# J-Shaped Relationship between Blood Pressure and Mortality in Hypertensive Patients: New Insights from a Meta-Analysis of Individual-Patient Data

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Background: **Population-based longitudinal studies of hypertension have usually shown a continuous and positive relationship between blood pressure and mortality. However, several studies in hypertensive patients receiving treatment have described this relationship as J-shaped, with an increased risk for events in patients with low blood pressure.**

Objective: **To assess the evidence for a J-shaped relationship between blood pressure and mortality and its relation to treatment.**

Design: **Meta-analysis of individual-patient data.**

Setting: **Seven randomized clinical trials from the INDANA (INdividual Data ANalysis of Antihypertensive intervention) database.**

Patients: **40 233 persons with hypertension (mean follow-up, 3.9 years).**

Intervention: **Primarily $\beta$-blockers or thiazide diuretics versus placebo or no treatment.**

Measurements: **Diastolic and systolic blood pressure and number of cardiovascular, noncardiovascular, and all-cause deaths in yearly periods of follow-up.**

Results: **The analysis included data on 1655 deaths (56% cardiovascular). A J-shaped relationship between diastolic blood pressure and risk for death was observed for total and cardiovascular mortality in treated patients (nadir, 84 and 80 mm Hg, respectively) and untreated patients (nadir, 90 and 85 mm Hg, respectively). For noncardiovascular deaths, the relationship was J-shaped in the treated group (nadir, 84 mm Hg) and negative in the control group. Similar results were observed for systolic blood pressure. The presence of patients with wide pulse pressure did not explain these findings.**

Conclusions: **The increased risk for events observed in patients with low blood pressure was not related to antihypertensive treatment and was not specific to blood pressure–related events. Poor health conditions leading to low blood pressure and an increased risk for death probably explain the J-shaped curve.**

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The benefit of antihypertensive treatments in reducing the risk for cardiovascular events in persons with high blood pressure has been well established (1–3). Despite this evidence, epidemiologic studies have shown that after adjustment for other risk factors, treated hypertensive patients with normalized blood pressure are still at higher risk for cardiovascular diseases than normotensive persons (4). Moreover, in clinical trials the observed risk reduction for coronary events has been smaller than could be expected from the log-linear relationship between blood pressure and risk according to epidemiologic data (5). Clinical trials have reported a 5– to 6–mm Hg difference between the diastolic blood pressures of treatment and control groups; the risk reduction of 14% (95% CI, 4% to 22%) for coronary events contrasts with the 20% to 25% reduction noted in epidemiologic reports. These discrepancies may be related to the existence of a J-shaped relationship between blood pressure and risk, in which treated patients with low blood pressure are at increased risk for coronary events.

The reports of a J-shaped relationship have come from longitudinal cohort studies of treated hypertensive patients (6–10) or clinical trial data on antihypertensive treatment groups and, in some trials, control groups (11–13). Interpretation of such results has varied. Some researchers have believed that overtreatment with blood pressure–reducing drugs may compromise coronary blood flow, especially in hypertensive patients with a history of myocardial infarction (14), while others have considered that the increased risk in patients with low blood pressure is independent of treatment and may be attributed to confounding factors related to deteriorating heath (12, 15, 16) or pulse pressure (17).

The INDANA (INdividual Data ANalysis of Antihypertensive intervention trials) project is a meta-analysis of individual-patient data collected from randomized clinical trials of antihypertensive medication versus pla-

cebo or no intervention, with follow-up for cardiovascular events and deaths (18). INDANA offers the opportunity to further explore the J-shaped curve. Specifically, this database allows assessment of the evolution of risk according to achieved blood pressure separately for treated and untreated patients who in all other aspects are similar because of the randomization process.

***Context***

Lowering blood pressure in hypertensive patients decreases the risk for cardiovascular events. However, clinical trials show a discrepancy between observed and expected risk reduction, possibly because of a J-shaped relationship between blood pressure and risk reduction.

