

# Predictive Value of Clinic and Ambulatory Heart Rate for Mortality in Elderly Subjects With Systolic Hypertension

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**Objective:** To examine the association of clinic and ambulatory heart rate with total, cardiovascular, and noncardiovascular death in a cohort of elderly subjects with isolated systolic hypertension from the Systolic Hypertension in Europe Trial.

**Methods:** A total of 4682 patients participated, whose untreated blood pressure on conventional measurement at baseline was 160 to 219 mm Hg systolic and lower than 95 mm Hg diastolic. Clinic heart rate was the mean of 6 readings during 3 visits. Ambulatory heart rate was recorded with a portable intermittent technique in 807 subjects.

**Results:** Raised baseline clinic heart rate was positively associated with a worse prognosis for total, cardiovascular, and noncardiovascular mortality among the 2293 men and women taking placebo. Subjects with heart rates higher than 79 beats/min (bpm) (top quintile) had a 1.89 times greater risk of mortality than subjects with heart rate lower than or equal to 79 bpm (95% confidence interval, 1.33-2.68 bpm). In a Cox regression analysis, predictors of time to death were heart rate ( $P < .001$ ), age

( $P < .001$ ), serum creatinine level ( $P = .001$ ), presence of diabetes ( $P = .002$ ), previous cardiovascular disease ( $P = .01$ ), triglyceride readings ( $P = .02$ ), smoking ( $P = .04$ ), and elevated systolic blood pressure ( $P = .05$ ), while total cholesterol level was found to be nonsignificant in the model. In the ambulatory monitoring subgroup, clinic and ambulatory heart rates predicted noncardiovascular but not cardiovascular mortality. However, in a Cox regression analysis in which clinic and ambulatory heart rates were included, a significant association with noncardiovascular mortality was found only for clinic heart rate ( $P = .004$ ). In the active treatment group, the weak predictive power of clinic heart rate for mortality disappeared after adjustment for confounders.

**Conclusions:** In untreated older patients with isolated systolic hypertension, a clinic heart rate greater than 79 bpm was a significant predictor of all-cause, cardiovascular, and noncardiovascular mortality. Ambulatory heart rate did not add prognostic information to that provided by clinic heart rate.

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SEVERAL EPIDEMIOLOGIC studies have shown that some major risk factors for atherosclerosis such as total cholesterol level and smoking status tend to lose their predictive power for morbidity and mortality in old age.<sup>1-4</sup> In recent years, evidence has been accumulating that high heart rate is an important risk factor for cardiovascular and noncardiovascular death in middle-aged<sup>5-9</sup> as well as in elderly<sup>10,11</sup> normotensive subjects. Much less is known about whether heart rate is a risk factor for mortality also in hypertensive individuals because only a few studies have examined this relationship in the hypertensive segment of 2 populations,<sup>12,13</sup> and

to the best of our knowledge, no study has been conducted in elderly subjects with hypertension. Another point that needs to be clarified is whether there are sex differences in the impact of a potentially modifiable risk factor such as heart rate on mortality in hypertensive individuals. In the Framingham Study, a significant association between heart rate and mortality was found in men and women with hypertension.<sup>12</sup> In contrast, the more recent study by Benetos et al<sup>13</sup> found a relationship between heart rate and mortality among men but not women with hypertension.

Nearly all epidemiologic studies on the predictive value of fast heart rate for mortality were based on clinic heart rate

(ie, pulse rate measured by a physician or a nurse). The only study that used 24-hour ambulatory heart rate failed to compare the predictive power of ambulatory heart rate with that of clinic heart rate.<sup>10</sup> Thus, it is not known whether heart rate recorded throughout the day while subjects engage in their routine activities can improve the predictive value for mortality provided by heart rate measured in the clinic.

The aim of the present study was to assess whether high heart rate is associated with increased mortality in elderly men and women with isolated systolic hypertension from the Systolic Hypertension in Europe (Syst-Eur) Trial,<sup>14</sup> and to ascertain whether the prognostic accuracy of clinic heart rate could be improved by heart rate measured out of the office with portable intermittent technique.

## METHODS

The protocol of the Syst-Eur Trial was approved by the Ethics Committees of the University of Leuven and the participating centers (n=198). The inclusion and exclusion criteria, the definition of end points, and the procedures for recruitment and randomization have been reported elsewhere.<sup>14</sup> Eligible patients were 60 years or older. On conventional measurement, they had a sitting systolic blood pressure (BP) of 160 to 219 mm Hg with diastolic BP below 95 mm Hg. These entry criteria were based on the mean of 6 BP readings obtained during the placebo run-in period (2 readings at 3 visits 1 month apart). At each visit, clinic heart rate was measured twice in the sitting position. Clinic heart rate was defined as the mean of the 6 measurements obtained during the run-in period. Sinus tachycardia and sinus bradycardia were not reasons for exclusion.

Cardiovascular complications were present in 1395 subjects. Of these, 41% and 7% had clinical signs of coronary heart disease and cerebrovascular disease, respectively. Electrocardiographic changes compatible with left ventricular hypertrophy were detected in 44% of the patients. The remaining 8% had a combination of these disorders or other vascular lesions.

