

Pulse Pressure Not Mean Pressure Determines Cardiovascular Risk in Older Hypertensive Patients

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Background: Current guidelines for the management of hypertension rest almost completely on the measurement of systolic and diastolic blood pressure. However, the arterial blood pressure wave is more correctly described as consisting of a pulsatile (pulse pressure) and a steady (mean pressure) component.

Objective: To explore the independent roles of pulse pressure and mean pressure as determinants of cardiovascular prognosis in older hypertensive patients.

Methods: This meta-analysis, based on individual patient data, pooled the results of the European Working Party on High Blood Pressure in the Elderly trial (n = 840), the Systolic Hypertension in Europe Trial (n = 4695), and the Systolic Hypertension in China Trial (n = 2394). The relative hazard rates associated with pulse pressure and mean pressure were calculated using Cox regression analysis, with stratification for the 3 trials and with adjustments for sex, age, previous cardiovascular complications, smoking, and treatment group.

Results: A 10-mm Hg wider pulse pressure increased the

risk of major cardiovascular complications; after controlling for mean pressure and the other covariates, the increase in risk ranged from approximately 13% for all coronary end points ($P = .02$) to nearly 20% for cardiovascular mortality ($P = .001$). In a similar analysis, mean pressure predicted the incidence of cardiovascular complications but only after removal of pulse pressure as an explanatory variable from the model. Furthermore, the probability of a major cardiovascular end point increased with higher systolic blood pressure; at any given level of systolic blood pressure, it also increased with lower diastolic blood pressure, suggesting that the wider pulse pressure was driving the risk of major complications.

Conclusions: In older hypertensive patients, pulse pressure not mean pressure is the major determinant of cardiovascular risk. The implications of these findings for the management of hypertensive patients should be further investigated in randomized controlled outcome trials in which the pulsatile component of blood pressure is differently affected by antihypertensive drug treatment.

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ARTERIAL HYPERTENSION mechanically stresses the endothelium and the deeper layers of the arterial wall. The ensuing arterial lesions lead in the long run to debilitating and lethal complications, in particular stroke and myocardial infarction. The current guidelines for the management of hypertension rest almost completely on the measurement of systolic and diastolic blood pressure, 2 specific inflection points of the blood pressure wave, which are usually considered in isolation.^{1,2} However, blood pressure propagates through the arterial tree as a repetitive continuous wave and is more accurately described as consisting of a pulsatile component (pulse pressure) and a steady component (mean pressure).³ The former depends on ventricular ejection, arterial stiffness, and the

timing of wave reflections, whereas cardiac output and peripheral vascular resistance are the major determinants of mean pressure.

Several observational studies⁴⁻¹³ produced evidence suggesting that in middle-aged and older people pulse pressure may be a better predictor of cardiovascular complications than mean pressure. However, these findings require further clarification. Pulse pressure widens with advancing age,¹⁴ so the outcome trials in elderly hypertensive patients may provide a database particularly suitable to explore the independent roles of pulse pressure and mean pressure as determinants of cardiovascular prognosis. To address this issue with sufficient statistical power, the present study pooled the results of 3 placebo-controlled trials in elderly patients with hypertension: the European Working Party on High

SUBJECTS AND METHODS

STUDY PROTOCOLS

The EWPHE, Syst-Eur, and Syst-China had a placebo-controlled, parallel-group design, which is described in detail elsewhere.¹⁵⁻¹⁷ Eligible patients had to be at least 60 years old. During a 3-month run-in period using single-blind placebo, the patients were required to have average sitting systolic and diastolic blood pressures as follows: 160 to 239 mm Hg systolic and 90 to 119 mm Hg diastolic in the EWPHE¹⁵ and 160 to 219 mm Hg systolic and less than 95 mm Hg diastolic in Syst-Eur¹⁶ and Syst-China.¹⁷

Before randomization^{15,16} or alternate allocation¹⁷ to double-blind treatment with active medication or placebo, the patients were stratified by center, sex, and cardiovascular complications in each of the 3 trials¹⁵⁻¹⁷ and in addition by age in the EWPHE.¹⁵ Active treatment was initiated with a fixed combination of hydrochlorothiazide plus triamterene (25 mg plus 50 mg, respectively, once or twice daily) in the EWPHE¹⁵ and with nitrendipine (10-40 mg/d) in Syst-Eur¹⁶ and Syst-China.¹⁷ In treatment-resistant patients, the first-line drug was combined with methyl-dopa (0.25-2 g/d) in the EWPHE,¹⁵ with enalapril maleate (5-20 mg/d) and/or hydrochlorothiazide (12.5-25 mg/d) in Syst-Eur,¹⁶ or with captopril (12.5-50 mg/d) and/or hydrochlorothiazide (12.5-50 mg/d) in Syst-China.¹⁷ The patients in the control groups received matching placebos.