***Contribution***

The authors analyzed individual-patient data from seven randomized clinical trials of both treated and untreated hypertensive patients. All-cause death rates were higher among patients with high diastolic pressure and those with low diastolic pressure. Low diastolic pressure was associated with an increased death rate, even among untreated patients.

***Implications***

Excessive antihypertensive treatment may increase the death rate. Poor health may also cause low blood pressure and increase the risk for death.

*–The Editors*

## METHODS

### Study Sample

Data from five randomized clinical trials in elderly patients (Coope and Warrender [13]; European Working Party on High Blood Pressure in Elderly patients [EWPHE] [19], Medical Research Council trial in older adults [MRC2] [20], Systolic Hypertension in the Elderly Program [SHEP] [21], and Swedish Trial in Old Patients [STOP] [22]) and two trials in middle-aged patients (Hypertension Detection and Follow-up Program [HDFP] [23] and Medical Research Council trial in mild hypertension [MRC1] [24]) were pooled in a common file with information on baseline patient characteristics, blood pressure measurements over time, and occurrence of major clinical events.

For this analysis, we did not use the data from three other trials available at the INDANA coordinating center. First, the Multiple Risk Factor Intervention Trial (MRFIT) (25) could not directly relate a change in cardiovascular risk to a change in blood pressure because this study assessed the effects of cholesterol and smoking reduction in addition to that of blood pressure reduction. Next, we excluded the Australian National Blood Pressure Study (ANBPS) data (26) because of the risk for informative censoring (the end point was a combined criteria that included several soft events directly related to hypertension). Finally, the Veterans Administration–National Heart, Lung, and Blood Institute feasibility trial (VA–NHLBI) (27) had not been pooled in the database at the time of analysis but would have contributed only marginally to the overall results because few events were observed.

### Blood Pressure Data

We did not include blood pressure at study entry in the analysis because these values were heavily conditioned by the trial-specific selection criteria for blood pressure. At least one blood pressure measurement per each year of follow-up was available. For trials that obtained several measurements per year, we used in our analysis the measurement obtained closest to the annual visit. Because systolic blood pressure in HDFP was measured only after 5 years of follow-up, this trial was not included in statistical analyses involving systolic blood pressure or pulse pressure.

### Clinical Events and Follow-up

After study entry (baseline), the trials in the database monitored patients for occurrence of myocardial infarction, stroke, and death during a mean follow-up period ranging from 2.2 years in STOP to 5.8 years in MRC2. To make our results more robust, we focus on fatal events (classified as cardiovascular or noncardiovascular death). We did not analyze nonfatal events because they were monitored and reported less consistently than fatal events (for example, HDFP did not note the time to occurrence of strokes and EWPHE did not record nonfatal events after the occurrence of a nonfatal end point). In the analysis, follow-up for mortality started 1 year after randomization. For each subsequent yearly period, the risk for death was assessed according to the systolic and diastolic blood pressures obtained closest to the beginning of the year.

*Table 1.* **Patient Events in Each Study Recorded during Follow-up between 1 Year after Study Inclusion and End of Study Follow-up***

| Study (Reference) | Patients | Mean Follow-up | Mean Age | Male Patients | Total Deaths | Cardiovascular Deaths |
|---|---|---|---|---|---|---|
| | *n* | *y* | | *%* | *n* | |
| Coope and Warrender (13) | 859 | 3.6 | 69.0 | 30.1 | 103 | 69 |
| EWPHE (19) | 732 | 4.2 | 71.5 | 29.5 | 128 | 71 |
| HDFP (23) | 10 819 | 3.9 | 50.7 | 53.9 | 375 | 215 |
| MRC1 (24) | 17 307 | 4.0 | 52.1 | 52.1 | 338 | 195 |
| MRC2 (20) | 4334 | 4.8 | 70.3 | 41.4 | 387 | 218 |
| SHEP (21) | 4678 | 3.4 | 71.6 | 43.1 | 275 | 131 |
| STOP (22) | 1504 | 1.3 | 75.6 | 36.7 | 49 | 27 |
| All studies | 40 233 | 3.9 | 57.5 | 48.9 | 1655 | 926 |

* EWPHE = European Working Party on High Blood Pressure in Elderly patients; HDFP = Hypertension Detection and Follow-up Program; MRC1 = Medical Research Council trial in mild hypertension; MRC2 = Medical Research Council trial in older adults; SHEP = Systolic Hypertension in the Elderly Program; STOP = Swedish Trial in Old Patients.