Eligible patients were randomized to double-blind treatment with active medication or placebo. The study medications were stepwise titrated and combined to reduce the sitting systolic BP by 20 mm Hg or more to lower than 150 mm Hg.<sup>14</sup> Active treatment was initiated with nitrendipine (10-40 mg/d). If necessary, the dihydropyridine calcium channel blocker was combined with or replaced by enalapril maleate (5-20 mg/d), hydrochlorothiazide (12.5-25 mg/d), or both drugs. In the control group, identical placebos were used in the same way.

The survey questionnaire included family history, smoking habits, alcohol consumption, medications, and history of major chronic conditions diagnosed by a physician. Diabetes at entry was defined, according to the 1985 criteria of the World Health Organization,<sup>15</sup> as a history of diabetes mellitus, treatment with antidiabetic drugs, or a fasting or nonfasting random blood glucose level of at least 141 or 200 mg/dL (7.8 or 11.1 mmol/L), respectively. All subjects gave written informed consent after the nature of the procedures had been fully explained. All major end points were assessed by a blinded end point committee, which identified nonfatal events and all causes of death by reviewing the patient files and other source documents, by requesting detailed written information from the investigators, or by both approaches.<sup>14</sup>

## AMBULATORY MONITORING

Among the 198 centers participating in the main trial, 46 opted to enroll patients for the ambulatory BP monitoring (ABPM) project. Twenty-four-hour ambulatory BP and heart rate were recorded at entry with properly validated monitors programmed to obtain measurements at intervals no longer than 30 minutes.<sup>16</sup> Editing criteria encoded in the device were disabled or set at limits as wide as possible. Other details on the procedures used for ABPM have been reported previously.<sup>16</sup>

## DATA ANALYSIS

Clinic heart rate changes during follow-up were analyzed using the difference between baseline heart rate and heart rate measured at the various visits. Of 836 randomized patients with ABPM at baseline, 29 (3.5%) were excluded because more than 20% of the required readings were unavailable. In addition, 1 patient with a pacemaker was excluded. The remaining 807 patients had their baseline recordings before randomization (n=694) or shortly after randomization (n=113; median, 4 months; interquartile range, 2-5 months). Ambulatory recordings were not edited. Means of ambulatory measurements were weighted by the interval between consecutive readings. Daytime and nighttime heart rates were calculated from short, fixed clock time periods ranging from 10 AM to 8 PM and from 12 AM to 6 AM, respectively.<sup>17</sup>

## STATISTICS

We used SAS software, version 8 (SAS Institute Inc, Cary, NC) for database management and statistical analysis. The significance of mean unadjusted differences was determined from the normal *z* distribution. Proportions were compared by the  $\chi^2$  statistic and survival curves by the log-rank statistic. Heart rate was divided into quintiles, and then mortality rates were computed within each quintile. Relative risks of mortality for the upper heart rate quintile relative to the other 4 quintiles were computed based on multiple Cox regressions adjusted for significant covariates.

The associations between heart rate and time to mortality were assessed using a log-linear Cox proportional hazards regression model. Age, body mass index (represented as the weight in kilograms divided by the height in meters squared), systolic BP, and levels of total serum cholesterol, triglycerides, glucose, uric acid, and creatinine were fitted as continuous variables. The categorical variables were grouped into classes such that smoking, consuming alcohol, having diabetes, and preexisting cardiovascular disease were scored 1, and the lack of this status scored 0. Data are presented as mean  $\pm$  SD or median (95% confidence interval [CI]) where appropriate. Statistical analyses were based on the intention-to-treat principle and 2-sided tests at a significance level of .05.

## RESULTS

### BASELINE EXAMINATION

A total of 4695 patients (1557 men and 3138 women) were recruited over 8 years, and median follow-up was 24 months (range, 1-97 months). Thirteen subjects with pacemakers were excluded, leaving 4682 subjects available for analysis. Age was 70.2  $\pm$  6.7 years in the placebo group (n=2293) and 70.3  $\pm$  6.7 years in the active treatment group (n=2389). Clinic sitting BP was 173.9  $\pm$  10.1/85.5  $\pm$  5.9 mm Hg in the placebo group and 173.8  $\pm$  9.9/

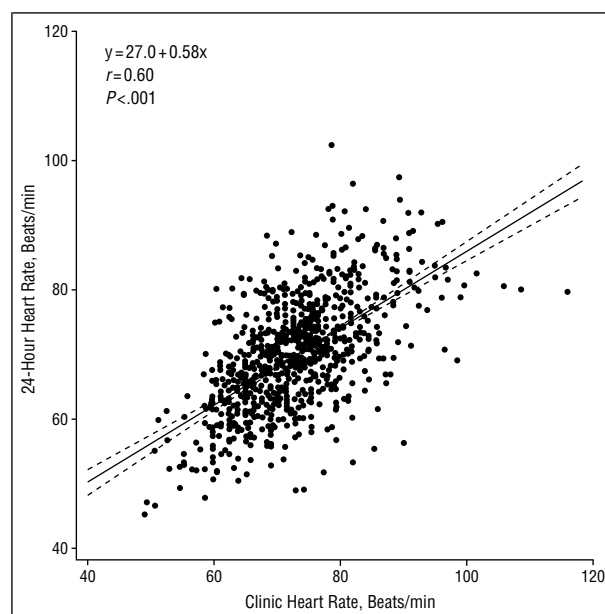
85.5 ± 5.8 mm Hg in the treatment group (difference not significant). Clinic heart rate was similar in the 2 groups (73.0 ± 8.1 vs 73.2 ± 7.9 beats/min [bpm]; difference not significant). No difference in body mass index, serum cholesterol level, the use of tobacco and alcohol, previous cardiovascular complications, or previous antihypertensive treatment was observed between the 2 groups. None of the subjects considered for this analysis had atrial fibrillation or other relevant arrhythmias at baseline assessment. Other clinical characteristics of the treatment group at randomization have been reported elsewhere.<sup>14</sup> The 496 women and 311 men with reliable 24-hour ABPM at baseline had similar clinical characteristics to those of the whole group.

