Pulsatile blood pressure component as predictor of mortality in hypertension: a meta-analysis of clinical trial control groups

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Objective **Although current guidelines rest exclusively on the measurement of systolic and diastolic blood pressures, the arterial pressure wave is more precisely described as consisting of a pulsatile (pulse pressure) and a steady (mean pressure) component. This study explored the independent roles of pulse pressure and mean pressure as predictors of mortality in a wide range of patients with hypertension.**

Design and methods **This meta-analysis, based on individual patient data, has combined results from the control groups of seven randomized clinical trials conducted in patients with systolo-diastolic or isolated systolic hypertension. The relative hazard rates associated with pulse pressure and mean pressure were calculated using Cox's proportional hazard regression models with stratification for the seven trials and with adjustment for sex, age, smoking and the other pressure.**

Results **A 10 mmHg wider pulse pressure at baseline, which corresponds to approximately one-half of its standard deviation, was independently associated with an increase in risk by 6% for total mortality ($P = 0.001$), 7% for cardiovascular mortality ($P = 0.01$), and 7% for fatal coronary accidents ($P = 0.03$).The corresponding increase in risk of fatal stroke was similar (+6%, $P = 0.27$) but there were too few strokes to reach statistical significance. In similar analyses, mean pressure was not identified as an independent predictor of these outcomes. Significant interactions of pulse pressure or mean pressure with age suggested that the prognostic power of pulse pressure for fatal stroke was more important at higher age ($P = 0.04$), whereas the prognostic power of mean pressure for coronary mortality was greatest in the young ($P = 0.01$).**

Conclusions **In hypertensive patients pulse pressure, not mean pressure, is associated with an increased risk of fatal events. This appears to be true in a broad range of patients with hypertension. *J Hypertens* 20:145–151 © 2002 Lippincott Williams & Wilkins.**

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Introduction

An elevated blood pressure acts in arteries as an injuring mechanical force, which may contribute to the development of atherosclerosis and to the increase in cardiovascular risk. The current guidelines for the detection and management of hypertension [1,2] rest on the measurement of the extreme values of blood pressure during the heart cycle, that is systolic and diastolic blood pressure. However, the arterial pressure wave is more precisely described as consisting of a pulsatile (pulse pressure) and a steady (mean pressure) component. Several observational studies showed that pulse pressure may be an independent predictor of cardiovascular risk in the population [3–8], in hypertensive patients [9–13], in survivors of myocardial infarction [14], and in patients with left ventricular dysfunction [15]. A recently conducted analysis of the combined data from the EWPHE [16], Syst-Eur [17] and Syst-China [18] trials, showed that in elderly hypertensives, of whom most had isolated systolic hypertension, pulse pressure and not mean pressure predicted subsequent cardiovascular events [19]. However, it has not yet been fully studied whether this finding is consistent in hypertensives with wider age and blood pressure range. The collaboration within the framework of the INDANA project [20] allowed us to examine this question.

Methods

In this overview, we included seven trials (Table 1). Six of these (EWPHE [16], HEP [21], MRC1 [22], MRC2 [23], SHEP [24], STOP [25]) had been incorporated in the INDANA database. The data of the Systolic Hypertension in Europe (Syst-Eur) Trial [17] and of the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial [16] are held by the Study Co-ordinating Office at the Hypertension Unit of the University of Leuven, where this analysis was designed and conducted. Of the trials included in the INDANA database, we excluded the following: Multiple Risk Factors Intervention Trial [26] (MRFIT) and Hypertension Detection and Follow-up Program [27] because the control groups were not left untreated. The Australian Trial in Mild Hypertensives [28] was excluded because the final mortality survey was not carried out. The trials included tested different antihypertensive regimens. To test the predictive value of blood pressure components irrespective of treatment, we decided to include the data from the control groups only. Finally, only the mortality data were analysed, because in some trials such as EWPHE [16], non-fatal events were not recorded in patients who withdrew from double-blind treatment. Furthermore, fatal events are less easily misclassified than non-fatal ones and the definitions of the non-fatal events differed among several of the trials.