In the 3 trials, systolic and phase V diastolic blood pressure were measured after at least 3 minutes of rest in the sitting position at 2 to 3 different visits during the placebo run-in period.¹⁵⁻¹⁷ The baseline blood pressure was defined as the average of all sitting readings obtained during the run-in period. Pulse pressure was the difference between systolic and diastolic blood pressures. Mean pressure was calculated as diastolic blood pressure plus one third of pulse pressure. In the present analysis, the definition of events was the same for the 3 trials. Thus, the end points reported in the present analysis did not include those classified as nonfatal, nonmorbidity in the EWPHE.

STATISTICAL ANALYSIS

Database management and statistical analysis were performed with SAS software, version 6.12 (SAS Institute Inc, Cary, NC). Event rates in the tertiles of the pulse pressure distributions were compared with 2-tailed tests by computing the standardized normal deviate. Pulse pressure and mean pressure were correlated with morbidity and mortality using the Cox proportional hazards model. Stratification of the Cox model accounted for the differences among the 3 trials. The data were analyzed by intention to treat for all end points, with the exception of the nonfatal complications in the EWPHE, which had only been recorded during the double-blind phase of this study.

Blood Pressure in the Elderly trial (EWPHE),¹⁵ the Systolic Hypertension in Europe Trial (Syst-Eur),¹⁶ and the Systolic Hypertension in China Trial (Syst-China).¹⁷

Table 1. Characteristics of the Patients at Entry in the 3 Trials*

Characteristic	EWPHE	Syst-Eur	Syst-China
No. of patients	840	4695	2394
Male, No. (%)	254 (30.2)	1557 (33.2)	1541 (64.4)
Active treatment, No. (%)	416 (49.5)	2398 (51.5)	1253 (52.3)
Age, mean \pm SD, y	71.8 \pm 8.0	70.2 \pm 6.7	66.6 \pm 5.5
Systolic blood pressure, mean \pm SD, mm Hg	182.6 \pm 16.5	173.8 \pm 10.0	170.5 \pm 11.1
Diastolic blood pressure, mean \pm SD, mm Hg	100.5 \pm 7.1	85.5 \pm 5.9	86.1 \pm 6.7
Pulse pressure, mean \pm SD, mm Hg	82.1 \pm 16.0	88.4 \pm 11.2	84.4 \pm 12.4
Mean pressure, mean \pm SD, mm Hg	127.9 \pm 8.2	114.9 \pm 5.3	114.2 \pm 6.1
Body mass index, mean \pm SD, kg/m ²	26.4 \pm 4.5	27.0 \pm 4.1	23.9 \pm 3.4
Serum cholesterol, mean \pm SD, mmol/L†	6.4 \pm 1.3	6.0 \pm 1.2	5.1 \pm 1.2
Cardiovascular complications, No. (%)	300 (35.7)	1402 (29.9)	269 (11.2)
Current smokers, No. (%)	143 (17.0)	343 (7.3)	737 (30.8)

*EWPHE indicates European Working Party on High Blood Pressure in the Elderly trial¹⁵; Syst-Eur, Systolic Hypertension in Europe Trial¹⁶; and Syst-China, Systolic Hypertension in China Trial.¹⁷

†To convert serum cholesterol values to conventional units (milligrams per deciliter), divide by 0.02586.

RESULTS

CARDIOVASCULAR END POINTS IN TERTILES OF PULSE PRESSURE

The main characteristics of the patients enrolled in the EWPHE, Syst-Eur, and Syst-China appear in **Table 1**. Overall, pulse pressure ranged from 42 to 154 mm Hg and mean pressure from 80 to 157 mm Hg. In a first step of the analysis, the crude incidence rates of all fatal and nonfatal cardiovascular end points were calculated in tertiles of pulse pressure in the 2 treatment groups of each of the 3 trials separately (**Figure 1**). In all instances, with the exception of the placebo group in Syst-Eur ($P = .20$), the occurrence of all fatal and nonfatal cardiovascular end points was significantly greater in the highest compared with the lowest tertile of pulse pressure.