Clinic and 24-hour heart rates were approximately normally distributed. In the ABPM subgroup, clinic heart rate was 3.8 ± 8.0 bpm higher than average 24-hour heart rate ( $P < .001$ ) and 1.1 ± 9.1 bpm higher than average daytime heart rate ( $P < .001$ ). Clinic and 24-hour heart rates correlated with each other (**Figure 1**).

Clinic and ambulatory heart rates were higher in women than in men, in subjects without cardiovascular complications than in those with complications, and in diabetic than nondiabetic patients (**Table 1**). No differences in heart rate were found by smoking status. However, clinic heart rate but not ambulatory heart rate was lower in patients consuming alcohol than in nondrinkers. Baseline clinic heart rate was slightly higher in subjects taking cardiac glycosides ( $n = 151$ ; 74.4 ± 9.4 bpm) or bronchodilators ( $n = 159$ ; 75.4 ± 8.6 bpm) than in the rest of the group (73.0 ± 7.9 bpm;  $P < .001$  vs both drugs combined). Similar heart rate differences were observed at the last follow-up visit.

In single regression analysis in the whole group, clinic heart rate showed a significant positive association with age, systolic BP, diastolic BP, and levels of glucose, triglycerides, and cholesterol, and a negative asso-

ciation with hemoglobin values (**Table 2**). In multiple regression analysis, clinic heart rate was independently associated with sex ( $P < .001$ ), age ( $P < .001$ ), diastolic BP ( $P < .001$ ), triglyceride levels ( $P = .02$ ), smoking ( $P = .003$ ), alcohol drinking (negative,  $P < .001$ ), cardiovascular complications ( $P = .008$ ), and diabetes ( $P < .001$ ). In the ABPM subgroup, 24-hour heart rate showed significant correlations with diastolic BP and triglyceride levels. These associations were present also in the multivariable regression analysis ( $P < .001$  and  $P = .03$ , respectively).



**Figure 1.** Correlation between clinic heart rate and mean 24-hour heart rate at baseline in 807 patients with isolated systolic hypertension.

**Table 1. Baseline Heart Rate in Subgroups According to Sex, Smoking, Alcohol Drinking, History of Cardiovascular Complications, and Diabetes\***

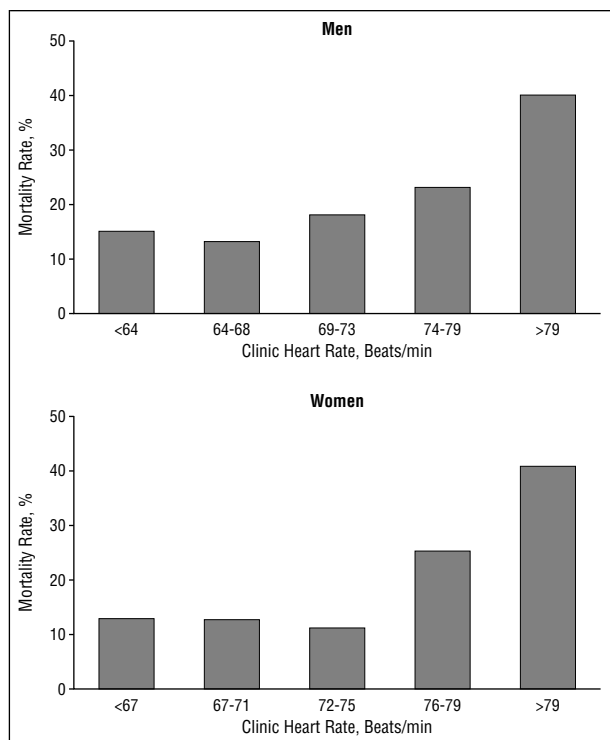
Characteristic	Whole Population, Clinic (n = 4682)	P Value	Ambulatory Blood Pressure Monitoring Subgroups (n = 807)							
			Clinic	P Value	24-Hour	P Value	Daytime	P Value	Nighttime	P Value
Men	72.0 ± 8.5	<.001	72.5 ± 9.7	<.05	68.0 ± 9.2	<.001	72.9 ± 10.5	<.001	60.6 ± 9.3	<.001
Women	73.7 ± 7.7		74.1 ± 8.6		71.0 ± 8.4		75.7 ± 9.7		63.1 ± 8.6	
Smokers	73.2 ± 8.7	NS	74.5 ± 9.1	NS	72.0 ± 9.8	NS	74.6 ± 10.2	NS	63.3 ± 10.5	NS
Nonsmokers	73.1 ± 8.0		73.4 ± 9.1		69.8 ± 8.8		74.6 ± 10.1		62.1 ± 8.8	
Nondrinkers	73.5 ± 7.7	<.001	74.2 ± 8.8	<.001	72.0 ± 8.9	NS	74.8 ± 10.3	NS	62.5 ± 9.1	NS
Occasional drinkers (<1 unit/d)	71.5 ± 8.7		74.1 ± 8.6		68.8 ± 8.0		73.9 ± 9.0		61.0 ± 7.9	
Moderate and heavy drinkers (≥1 unit/d)	72.1 ± 8.6	<.001	73.6 ± 10.3	NS	69.8 ± 9.7	NS	74.5 ± 10.7	NS	62.3 ± 9.5	NS
History of cardiovascular complications	72.6 ± 8.0	NS	72.2 ± 9.0	NS	68.7 ± 9.6	<.05	73.3 ± 11.0	<.05	60.9 ± 9.3	<.05
No history of cardiovascular complications	73.4 ± 8.0		74.0 ± 9.1		70.3 ± 8.5		75.0 ± 9.7		62.6 ± 8.8	
Diabetes	74.8 ± 7.7	<.001	76.3 ± 9.2	<.01	72.2 ± 9.1	<.05	76.9 ± 10.8	<.05	64.2 ± 9.1	<.05
Nondiabetes	72.9 ± 8.0		73.2 ± 9.0		69.6 ± 8.8		74.3 ± 10.0		61.9 ± 8.9	