### Statistical Analysis

As a first descriptive approach, we estimated the adjusted death rates by treatment group in successive categories of ongoing diastolic blood pressure (≤65, 66 to 75, 76 to 85, 86 to 95, 96 to 105, ≥106 mm Hg) and systolic blood pressure (≤120, 121 to 130, 131 to 140, 141 to 150, 151 to 160, 161 to 170, 171 to 180, ≥181 mm Hg) while controlling for any confounding effect of age, sex, study, and year of blood pressure measurement since study entry (28). For all patients, each successive 1-year period of follow-up was used to relate the blood pressure level at the beginning of that period to the risk for death during that period. This method allowed us to consider the influence of blood pressure on risk as it evolved over time. We used a Poisson linear regression model to relate the risk for dying (on a log scale) to the set of covariates (29). In addition to blood pressure, age, and time since entry (with each updated at every period), the other covariates were sex, history of medical events (myocardial infarction, stroke, and diabetes) before study entry, and smoking habits. Occurrence of nonfatal myocardial infarctions during follow-up was a further time-dependent covariate. To determine whether the relationship between blood pressure and risk was J-shaped, we fitted a model with both a linear and a quadratic (squared) term for blood pressure. This model assumes a curved relationship, with the risk for death decreasing to a minimum value with decreasing blood pressure before eventually increasing. Next, we estimated the minimum (nadir) and associated confidence interval from the coefficients of the linear and quadratic terms and their variance (30). Finally, to verify that an increase in risk with lower blood pressure was not a result of constraints of the quadratic model, we fitted blood pressure measurements at the left and right of the nadir with two independent curvilinear relationships, as proposed by Goetghebeur and Pocock (31). We repeated such modeling by using increasing nadir values (at intervals of 2 mm Hg for diastolic blood pressure and 5 mm Hg for systolic blood pressure) and determined the optimum nadir by the model with the best goodness of fit.

We performed all statistical analyses by using the SAS software package for Windows, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

### Role of the Funding Source

The funding source had no role in the collection, analysis, and interpretation of the data or in the decision to submit the paper for publication.

## RESULTS

Of the 40 777 patients randomly assigned to active treatment or control groups in the seven trials, we analyzed data on the 40 233 total patients alive at 1 year after study entry (**Table 1**). The mean follow-up was 3.9 years. Among the patients in our analysis, 48.9% ($n$ = 19 692) were men and 27.7% ($n$ = 11 107) were current smokers; 1312 patients (3.3%) had a history of myocardial infarction, 464 (1.1%) had a history of stroke, and 1420 (3.5%) had a history of diabetes mellitus. We could not include data on 31 995 1-year periods of follow-up (18.7%) in assessing a possible relation

between fatal events and diastolic blood pressure because of missing blood pressure measurements. Overall, our analysis comprised data on 1655 deaths (56% of which were caused by cardiovascular events) during 126 908 total patient-years of follow-up.

One year after study entry, mean diastolic blood pressure in each trial was significantly lower in the active treatment group than in the control group; the mean 1-year difference in diastolic blood pressure between treatment groups ranged from 4.3 mm Hg in SHEP to 9.3 mm Hg in STOP (**Table 2**). During the subsequent years of follow-up, the diastolic blood pressure decreased slightly (mean, 0.5 mm Hg/y), but the difference between the active treatment and control groups remained.