The outcomes studied included: total mortality, cardiovascular mortality, fatal stroke, and fatal coronary heart disease. The events have been defined as in the INDANA database [20]. Fatal coronary events included fatal myocardial infarction and sudden death (any death of unknown cause occurring within 24 h upon onset of symptoms). Cardiovascular mortality comprised fatal stroke, fatal coronary heart disease, fatal heart failure and other fatal cardiovascular events.

Database management and statistical analysis of the individual patient data from control groups were performed with SAS software (SAS Institute Inc, Cary, North Carolina, USA) [29]. First, after stratification for trial and adjustment for age and sex, we subdivided the distribution of systolic, diastolic, pulse pressure and mean pressure into thirds, and counted the incidence rates in those thirds. Logistic regression with pressure tertiles coded as single three-level categorical variables, was used to test for the linear trend. Then, pulse pressure and mean pressure were correlated with mortality using Cox's proportional hazard model. We report the relative hazard rates (RHR) for a 10 mmHg wider pulse pressure or a 5 mmHg higher mean pressure at baseline, which approximated to one-half of their respective standard deviations when the data were pooled. Stratification of the model accounted for the differences between the trials. The consistency of the results across studies was assessed by the application of a heterogeneity test [30]. Finally, to test the hypothesis that the risk attributable to pulse or mean pressure would be different at different ages, we tested the interaction between age and pulse pressure or mean pressure, respectively, after adjustment for confounders and the other pressure.

Results

The general characteristics

The control groups comprised 17 239 patients. Their main characteristics are given in Table 1. Systolic and diastolic blood pressures averaged ($\pm$ SD) 170.4 ± 18.3 and 92.9 ± 11.0 mmHg, respectively; pulse pressure averaged ($\pm$SD) 77.5 ± 20.8 mmHg and mean pressure 118.7 ± 9.9 mmHg. The coefficient of correlation between pulse pressure and mean pressure amounted to 0.17 ($P < 0.001$), and that between pulse pressure and systolic blood pressure was 0.85 ($P < 0.001$). Median age was 62.7 years and ranged from 26.3 to 97.0 years. Approximately one-quarter of all patients were younger than 50 years, particularly because of inclusion of the MRC1 trial.

Table 1 **Characteristics of patients included in the control groups of the reviewed trials**

Trial	SHEP	Syst-Eur	MRC2	HEP	MRC1	EWPHE	STOP
Main reference	24	17	23	21	22	16	25
Mean age at entry (years)	71.5	70.2	70.3	69.1	52.1	71.9	75.6
Systolic pressure at entry (mmHg)	170.1	173.9	184.4	196.5	161.6	182.4	195.3
Diastolic pressure at entry (mmHg)	76.7	85.5	90.8	97.4	98.3	100.5	101.7
Pulse pressure at entry (mmHg)	93.4	88.5	93.6	99.1	63.3	81.8	93.6
Mean pressure at entry (mmHg)	107.8	115.0	122.0	130.5	119.4	127.8	132.9
Number of patients in control group	2371	2297	2213	465	8654	424	815
Women (%)	57	66	58	68	48	71	62
Smokers (%)	12.9	7.1	21.9	17	29.3	15.8	7.6
Median follow-up (years)	4.4	2.0	6.0	3.5	5.3	4.4	2.1
All-cause deaths (rate per 1000 patient–years)	23.7	25.2	24.8	33.7	5.9	76.8	35.4
Cardiovascular deaths (rate per 1000 patient–years)	11.0	14.0	14.1	24.1	3.2	47.9	23.1
Fatal strokes (rate per 1000 patient–years)	1.4	3.2	3.3	7.2	0.6	16.0	8.4
Fatal coronary heart diease (rate per 1000 patient–years)	7.1	7.5	8.6	13.5	2.3	17.0	11.2

The trials are in order of diastolic blood pressure at entry.

Analysis in tertiles of pressure components

With stratification for trial and adjustment for age and sex, cardiovascular mortality increased from the lowest to the highest tertile of systolic pressure and pulse pressure (Fig. 1). For systolic pressure this trend was significant not only for cardiovascular mortality, but also for stroke mortality and all deaths. For pulse pressure, in addition to cardiovascular mortality, the trend was significant for fatal coronary heart disease and total mortality. The corresponding associations with diastolic pressure and mean pressure were not significant.