\*Data are mean ± SD beats per minute. NS indicates not significant. An alcohol unit is 1 drink, or about 10 g of alcohol.

**Table 2. Correlates of Heart Rate in Single Regression Analysis\***

Variable	Whole Population, Clinic (n = 4682)		Ambulatory Blood Pressure Monitoring Subgroup (n = 807)							
	Clinic	P Value	Clinic	P Value	24-Hour	P Value	Daytime	P Value	Nighttime	P Value
Age	0.070	<.001	0.100	<.01	0.043	NS	0.016	NS	0.069	<.05
Body mass index	-0.017	NS	-0.057	NS	0.035	NS	0.030	NS	0.065	NS
Baseline systolic blood pressure	0.036	<.05	0.053	NS	0.048	NS	0.043	NS	0.078	<.05
Baseline diastolic blood pressure	0.048	<.01	0.056	NS	0.188	<.001	0.222	<.001	0.144	<.001
Fasting glucose	0.109	<.001	0.113	<.01	0.075	NS	0.056	NS	0.075	NS
Triglycerides	0.046	<.01	0.083	<.05	0.089	<.05	0.067	NS	0.11	<.01
Total cholesterol	0.027	NS	0.103	<.01	0.052	NS	0.066	NS	0.018	NS
Hemoglobin	-0.047	<.01	-0.047	NS	-0.030	NS	-0.007	NS	-0.010	NS

\*Values are Pearson correlation coefficients. NS indicates not significant.



**Figure 2.** Mortality rate in the men and women in the placebo group divided into quintiles of clinic heart rate at baseline.

### TREATMENT AND HEART RATE DURING FOLLOW-UP

Among the subjects in the placebo group, heart rate tended to decline during the follow-up, whereas it slightly increased in the subjects in the treatment group. At the last follow-up visit, in the intention-to-treat analysis, heart rate had fallen by  $0.37 \pm 9.0$  bpm ( $P = .05$ ) in the placebo group, whereas it tended to increase by  $0.33 \pm 8.8$  bpm ( $P = .07$ ) in the actively treated group. The between-group difference was 0.70 bpm (95% CI, 0.19-1.21 bpm). At the time of the last heart rate measurement, 1905 patients in the placebo group and 2168 patients in the active treatment group were still undergoing double-blind treatment. Among the 1857 patients taking active nitrendipine, there was no statistically significant relationship between the

heart rate change after treatment and the daily dose of the drug. Heart rate decreased by  $0.72 \pm 9.0$  bpm in the subjects taking 10 mg ( $n = 343$ ), increased by  $0.94 \pm 8.0$  bpm in those taking 20 to 30 mg ( $n = 644$ ), and increased by  $0.88 \pm 9.2$  bpm in those taking 40 mg ( $n = 870$ ) (differences not significant).

Of the 807 patients included in the ABPM project, 265 in the placebo group and 270 in the active treatment group underwent a reassessment of their ambulatory heart rate after randomization. At the last ABPM recording, 24-hour heart rate had fallen by  $0.81 \pm 7.8$  bpm ( $P = .09$ ) in the placebo group and by  $0.62 \pm 7.1$  bpm ( $P = .15$ ) in the active treatment group. The absolute reduction in 24-hour pulse rate in the placebo group was thus  $-0.19$  (95% CI,  $-1.46$  to  $1.07$ ) bpm.