As a first descriptive analysis, we plotted successive categories of diastolic and systolic blood pressure (**Figures 1 and 2**) for the total death rates in all seven trials combined, with adjustment for age, sex, and time (in years) since study inclusion. In the active treatment and control groups, both ends of the diastolic blood pressure distribution had higher rates of all-cause mortality. Among control patients, the overall death rate was lowest in patients whose achieved diastolic blood pressure was 86 to 95 mm Hg; in patients receiving active treatment, the lowest rate occurred in the 76– to 85–mm Hg category. Similar trends were observed separately for cardiovascular and noncardiovascular deaths. Especially noteworthy is the sharp increase observed in the noncardiovascular deaths at low levels of diastolic blood pressure in untreated patients (**Figure 1**). As shown in **Figure 2**, we found similar results for systolic blood pressure.

When we fitted a continuous quadratic model to the data, we observed strong evidence of a curvilinear relationship or a negative linear relationship between diastolic blood pressure and risk for all outcomes in active treatment and control patients (**Table 3**). We estimated the diastolic blood pressure corresponding to the lowest risk for death; we found this value to be lower for cardiovascular deaths compared with noncardiovascular deaths and consistently lower in the active treatment group compared with the control group.

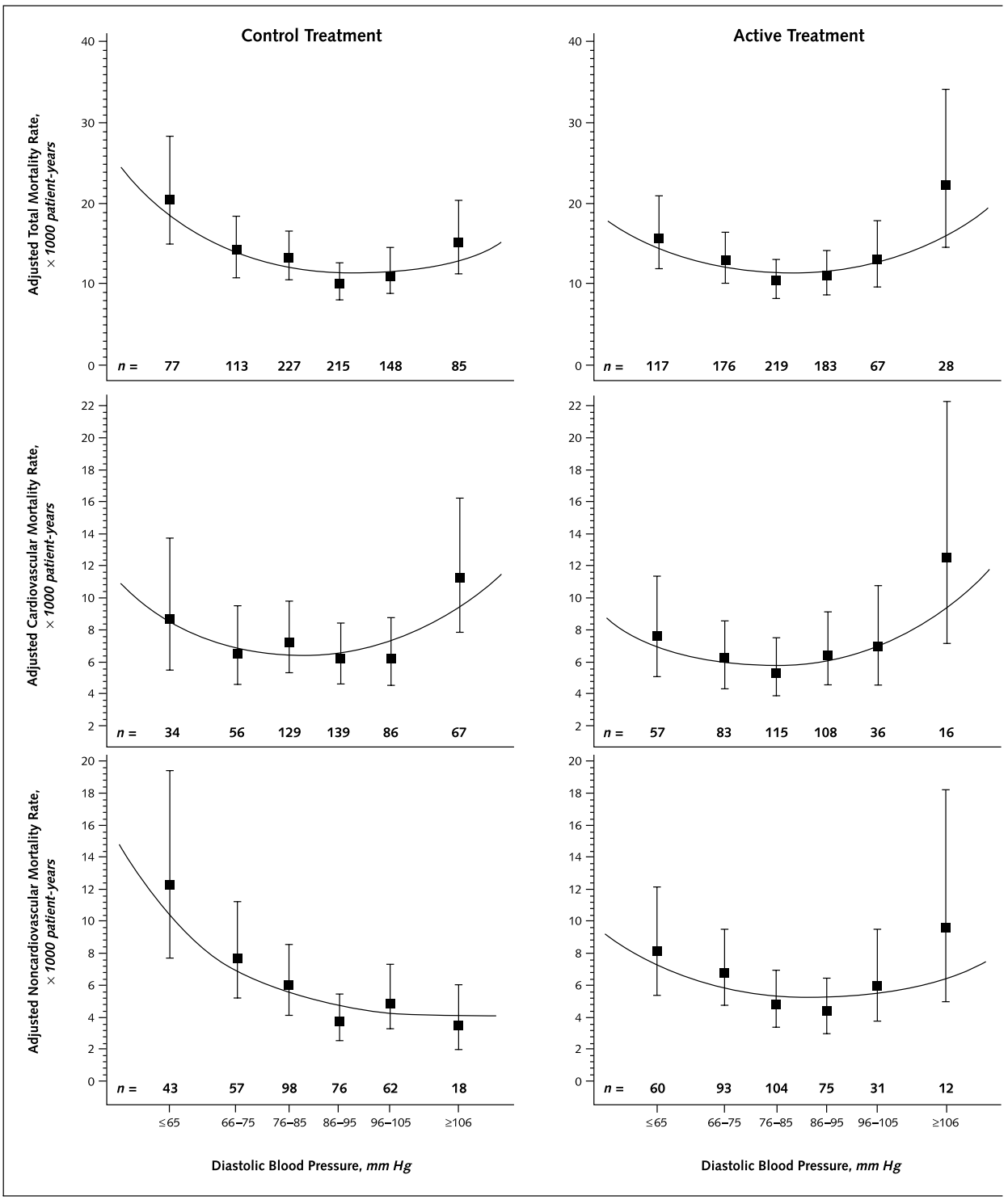
By modeling the data to the left and right of the nadir with two independent quadratic functions, we found that the risk for total, cardiovascular, and noncardiovascular deaths in active treatment and control patients increased as diastolic blood pressure decreased. A curvilinear relationship was also shown between systolic