PULSE PRESSURE AND MEAN PRESSURE AS INDEPENDENT RISK FACTORS

In a further step of the analysis, the risks associated with pulse pressure and mean pressure were adjusted for sex, age, previous cardiovascular complications, smoking, and active treatment. In addition, the relative hazard rates for pulse pressure were also adjusted for mean pressure and vice versa (**Table 2**). In each trial, with the exception of only the coronary end points in Syst-Eur, pulse pressure was associated with a risk ratio greater than unity; the hazard rates were statistically significant for cardiovascular mortality and all cardiovascular end points in the EWPHE, for fatal and nonfatal stroke in Syst-Eur, and for all end points considered in the analysis in Syst-China. Overall, in Cox regression with stratification for the 3 trials and with adjustment for the other covariates,

a 10-mm Hg wider pulse pressure was correlated with an increase in the risk of any end point by approximately 10% to 20% (Table 2).

Mean pressure adjusted for pulse pressure and the same set of possible confounders was not identified as a consistent and significant predictor of risk (Table 2). However, without the adjustment for pulse pressure, the hazard rates associated with a 10-mm Hg increase in mean pressure were 1.16 (95% confidence interval [CI], 1.03-1.32; $P = .02$) for total mortality, 1.17 (95% CI, 0.99-1.38; $P = .06$) for cardiovascular mortality, 1.09 (95% CI, 0.98-1.27; $P = .12$) for all cardiovascular end points, 1.21 (95% CI, 1.00-1.44; $P = .05$) for fatal and nonfatal stroke, and 1.08 (95% CI, 0.89-1.32; $P = .44$) for fatal and nonfatal coronary end points.

Pulse pressure and mean pressure were both calculated from systolic and diastolic blood pressure. To exclude the possibility that a mathematical artifact in these calculations led to the identification of pulse pressure rather than mean pressure as an independent risk factor, continuous risk functions were plotted for systolic blood pressure at fixed levels of diastolic blood pressure (Figure 2). The 2-year probability of a major cardiovascular end point increased with higher systolic blood pressure ($P < .001$). However, at any given level of systolic blood pressure, the risk also increased ($P = .001$) with lower diastolic blood pressure, suggesting that the wider pulse pressure was driving the risk of major complications.

COMMENT

The major finding of this study was that across 3 outcome trials involving older patients with systolic and diastolic hypertension¹⁵ or patients with isolated systolic hypertension,¹⁶⁻¹⁸ pulse pressure at entry—not mean pressure—independently predicted the incidence of cardiovascular complications and all-cause mortality. These results were consistent in white and Asian patients. Adjustments for active antihypertensive drug treatment and other possible confounders did not remove the relationship with pulse pressure. On the other hand, the present findings must be cautiously interpreted. The positive and independent correlation between pulse pressure and the incidence of cardiovascular complications does not necessarily imply a causal or reversible relationship. In addition, whether the present findings may be extrapolated to younger or middle-aged patients remains to be elucidated.

The Hypertension Detection and Follow-up Program reported that all-cause mortality increased by 11% per 10-mm Hg increment in pulse pressure but only by 8% and 5% for similar increases in systolic and diastolic blood pressures, respectively.¹⁹ The Framingham Heart Study demonstrated that in the general population systolic blood pressure was a better predictor of cardiovascular risk than diastolic blood pressure, particularly for patients older than 50 years,²⁰ and that at any level of entry diastolic blood pressure, cardiovascular risk increased with systolic blood pressure. Similar findings were reported in a large cohort of middle-aged white men.^{5,13} Darné et al⁴ were among the first to notice that pulse pres-