### HEART RATE AND MORTALITY IN THE PLACEBO GROUP

During the follow-up period, 147 patients died in the placebo group. Of these deaths, 82 were due to cardiovascular disease causes, 27 to cancer, 22 to disorders of the respiratory system, 4 to gastrointestinal disease, 3 to accidents, 2 to hepatic failure, and 6 to other noncardiovascular disease causes, while for 1 death the cause remained unknown. Baseline heart rates were  $72.8 \pm 8.0$  bpm in people who survived, and  $74.9 \pm 8.6$ ,  $75.3 \pm 11.7$ ,  $75.3 \pm 7.9$ , and  $80.5 \pm 7.3$  bpm in those who died from cardiovascular causes, cancer, lung diseases, and other causes, respectively.

**Figure 2** shows the relationship between clinic heart rate and all-cause mortality rate by quintiles of heart rate in the patients of the placebo group stratified by sex. Similar trends were observed in the 2 sexes, as mortality rate was rather stable up to the third quintile, showed an increase from the third to the fourth quintile, and showed a further marked increment from the fourth to the top quintile. The association between heart rate and mortality was equally strong in the patients with and without cardiovascular complications. In men, markers of poor health such as hemoglobin or hematocrit values or body mass index did not vary across the heart rate quintiles. In women, body mass index was slightly lower among the subjects of the top heart rate quintile (27.0) than among the subjects of the other 4 quintiles (range, 27.2-

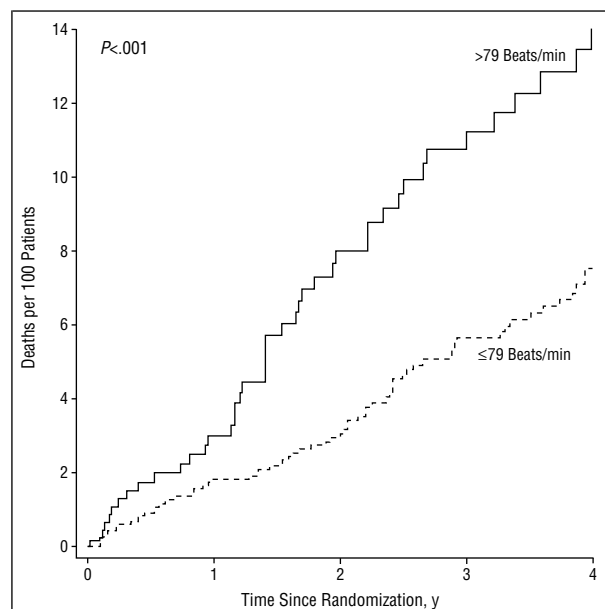
28.2) ( $P = .02$ ), while no between-quintile differences were observed for levels of hemoglobin and hematocrit. Subjects whose heart rate was in the top quintile showed an increased mortality rate compared with those in the lower quintiles (**Figure 3**).

As the association between heart rate and mortality was similar in the 2 sexes, in the subgroup of patients participating in the ABPM project, men and women were considered together, adjusting for sex (**Table 3**). In this subgroup, the positive relationship between clinic heart rate and the incidence of fatal end points was confirmed. Trends for 24-hour, daytime, and nighttime heart rates were similar to those for clinic heart rate.

Univariate and multivariable Cox regression analyses were performed to calculate the risk in the top quintile of heart rate relative to the other quintiles (**Table 4**). In multivariable analyses, simultaneous adjustments were applied for sex, age, current smoking, drinking status, systolic BP, previous cardiovascular complications, diabetes at entry, and hemoglobin levels. The incidence of fatal end points in the whole placebo group was 89% higher (95% CI, 33%-168%) in the upper quintile of clinic heart rate than in the other quintiles (**Table 5**). The predictive power of a high clinic heart rate was stronger for noncardiovascular than for cardiovascular mortality. Additional adjustments for body mass index, cholesterol, triglycerides, serum creatinine, serum uric acid, hemoglobin, and hematocrit values did not change the strength of the heart rate–mortality association.

Heart rate did not predict any of the nonfatal end points. Inclusion of treatment with cardiac glycosides

and with bronchodilators (dummy variables) virtually did not affect the risk of total mortality (1.88; 95% CI, 1.33-2.67;  $P < .01$ ) or cardiovascular mortality (1.60; 95% CI, 0.99-2.58;  $P = .05$ ). In the ABPM subgroup, a high clinic or ambulatory heart rate was a significant



**Figure 3.** Kaplan-Meier survival curves for all-cause mortality in 2293 elderly men and women with isolated systolic hypertension treated with placebo, stratified by heart rate level. Patients in the top heart rate quintile ( $>79$  beats/min) were compared with patients in the 4 lower quintiles ( $\leq 79$  beats/min).