*Table 2.* **Blood Pressure 1 Year after Study Inclusion in Active Treatment and Control Groups***

| Study (Reference) | Patients | Diastolic Blood Pressure | Systolic Blood Pressure | Mean Blood Pressure† |
|---|---|---|---|---|
| | *n* | ← *mm Hg* → | | |
| Coope and Warrender (13) | | | | |
| Control group | 439 | 94.2 ± 13.8 | 188.0 ± 23.7 | 125.5 ± 14.6 |
| Active treatment group | 406 | 87.1 ± 10.8 | 173.1 ± 20.6 | 115.7 ± 11.9 |
| EWPHE (19) | | | | |
| Control group | 348 | 96.3 ± 12.2 | 173.3 ± 23.9 | 122.0 ± 14.5 |
| Active treatment group | 348 | 87.7 ± 9.8 | 152.5 ± 18.5 | 109.3 ± 10.8 |
| HDFP (23) | | | | |
| Control group | 4883 | 94.0 ± 12.6 | NA | NA |
| Active treatment group | 5047 | 87.6 ± 11.0 | NA | NA |
| MRC1 (24) | | | | |
| Control group | 8273 | 91.9 ± 9.2 | 148.4 ± 17.6 | 110.7 ± 10.7 |
| Active treatment group | 8244 | 86.9 ± 8.6 | 137.8 ± 16.5 | 103.9 ± 10.0 |
| MRC2 (20) | | | | |
| Control group | 2098 | 86.5 ± 11.8 | 169.9 ± 17.2 | 114.3 ± 11.6 |
| Active treatment group | 2041 | 79.2 ± 11.0 | 153.9 ± 17.7 | 104.1 ± 11.1 |
| SHEP (21) | | | | |
| Control group | 2053 | 74.0 ± 10.4 | 156.5 ± 17.2 | 101.5 ± 10.5 |
| Active treatment group | 2152 | 69.7 ± 9.3 | 142.6 ± 15.7 | 94.0 ± 9.2 |
| STOP (22) | | | | |
| Control group | 719 | 97.1 ± 9.0 | 188.8 ± 19.0 | 127.6 ± 10.0 |
| Active treatment group | 732 | 87.8 ± 8.5 | 167.6 ± 19.4 | 114.4 ± 10.1 |

