in terms of cardiovascular end points by showing that the portion of the daytime ambulatory BP that was not already explained by the conventional BP could discriminate high-risk from low-risk patients. These results, obtained by life-table analysis in 1076 hypertensive patients, were later confirmed by multiple Cox regression in a subgroup of 761 patients who were untreated at baseline.[8] A smaller study of 137 newly referred hypertensive patients revealed that BP, when measured intra-arterially over 24 hours, significantly increased the prognostic accuracy of conventional BP readings.[6] A recent report from the same center included 479 patients followed up for an average of 9.1 years.[5] White-coat hypertension, defined as a conventional systolic BP of 140 to 180 mm Hg associated with a 24-hour intra-arterial BP of less than 140 mm Hg systolic and 90 mm Hg diastolic, was present in 126 patients. Compared with the patients with sustained hypertension, the former group had a 71% lower risk (95% CI, 10%-91%; $P = .04$) of experiencing cardiovascular events.[5] Verdecchia et al[26] followed up 1187 subjects with essential

Figure 2. Night-to-Day Ratio and 24-Hour Systolic Blood Pressure at Entry as Independent Predictors of the 2-Year Incidence of Cardiovascular End Points in the Placebo Group



Using multiple Cox regression, the event rate was standardized to female sex, 69.6 years (mean age), no previous cardiovascular complications, nonsmoking status, and residence in western Europe. Incidence is given as a fraction (ie, 0.02 is an incidence of 2 events per 100 people).

Figure 3. Systolic Blood Pressure on Conventional, 24-Hour, Daytime, and Nighttime Measurement at Entry as Predictors of the 2-Year Incidence of Cardiovascular End Points in the Placebo Group



Incidence is given as a fraction (ie, 0.02 is an incidence of 2 events per 100 people). Using multiple Cox regression, the event rate was standardized to female sex, 69.6 years (mean age), no previous cardiovascular complications, nonsmoking status, and residence in western Europe.

hypertension and 205 normotensive control subjects for up to 7.5 years (mean, 3.2 years), all of whom underwent baseline off-therapy BP monitoring. In the hypertensive patients, the prevalence of white-coat hypertension, defined as a daytime BP of less than 136/87 mm Hg in men and less than 131/86 mm Hg in women, was 19.2%. After adjustment for traditional markers of cardiovascular risk, morbidity did not differ between the normotensive subjects and the white-coat hypertensive group ($P = .83$).[26] Recently, Ohkubo et al[27] found in 1542 residents of a rural Japanese community aged 40 years or older that the 24-hour systolic and diastolic BP were significantly and curvilinearly correlated with total mortality. This second-order relationship persisted after cumulative adjustments for sex, age, and other cardiovascular risk factors. However, the Japanese group did not report whether the correlation remained after adjusting for the conventional BP at baseline or after excluding the noncardiovascular deaths.[27]

The hypothesis that nondipping would be associated with greater cardiovascular risk[28] is not generally accepted.[29] Poor reproducibility of the dipping status[30] and the use of varying definitions for nondipping[26,31] sustain the controversy. To avoid the use of arbitrary thresholds, we analyzed the night-to-day BP ratio as a continuous variable. We confirmed the hypothesis of an inverse association between cardiovascular risk and BP decreasing at night.[28] Indeed, with adjustment for the 24-hour BP and other risk factors,[21] the cardiovascular risk in the placebo group increased by 41% for each 10% increment in the night-to-day ratio. In addition, in the placebo group and in all patients combined, the nighttime BP behaved as a more consistent predictor of major end points than the daytime BP. The influence of physical and psychoemotional stress may weaken the predictive power of daytime BP, whereas the greater uniformity resulting from sleeping may help to demonstrate correlations with nighttime BP. The smaller mean within-subject coefficient of variation for nighttime BP than for daytime BP supports this hypothesis. An additional explanation for the close correlation between cardiovascular risk and nighttime BP is that both could be linked to a common pathophysiologic mechanism, such as an increased sympathetic tone[32] or renal dysfunction necessitating a higher nighttime BP to sustain natriuresis.[33] Prospective studies showed a greater incidence of cardiovascular complications during the early morning hours.[34] In contrast with these findings, we found in the placebo group that a 1-mm Hg per hour steeper increase in the morning systolic BP was associated with an 8% lower incidence of cardiovascular end points. However, this relationship was adjusted for the daytime BP, so that a steeper increase in the morning BP was also an index of a lower nighttime BP, which in turn was associated with lower cardiovascular risk.

In conclusion, in older patients with isolated systolic hypertension, ambulatory systolic BP, especially when measured at night or when exceeding 142, 145, or 132 mm Hg, respectively, on 24-hour, daytime, and nighttime measurement was a significant predictor of cardiovascular complications over and above conventional systolic BP.

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Funding/Support: The Syst-Eur Trial was a concerted action of the BIOMED Research Program sponsored by the European Union. The trial was carried out in consultation with the World Health Organization (Geneva, Switzerland), the International Society of Hypertension, the European Society of Hypertension, and the World Hypertension League. The trial was sponsored by Bayer AG (Wuppertal, Germany). The National Fund for Scientific Research (Brussels, Belgium) provided additional support. Study medication was donated by Bayer AG and Merck Sharpe and Dohme Inc, West Point, Pa.

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There is no form of lead-poisoning which more rapidly and thoroughly pervades the blood and bones and marrow than that which reaches the young author through mental contact with type-metal. . . . So the man or woman who has tasted type is sure to return to his old indulgence sooner or later.
—Oliver Wendell Holmes (1809-1894)