**Table 3. All-Cause Mortality by Quintiles of Heart Rate in the Patients Randomized to Placebo\***

Characteristic	First Quintile	Second Quintile	Third Quintile	Fourth Quintile	Fifth Quintile
<b>Whole Placebo Group (n = 2293)</b>					
Clinic heart rate					
Heart rate interval	<66.6	<71	<75	$\leq 79$	>79
No. of subjects	444	465	475	438	471
Mean clinic heart rate	61.8	68.9	72.9	76.9	84.3
Mortality†	18.1	14.7	23.0	27.1	40.9
<b>Ambulatory Blood Pressure Monitoring Subgroup (n = 393)</b>					
Clinic heart rate					
Heart rate interval	$\leq 65.5$	66 to 69	70 to 75	76 to 80	>80
No. of subjects	79	75	79	84	76
Mean clinic heart rate	61.5	68.1	72.9	77.6	87.3
Mortality†	18.9	16.1	14.3	31.2	35.8
24-Hour heart rate					
Heart rate interval	<62.8	62.8 to <67.4	67.4 to <71.9	71.9 to <77.9	>77.9
No. of subjects	78	78	78	79	79
Mean 24-hour heart rate	58.3	65.1	69.6	74.7	83.1
Mortality†	19.9	23.4	17.7	17.8	38.1
Nighttime heart rate					
Heart rate interval	<55.7	55.7 to <59.8	59.8 to <64.2	64.2 to <70.4	>70.4
No. of subjects	78	78	79	79	78
Mean nighttime heart rate	50.9	58.0	62.0	66.9	75.7
Mortality†	15.6	21.7	26.1	17.1	37.3
Daytime heart rate					
Heart rate interval	<66.7	66.7 to <71.3	71.3 to <77.2	77.2 to <83.3	>83.3
No. of subjects	78	78	79	79	79
Mean daytime heart rate	61.0	69.1	74.2	80.2	89.9
Mortality†	21.7	58.8	14.8	22.1	32.8

\*All heart rates are expressed in beats/min.  
†Deaths per 1000 patients per year.

predictor for noncardiovascular but not cardiovascular mortality. The predictive power of conventional and ambulatory heart rates for noncardiovascular mortality was confirmed when heart rate was entered as a continuous variable in the Cox models (Table 5). Only high 24-hour ambulatory heart rate predicted increased mortality from cancer, with a relative hazard ratio of 2.56 (95% CI, 1.10-5.60). However, when clinic heart rate and ambulatory heart rate were entered simultaneously in the Cox analysis, only clinic heart rate remained a significant associate of noncardiovascular mortality ( $P=.004$ ). Inclusion of treatments in the regression analyses did not alter the results.

### HEART RATE AND MORTALITY IN THE TREATED GROUP

In treated patients, clinic heart rate at entry was a weak predictor of total and noncardiovascular mortality with

crude hazard ratios amounting to 1.22 ( $P=.05$ ) and 1.32 ( $P=.05$ ), respectively. After adjustment for confounders, clinic heart rate was no longer associated with outcome. All ambulatory heart rates were unrelated to mortality and to nonfatal cardiovascular events.

### COMMENT

#### CLINIC HEART RATE AND MORTALITY

The present results show that fast heart rate is an important predictor of mortality in elderly patients with isolated systolic hypertension. An important finding in the present investigation was that clinic heart rate had similar predictive power to that of heart rate recorded out of the office for 24 hours. In a regression analysis that included both heart rates, ambulatory heart rate was not a significant predictor of mortality over and above clinic heart rate.

**Table 4. Univariable and Multivariable Cox Analyses of Risk Function for All-Cause Mortality in the Placebo Group\***

Variable	Univariable			Multivariable†		
	Wald $\chi^2$	$\chi^2$ P Value	Risk Ratio (95% CI)	Wald $\chi^2$	$\chi^2$ P Value	Risk Ratio (95% CI)
Clinic heart rate (top quintile vs others)	15.2	<.001	1.97 (1.40-2.76)	11.6	<.001	1.94 (1.33-2.84)
Age (+10 years)	115.4	<.001	3.12 (2.53-3.83)	58.8	<.001	2.71 (2.10-3.49)
Sex† (0,1)	6.8	.009	1.54 (1.12-2.14)	4.1	.04	1.61 (1.02-2.56)
Cardiovascular complications† (0,1)	26.8	<.001	2.35 (1.70-3.25)	5.3	.02	1.53 (1.07-2.21)
Smoking† (0,1)	12.1	<.001	2.20 (1.41-3.44)	4.5	.03	1.79 (1.04-3.07)
Drinking alcohol† (0,1)	2.5	.11	0.73 (0.49-1.08)	1.8	.18	0.72 (0.45-1.16)
Diabetes† (0,1)	10.6	.001	2.00 (1.32-3.04)	9.9	.002	2.23 (1.35-3.67)
Systolic blood pressure (+10 mm Hg)	10.2	.001	1.24 (1.09-1.41)	3.2	.08	1.15 (0.99-1.34)
Body mass index (+1 kg/m <sup>2</sup> )	9.6	.002	0.93 (0.89-0.98)	1.2	.27	1.03 (0.98-1.08)
Total cholesterol (+1 mmol/L)	5.7	.02	0.84 (0.72-0.97)	0.1	.96	1.00 (0.85-1.17)
Triglycerides (+1 mmol/L)	5.5	.02	0.75 (0.59-0.95)	3.9	.05	0.76 (0.58-1.00)
Uric acid (+0.1 mmol/L)	0.3	.61	0.95 (0.78-1.16)	2.0	.16	0.85 (0.67-1.07)
Creatinine (+10 $\mu$ mol/L)	27.6	<.001	1.23 (1.14-1.32)	10.0	.002	1.17 (1.06-1.28)
Hemoglobin (+1 mmol/L)	9.0	.003	0.73 (0.60-0.90)	3.7	.05	0.80 (0.64-1.00)

\*CI indicates confidence interval.