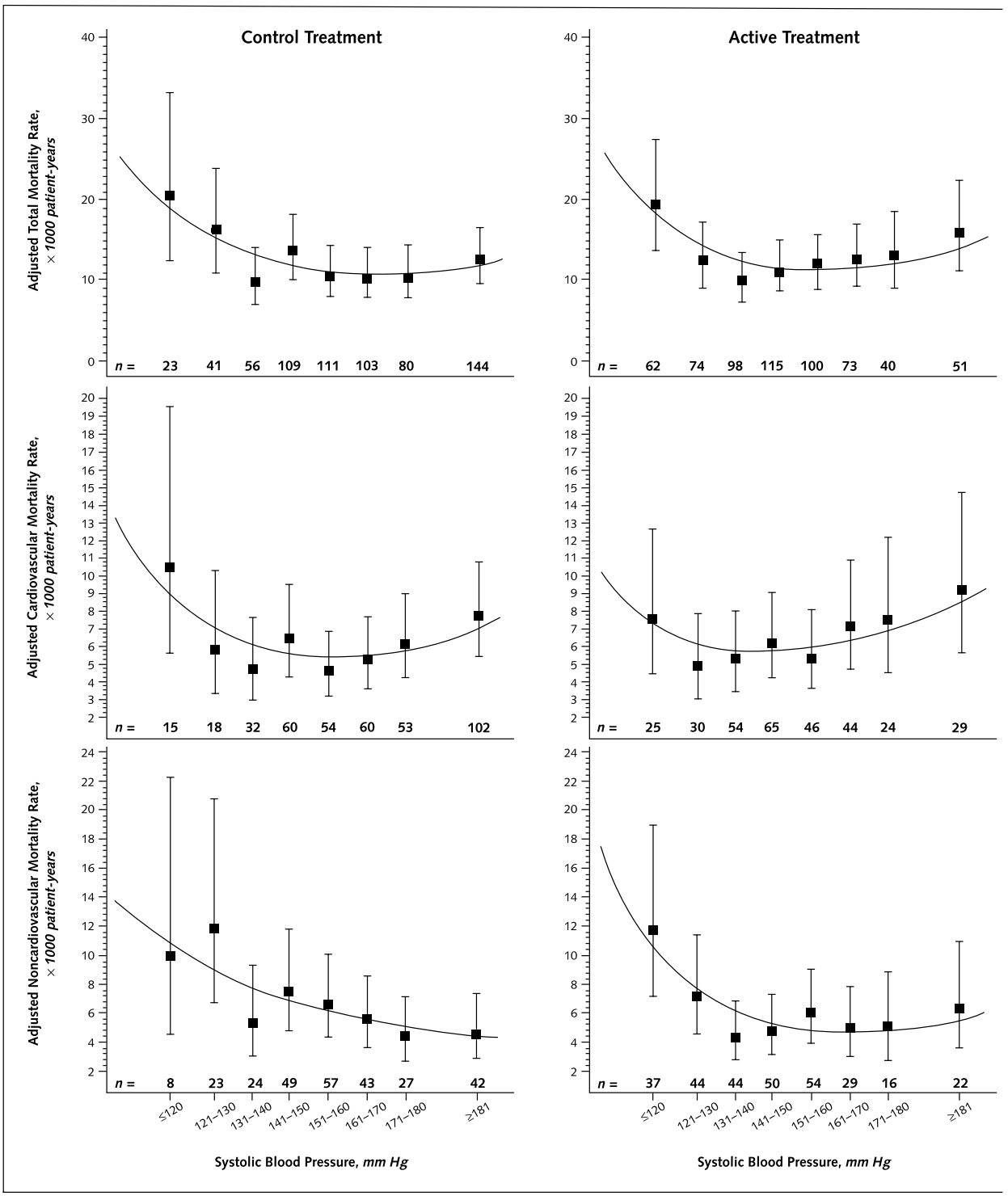
* Values with the plus/minus sign are the mean ± SD. EWPHE = European Working Party on High Blood Pressure in Elderly patients; HDFP = Hypertension Detection and Follow-up Program; MRC1 = Medical Research Council trial in mild hypertension; MRC2 = Medical Research Council trial in older adults; NA = not available at 1 year; SHEP = Systolic Hypertension in the Elderly Program; STOP = Swedish Trial in Old Patients.
† Calculated as ([2 × diastolic blood pressure] + systolic blood pressure)/3.