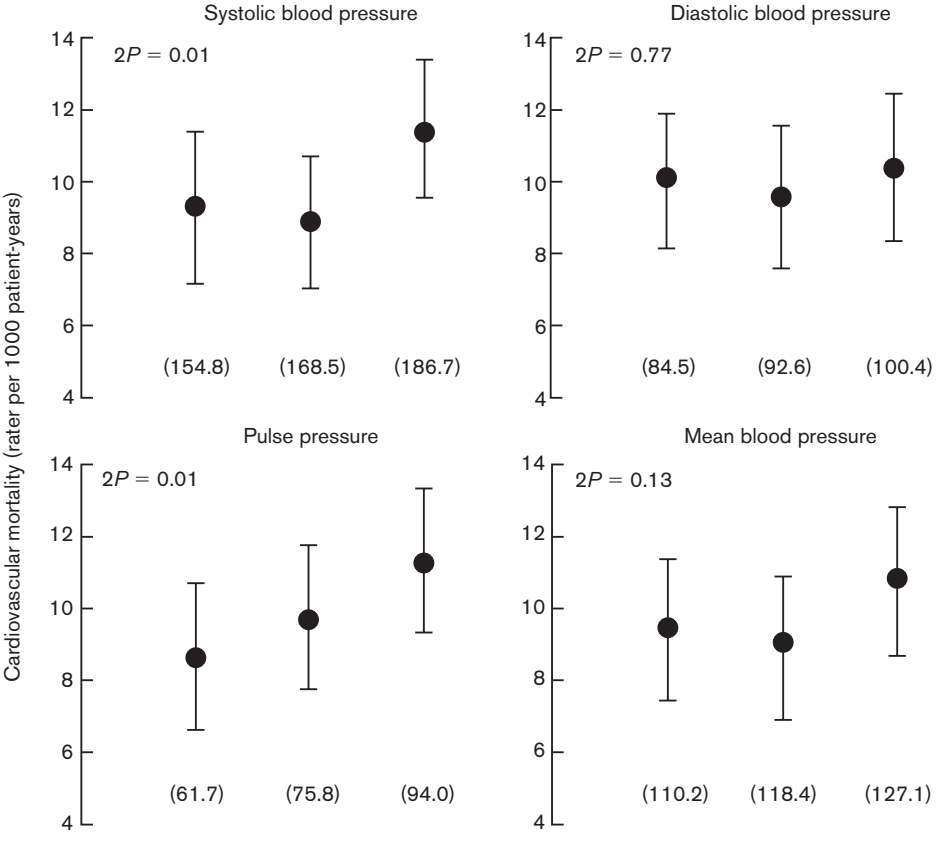
Cox regression analysis

In Cox regression with pulse pressure or mean pressure as the main explanatory variable, we stratified for trial and allowed for sex, age, smoking, and the alternative pressure component, i.e., the hazard rates for pulse pressure were adjusted for mean pressure and vice versa. In none of these analyses the hypothesis of homogeneity across the trials was rejected ($\chi_6^2 \leqslant 11.8$, $P \geqslant 0.07$; Fig. 2 and Fig. 3). After adjustment for mean pressure and the other covariates, a 10 mmHg wider pulse pressure was associated with a higher risk of total [RHR 1.06, 95% confidence interval (CI) 1.03–1.10; $P = 0.001$], cardiovascular (RHR 1.07, 95% CI 1.01–1.13; $P = 0.01$), and coronary (RHR 1.07, 95% CI 1.01–1.15; $P = 0.03$) mortality (Fig. 2). However, this association was not statistically significant for stroke mortality. In similar analyses, mean pressure was not significantly associated with outcome (Fig. 3). When systolic and pulse pressure were included together in the models, neither of the two was significantly related to the risk of any of the studied end points.