†Men, smokers, alcohol consumers, and patients with a history of cardiovascular complications or diabetes are coded 1.

‡Analysis performed in 2151 subjects (of whom 124 died) with nonmissing values for all covariates.

**Table 5. Relative Hazard Rates for Heart Rate Measured in the Office and With Ambulatory Monitoring in the Whole Placebo Group and the Ambulatory Blood Pressure Monitoring Subgroup\***

	Dichotomous Analysis					
	Total Mortality	P Value	Cardiovascular Mortality	P Value	Noncardiovascular Mortality	P Value
<b>Whole Placebo Group</b>						
No. of end points	145		80		64	
Conventional heart rate	1.89 (1.33-2.68)	<.001	1.60 (0.99-2.59)	<.05	2.22 (1.31-3.74)	<.01
<b>Ambulatory Blood Pressure Monitoring Subgroup</b>						
No. of end points	39		22		17	
Conventional heart rate	1.64 (0.80-3.39)	NS	0.91 (0.30-2.80)	NS	2.91 (1.04-8.20)	<.05
24-Hour heart rate	1.54 (0.76-3.12)	NS	0.68 (0.22-2.11)	NS	3.42 (1.22-9.53)	<.05
Daytime heart rate	1.27 (0.60-2.65)	NS	0.32 (0.07-1.41)	NS	3.86 (1.38-10.8)	<.05
Nighttime heart rate	1.59 (0.77-3.30)	NS	0.71 (0.22-2.29)	NS	3.42 (1.23-9.53)	<.05

\*Relative hazard rates (95% confidence intervals) reflect the risk in the top quintile of heart rate vs the other quintiles (dichotomous analysis) or associated with a 10-beats/min increase in heart rate (continuous analysis). In this model, the number of deaths is 145 instead of 147 because 2 subjects had missing values for hemoglobin levels; the 145 total includes 1 death of unknown cause that could not be classified as either cardiovascular or noncardiovascular. Relative hazard rates were adjusted for sex, age, cardiovascular complications at entry, diabetes at entry, smoking and drinking habits, systolic blood pressure, and hemoglobin levels. Unless otherwise indicated, data are median (95% confidence interval) values. NS indicates not significant.

A number of epidemiologic studies have shown that high heart rate is associated with increased risk of death from either cardiovascular or noncardiovascular causes in middle-aged persons<sup>6-9</sup> and elderly subjects,<sup>10,11</sup> and that this effect is independent of other major risk factors for atherosclerosis. Fast heart rate has demonstrated predictive power for mortality in subjects with hypertension (greater impact in men than in women).<sup>12,13,18</sup> The present data demonstrate that in elderly subjects with systolic hypertension, the association between heart rate and total mortality is equally strong in men and women. Men and women with clinic heart rates higher than 79 bpm (top quintile) had an 89% increase in the adjusted risk of mortality compared with subjects with lower heart rates.

The relative importance of some traditional risk factors for cardiovascular disease seem to decline in old age. In agreement with the results of previous studies, the present data indicate that smoking has small predictive power for mortality in elderly subjects with systolic hypertension and that total cholesterol level has a negligible value.<sup>1-5,18</sup> In contrast, heart rate appeared to be an important predictor of risk in old age, and in the multivariable analysis its predictive power for mortality was comparable to that of diabetes or serum creatinine values. In both sexes, a marked increase in mortality was observed chiefly for the top quintile (heart rate >79 bpm). These results are in keeping with those from the elderly men of the Cardiovascular Study in the Elderly (CASTEL),<sup>11</sup> in which a sharp increase in the risk of mortality was found for a heart rate higher than 80 bpm.

Active treatment weakened the association between heart rate and mortality to a nonsignificant level when data were controlled for confounders and other risk factors for cardiovascular disease. This may be owing to drug-induced changes in heart rate after starting treatment. It is known that a possible adverse effect of calcium antagonists is reflex sympathetic activation, especially with faster-acting drugs.<sup>19</sup> On average, nitrendipine caused only a modest increase in heart rate (<1 bpm), and this may explain why it was beneficial in reducing cardiovascular events in

the Syst-Eur study.<sup>14</sup> However, changes in heart rate varied widely from patient to patient.

#### CLINIC VS AMBULATORY HEART RATE

Up to now, the predictive value of 24-hour heart rate for mortality has been tested only in 1 study. In 360 unselected men and 921 unselected women older than 60 years with heart disease, Aronow et al<sup>10</sup> documented an association of Holter monitor-recorded heart rate with cardiovascular mortality. Unfortunately, that study failed to compare the predictive power of ambulatory heart rate with that of clinic heart rate. In the present study, clinic heart rate and ambulatory heart rate showed a predictive power for mortality that was significant for death from noncardiovascular causes. However, ambulatory heart rate did not provide any prognostic information over and above clinic heart rate.