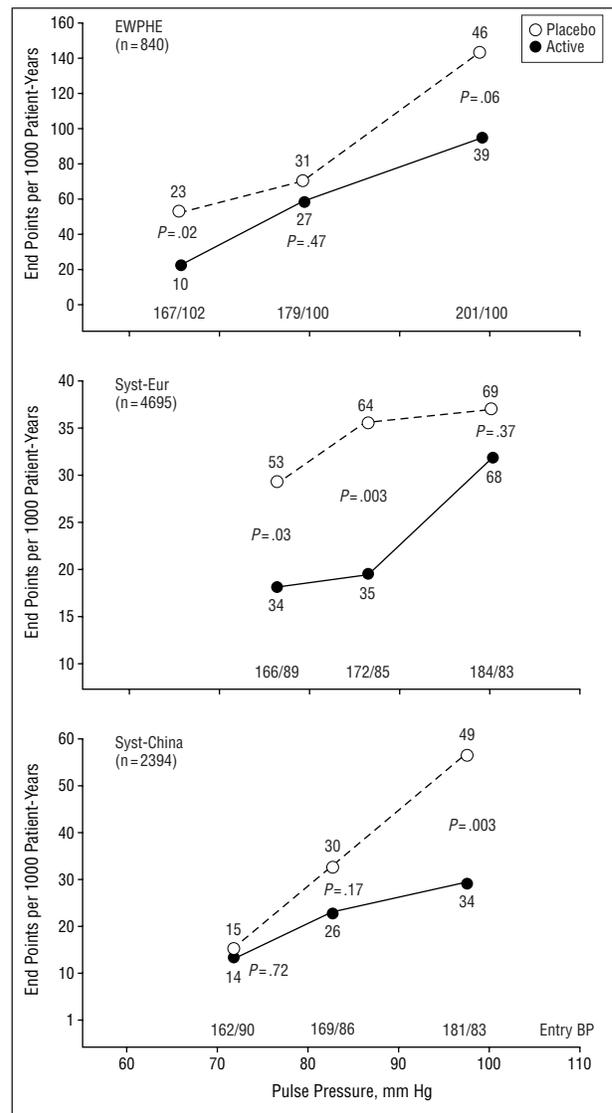


Figure 1. Incidence of all cardiovascular end points in tertiles of pulse pressure in the European Working Party on High Blood Pressure in the Elderly trial,¹⁵ Systolic Hypertension in Europe Trial,¹⁶ and Systolic Hypertension in China Trial.¹⁷ The number of events are given for each tertile. In each trial, the overall incidence of cardiovascular end points was significantly lower in the actively treated patients than in those taking placebo. P values are for the differences in the rates between corresponding tertiles of patients in the placebo or active treatment group. BP indicates blood pressure.

sure, in addition to mean pressure, was an independent cardiovascular risk factor, mainly for cardiac mortality, although only in women older than 55 years. More recently, several groups confirmed that pulse pressure in both hypertensive subjects⁷⁻¹⁰ and patients who had had myocardial infarctions¹¹ predicted coronary events and, to a lesser extent, stroke. These findings were consistent in men and women and even in treated hypertensive patients whose diastolic blood pressure was reduced to within the normal range.⁸⁻¹⁰

In the present analysis, the 2-year probability of a major cardiovascular end point increased with higher systolic blood pressure. In addition, extrapolation from the Cox regression model showed that at any given level of systolic blood pressure the cardiovascular risk also in-

Table 2. Adjusted Relative Hazard Rates Associated With a 10-mm Hg Increase in Pulse or Mean Pressure*

Characteristic	EWPHE	Syst-Eur	Syst-China	All†
Pulse pressure‡				
Total mortality	1.09 (0.97-1.23)	1.06 (0.96-1.17)	1.38 (1.23-1.57)¶	1.15 (1.07-1.22)¶
Cardiovascular mortality	1.17 (1.01-1.36)	1.10 (0.97-1.27)	1.48 (1.27-1.72)¶	1.22 (1.13-1.33)¶
Cardiovascular end points	1.15 (1.03-1.29)	1.06 (0.97-1.16)	1.38 (1.24-1.55)¶	1.17 (1.10-1.24)¶
Stroke	1.10 (0.90-1.36)	1.18 (1.03-1.36)	1.22 (1.04-1.41)	1.17 (1.07-1.29)¶
Coronary end points	1.08 (0.90-1.32)	0.97 (0.83-1.12)	1.64 (1.36-2.00)¶	1.13 (1.02-1.24)
Mean pressure§				
Total mortality	1.16 (0.94-1.44)	1.02 (0.83-1.23)	0.83 (0.65-1.04)	1.01 (0.90-1.14)
Cardiovascular mortality	1.22 (0.93-1.58)	0.89 (0.68-1.15)	0.72 (0.53-0.99)	0.97 (0.83-1.13)
Cardiovascular end points	1.12 (0.90-1.37)	0.93 (0.78-1.12)	0.83 (0.66-1.03)	0.96 (0.86-1.08)
Stroke	1.51 (1.05-2.18)	0.98 (0.74-1.31)	0.85 (0.63-1.15)	1.06 (0.89-1.27)
Coronary end points	1.09 (0.77-1.55)	1.05 (0.78-1.41)	0.76 (0.52-1.14)	0.97 (0.80-1.18)