Cox regression analysis after exclusion of MRC1 trial

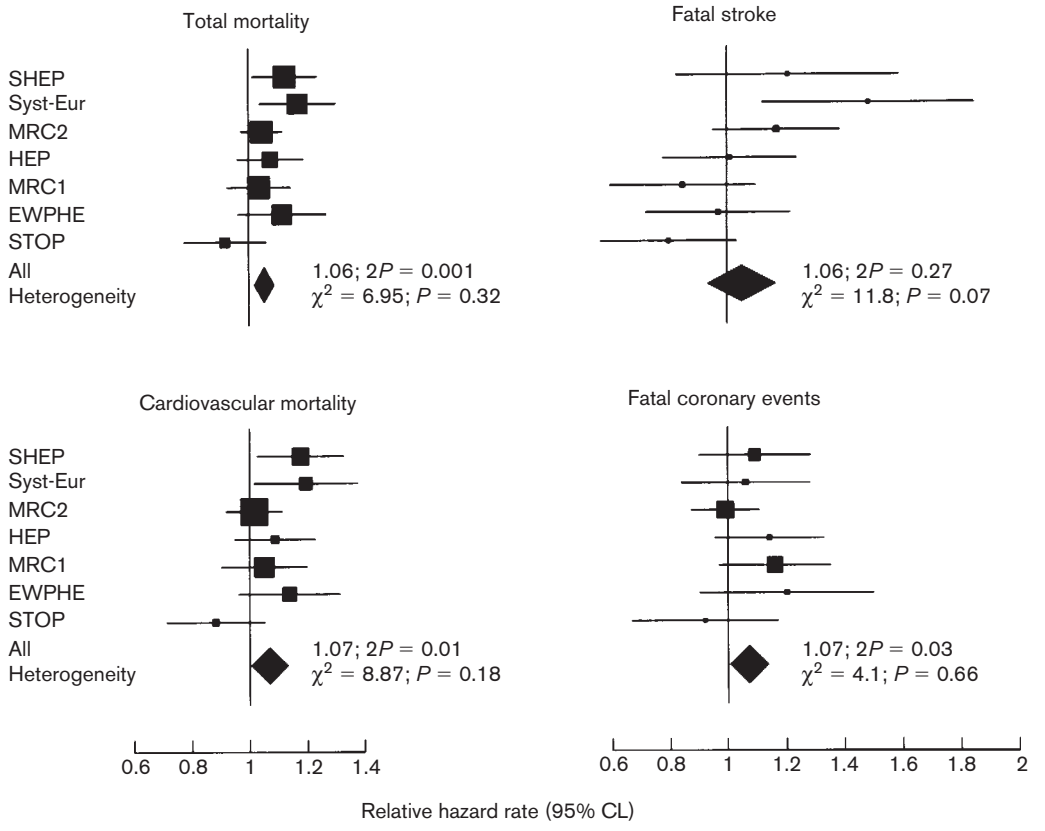
Because of the younger age of the patients in the MRC1 trial, Cox regression analysis was also performed without the results from this trial. After adjustment for mean blood pressure and the other covariates, a 10 mmHg wider pulse pressure was associated with a higher risk of total mortality (RHR 1.08, 95% CI 1.03–1.13; $P < 0.001$) and of cardiovascular mortality (RHR 1.07, 95% CI 1.01–1.14; $P = 0.01$). The relative hazard rates were not significant for cause-specific mortality.

Fig. 1



Rates (± SEM) of fatal cardiovascular events in the control groups of seven trials, plotted in thirds of the respective pressure components after stratification by trial and adjustment for age and sex; numbers between brackets represent mean within-tertile BP values. *P* values are for linear trends.

Fig. 2



Relative hazard rates of fatal outcome, independently associated with a 10 mmHg wider pulse pressure, adjusted for sex, age, smoking, and mean pressure, for each trial separately; the size of the squares corresponds to the numbers of events in each trial. Diamonds represent the 95% confidence intervals of the pooled estimates, after stratification by trial. Chi-square statistics for the heterogeneity of the data did not reach statistical significance.

The relationships between mean blood pressure and mortality were not significant, except for stroke mortality, which became significant upon exclusion of MRC1 patients from the analysis (RHR 1.10, 95% CI 1.00–1.21; $P = 0.05$).