A number of mechanisms have been postulated to explain the pathogenesis of the connection between elevated heart rate and mortality.<sup>5,20</sup> The clustering of several risk factors in subjects with fast heart rate may explain why cardiovascular morbidity is increased in individuals with high heart rate. As shown here and elsewhere,<sup>5,6,11,21</sup> clinic heart rate is correlated with systolic and diastolic BP and levels of fasting glucose, triglycerides, and total cholesterol. It has been postulated that sympathetic overactivity can be responsible for the increase in heart rate, BP, and metabolic abnormalities.<sup>5,20</sup> According to this hypothesis, fast heart rate measured in the clinic reflects a heightened sympathetic tone that in the long run can cause an insulin resistance state.<sup>5,20</sup> In the present study, heart rate was positively related to age. This may be owing to lack of physical training with advancing age or to the association of heart rate with arterial stiffness,<sup>22</sup> which is related to age. Experimental studies in monkeys have shown that heart rate can exert also a direct atherogenetic action on the arteries through increased wall stress.<sup>23,24</sup> Moreover, tachycardia can favor the occurrence of ventricular arrhythmias and sudden death.<sup>25</sup> These and other

Continuous Analysis					
Total Mortality	P Value	Cardiovascular Mortality	P Value	Noncardiovascular Mortality	P Value
<b>Whole Placebo Group</b>					
145		80		64	
1.40 (1.16-1.70)	<.001	1.23 (0.95-1.60)	NS	1.63 (1.22-2.18)	<.001
<b>Ambulatory Blood Pressure Monitoring Subgroup</b>					
39		22		17	
1.44 (1.04-1.98)	<.05	1.03 (0.66-1.60)	NS	2.36 (1.41-3.93)	<.01
1.16 (0.83-1.63)	<.05	0.85 (0.54-1.36)	NS	1.70 (0.99-2.91)	NS
1.05 (0.78-1.41)	NS	0.80 (0.54-1.19)	NS	1.52 (0.93-2.48)	NS
1.32 (0.96-1.82)	NS	1.03 (0.66-1.63)	NS	1.74 (1.09-2.79)	<.05

mechanisms have been discussed extensively elsewhere.<sup>5,20</sup>

In the Syst-Eur Trial, heart rate measured either in the clinic or under ambulatory conditions showed a strong association primarily with noncardiovascular mortality. Similar results were obtained in studies performed in general populations.<sup>6-9,13</sup> The association appeared particularly strong in the Framingham Study<sup>8,9</sup> and the Paris Prospective Study<sup>26</sup> in which the predictive power of heart rate for noncardiovascular death was second only to smoking. This finding suggests that heart rate is a nonspecific measure of health and mortality rates. Noncardiovascular causes of death are heterogeneous, making it difficult to perform subanalyses and draw conclusions. It is possible that heart rate is a surrogate for some unmeasured variables that may be causally linked to noncardiovascular mortality. For example, deaths from respiratory diseases are common in older subjects, as shown also by the present study, and augmented heart rate has been shown to be associated with degree of hypoxia.<sup>27</sup>

In the Framingham Study, reduced forced expiratory volume was a strong predictor of total mortality in subjects older than 50 years, but also after adjustment for that variable, heart rate remained a potent predictor of all-cause mortality.<sup>9</sup> In the present study, the predictive value of heart rate for total mortality remained virtually the same when markers of poor health such as body mass index and levels of hemoglobin, cholesterol, and creatinine were included in the Cox analysis. Moreover, the relationship between heart rate and death was equally strong in the subjects with or without cardiovascular complications, making it unlikely that the association between accelerated heart rate and mortality merely reflected poor health or an advanced, rapidly progressing disease.

In the Syst-Eur study, higher ambulatory heart rate was associated with increased cancer mortality. An association between heart rate and total cancer mortality has been described in previous studies both in male<sup>28</sup> and female<sup>29</sup> cohorts. Neurotrophic factors associated with sympathetic nervous system activity are believed to influence some types of cancer and might link mortality from various cancers to heart rate.<sup>30</sup> Increased social stress and other psychological factors could be underlying mechanisms that influence hemodynamic factors and cancer mortality. At the cellular and molecular levels, growth factors could be the link element between hemodynamic stress and the evolution of cancer, as postulated by some authors.<sup>31</sup>

## CLINICAL IMPLICATIONS

The association between clinic heart rate and mortality found in the present study suggests that tachycardia, though it may depend on the emotional stress related to the conditions of measurement, should not be considered innocent in elderly subjects with systolic hypertension. In agreement with previous reports,<sup>32</sup> a marked increase in risk was observed for a heart rate of 80 bpm or higher, a level well below that which is currently used to define tachycardia. This raises the question of whether drug-induced heart rate reduction might improve prog-

nosis in elderly hypertensive subjects with resting heart rates above that level.

The pathogenetic mechanism for the connection between tachycardia and mortality is still a subject for debate. If we consider heart rate merely a marker of altered autonomic tone, a drug that reduces sympathetic overactivity should be preferred in these subjects. On the other hand, subjects with faster heart rates during clinic examination also exhibited higher heart rates out of the office during activities of daily living, suggesting that the hemodynamic effects of fast heart rate can be deleterious. Thus, among first-line antihypertensive drugs,  $\beta$ -blockers and nondihydropyridine calcium antagonists may be useful for elderly hypertensive subjects with fast heart rates provided there are no contraindications to the use of these drugs.

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