*EWPHE indicates European Working Party on High Blood Pressure in the Elderly trial¹⁵; Syst-Eur, Systolic Hypertension in Europe Trial¹⁶; and Syst-China, Systolic Hypertension in China Trial.¹⁷ All hazard rates are presented with 95% confidence intervals in parentheses and were adjusted for sex, age, previous cardiovascular complications, smoking, and active treatment.

†Stratification of the Cox models accounted for differences among the 3 trials.

‡Also adjusted for mean pressure.

§Also adjusted for pulse pressure.

||P < .05.

¶P ≤ .001.

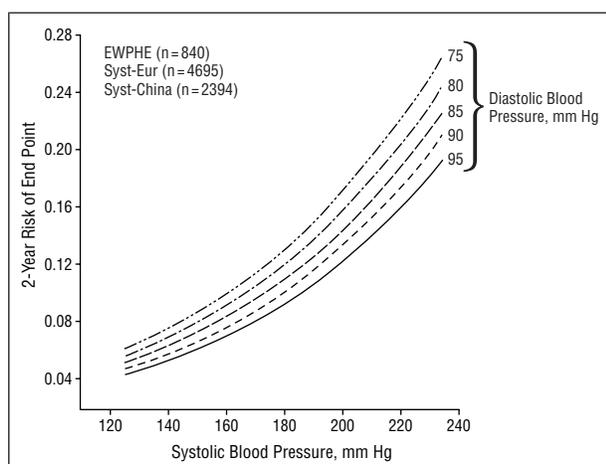


Figure 2. Risk associated with increasing systolic blood pressure at fixed levels of diastolic blood pressure. The 2-year probability of a cardiovascular end point was adjusted for active treatment, sex, age, previous cardiovascular complications, and smoking by Cox multiple regression with stratification for trial (European Working Party on High Blood Pressure in the Elderly trial,¹⁵ Systolic Hypertension in Europe Trial,¹⁶ and Systolic Hypertension in China Trial¹⁷).

creased with lower diastolic blood pressure. These findings confirmed the hypothesis that the wider pulse pressure was driving the risk of major complications. In Syst-Eur¹⁶ and Syst-China,¹⁷ the patients were recruited because they had a systolic blood pressure of 160 mm Hg or higher in the presence of a diastolic blood pressure below 95 mm Hg. However, also in the middle-aged white men randomized in the Multiple Risk Factor Intervention Trial, the greatest risk was observed in the subjects with the highest systolic blood pressure (≥ 160 mm Hg) and the lowest diastolic blood pressure (< 70 mm Hg) at enrollment.¹³

The present findings may have important clinical implications in terms of risk assessment and risk reduction.²¹ They suggest that accounting for the whole blood pressure curve, by considering the pulsatile and the steady

component of blood pressure, significantly improves the prediction of cardiovascular complications. For myocardial infarction, the underlying mechanism is not just the poor coronary perfusion associated with low diastolic blood pressure but also the generally reduced elasticity of the large arteries, which is a harbinger of vascular complications in all arterial beds.²² The repercussions of these findings for the diagnosis and management of hypertensive patients should be further investigated in randomized controlled clinical trials. In these future intervention studies, patients could be recruited on the basis of both the level of blood pressure and the width of pulse pressure. They could then be randomized to antihypertensive drugs, which act differently on the pulsatile component of blood pressure. Vasopeptidase inhibitors^{23,24} and nitric oxide donors²⁵ may possibly increase the distensibility of the large arteries and reduce pulse pressure, although their hypothesized benefit in terms of a reduction of cardiovascular morbidity and mortality still remains to be proven.

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