The interaction between age and pressure components

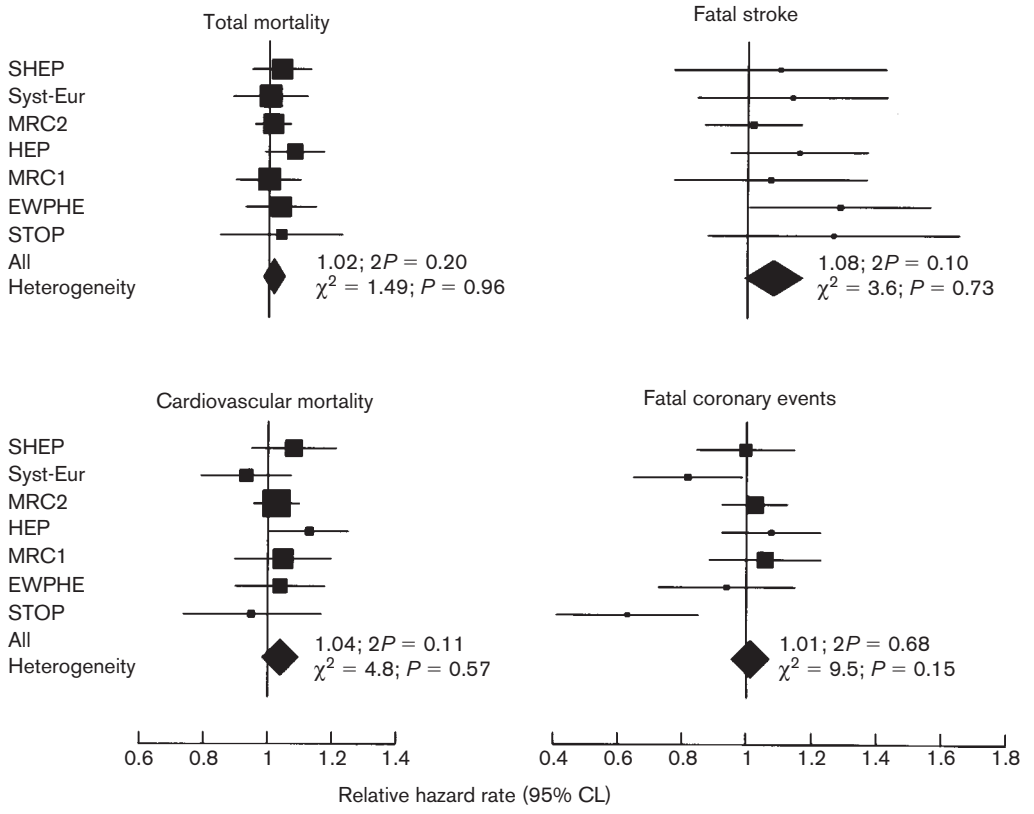
The interactions between age and, respectively, pulse pressure and mean pressure, were not statistically significant for all-cause mortality and for cardiovascular mortality. However, the pulse pressure–age interaction reached significance for stroke mortality ($P = 0.04$). The RHR was 0.71 in the youngest tertile (age $\leqslant$ 56 years) and was between 1.13 and 1.16 in the next three decades. The interaction between mean pressure and age was significant for fatal coronary heart disease ($P = 0.01$). The RHR amounted to 1.10 in the youngest tertile (age $\leqslant$ 56 years), 1.08 in the middle tertile (ages 56–68 years) and 0.97 at age $>$ 68 years.

Discussion

We found that in patients with hypertension a 10 mmHg wider pulse pressure is independently associated with 6–7% increases in the risk of death from any cause or from cardiovascular complications. These risks were consistent throughout a large pool of patients enrolled as controls and assigned to placebo or no medication in seven randomized clinical trials. After adjustment for pulse pressure and confounders, mean blood pressure did not significantly add to the estimation of prognosis. There was no significant effect of age on these findings

With regard to cause-specific mortality, we observed a significant association of pulse pressure with fatal coronary heart disease but not with stroke mortality, whereas mean blood pressure did not have significant predictive power for these outcomes. However, when we analysed the possible influence of age, we observed a positive interaction between pulse pressure and age for stroke mortality, and a negative one between mean pressure and age for fatal coronary artery disease, meaning that the prognostic value of pulse pressure for stroke became more important at older age and that the risk of a higher mean arterial pressure for coronary heart disease was highest at younger age.

Fig. 3



Relative hazard rates of fatal outcome, independently associated with a 5 mmHg higher mean pressure, adjusted for sex, age, smoking, and pulse pressure, for each trial separately; the size of the squares corresponds to the numbers of events in each trial. Diamonds represent the 95% confidence intervals of the pooled estimates, after stratification by trial. Chi-square statistics for the heterogeneity of the data did not reach statistical significance.

The overall results on total mortality and on cardiovascular mortality were not affected by exclusion of the MRC1 trial, which included patients from young age up to the age of 65 years, whereas the minimal age was at least 60 years in the other trials. However, the predictive power of pulse pressure for coronary mortality was no longer significant, whereas mean blood pressure gained importance for the prediction of fatal stroke.

The present results confirm and expand the previously reported findings in elderly hypertensive patients that pulse pressure, rather than mean pressure, is the major risk factor of adverse cardiovascular events. Early reports from the Framingham Heart Study emphasized that systolic blood pressure was a better independent predictor of cardiovascular risk than diastolic pressure, particularly in subjects over the age of 50 [31,32]; a more recent analysis revealed that pulse pressure is a better predictor of the incidence of coronary artery disease than systolic or diastolic pressure [7]. The results from the MRFIT study indicated that patients were at particularly high risk when an elevated systolic blood pressure at baseline ($\geqslant 160$ mmHg) was associated with a low diastolic pressure (< 70 mmHg) [33]. Darné *et al.* [3] were among the first to propose an independent role of pulse pressure as a risk factor, mainly for cardiac mortality, but only in women above 55 years of age. Several other groups confirmed the independent role of conventionally measured pulse pressure as a cardiovascular risk factor in the population [4–8], and in patients with hypertension [9–13], post-myocardial infarction [14] or left ventricular dysfunction [15]. It has also been observed that pulse pressure derived from 24 h ambulatory blood pressure monitoring is a potent predictor of cardiovascular outcome [11]. In a recently published meta-analysis, it was shown that in older patients with isolated elevation of systolic pressure, risk of death was positively associated with systolic blood pressure but inversely with diastolic pressure; consequently, the number of patients needed to be treated for 5 years to prevent one death was significantly lower in the high pulse pressure group [34].

Our estimation of the blood pressure–risk relationship could be influenced by the fact that the blood pressures were not freely observed but had to meet different entry criteria in each trial, and we advise caution when extrapolating these results to a more general population. However, the heterogeneity test confirmed the internal consistency of the results in a large collection of hypertensive patients enrolled in seven different trials. Moreover, in order to account for different trial designs, the analysis was stratified by trial.

In our Cox models, we tried to account for possible important confounders (sex, age and smoking, in addition to the other pressure). However, due to the lack of data for a large number of patients, we were unable to control for such factors as the level of total cholesterol or presence of diabetes mellitus.

Our analysis was not designed to check whether pulse pressure is a better predictor of mortality than systolic blood pressure. The role of pulse pressure as risk predictor was originally derived from an observation that in addition to the increase in risk of adverse events with rising systolic blood pressure, at any level of systolic blood pressure the lower the diastolic pressure, the higher the risk [19]. Only thereafter the question arose whether the pulsatile component would be more important than the steady component in the assessment of risk. Nevertheless, when we adjusted the pulse pressure for systolic pressure in the present analysis, neither of the two components remained a significant predictor of the mortality risk. This is what can be expected when so closely related variables are used in the same model. In fact, the strong interrelationship between systolic blood pressure and pulse pressure makes if difficult to distinguish between the role of the pulsatile component and of systolic blood pressure *per se*.

The present analysis was not designed to explain the possible mechanisms responsible for the better prediction of cardiovascular mortality by pulse pressure. However, it can be argued that hypertensive patients with increased pulse pressure are at increased risk of death because of more advanced arterial stiffness and atherosclerosis in various critical regions of the circulation, especially in coronary arteries and the arteries supplying the brain. In addition, increased pulsatile stretching may further damage the vasculature. For a diseased heart with atheromatous coronary arteries, a wide pulse pressure leads to less perfusion during diastole and a greater after-load, and thus higher wall tension due to stiffer conduit arteries. For the cerebral circulation, it means more mechanical force in systole, injuring vessels that lost their adaptive properties as a result of endothelial damage and stiffening, and a low perfusion during diastole.

In conclusion, the pooled results in control groups (without active treatment) of seven clinical trials, which included hypertensive patients with wide age and blood pressure range indicate that pulse pressure is an independent risk factor for overall and cardiovascular mortality. However, the present findings do not imply a causal relationship. In order to clarify the issue of whether or not lowering of pulse pressure would decrease cardiovascular morbidity and mortality, a specific, carefully designed clinical trial is needed.

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