*Figure 1.* **Age- and sex-adjusted rates of events in six categories of achieved diastolic blood pressure and predicted continuous relationship in active treatment and control groups.**




Event rates (*squares*) and 95% CIs (*bars*) are shown for the following categories of achieved diastolic blood pressure: ≤65, 66–75, 76–85, 86–95, 96–105, and ≥106 mm Hg. The number of events is shown below each bar.

*Figure 2.* **Age- and sex-adjusted rates of events in eight categories of achieved systolic blood pressure and predicted continuous relationship in active treatment and control groups.**




Event rates (*squares*) and 95% CIs (*bars*) are shown for the following categories of achieved systolic blood pressure: ≤120, 121–130, 131–140, 141–150, 151–160, 161–170, 171–180, ≥181 mm Hg. The number of events is shown below each bar.

blood pressure and total mortality (for active treatment and control patients), cardiovascular mortality (for control patients only), and noncardiovascular mortality (for active treatment patients). For noncardiovascular mortality, untreated patients showed a strong negative relationship. The double-quadratic model generally confirmed these results. As with diastolic blood pressure, the systolic blood pressures corresponding to the minimum risk were always lower in treated patients than in control patients.

When we repeated the analysis after censoring the follow-up periods subsequent to the occurrence of a nonfatal myocardial infarction, the results remained virtually unchanged. We calculated the following nadirs for the active treatment group: for total mortality, 83 mm Hg (CI, 74 to 91 mm Hg); for cardiovascular mortality, 78 mm Hg (CI, 63 to 87 mm Hg); and for noncardiovascular mortality, 90 mm Hg (CI, 77 to 125 mm Hg). In the control group, the nadir for total mortality was 93 mm Hg (CI, 87 to 102 mm Hg), and the nadir for cardiovascular mortality was 82 mm Hg (67 to 90 mm Hg); for noncardiovascular mortality, the relationship was strongly negative, as observed on all the data.

To assess whether results were sensitive to the level of the baseline diastolic blood pressure, we performed two subgroup analyses for total mortality: 1) in patients whose diastolic blood pressure at study entry was less than 90 mm Hg (median, 80 mm Hg) and 2) in patients with baseline diastolic blood pressure of 90 mm Hg or higher (median, 99). As shown in **Table 4**, the treated and control patients in these two groups had higher death rates at lower achieved diastolic blood pressures. The upturn to the left, as fitted by a curvilinear model, on the blood pressure data at the left side of the minimum point was in all cases statistically significant.

To control for the fact that higher pulse pressure levels in the lower categories of diastolic blood pressure may in itself explain the J-shaped curve, we fitted the model with pulse pressure as an additional covariable (using seven categories that ranged from <40 mm Hg to ≥90 mm Hg). In both the active treatment and control groups, the association between higher risk and decreasing diastolic blood pressure remained statistically significant ($P = 0.005$ and $P = 0.001$, respectively).

To verify whether patient characteristics could influence the results, we alternately stratified our data according to age at study entry (<70 years or ≥70 years), ongoing pulse pressure (<70 mm Hg or ≥70 mm Hg), and systolic blood pressure (<160 mm Hg or ≥160 mm Hg) and fitted the double quadratic model on total mortality. We found statistical evidence of an increased risk for death with lower achieved diastolic blood pressure in all strata, except in control patients with high systolic blood pressure (≥160 mm Hg), in treated patients with high pulse pressure (≥70 mm Hg), and in treated patients age 70 years or older.

The number of patients with a history of myocardial infarction or diabetes mellitus at baseline was insufficient to provide interpretable results in these two subgroups; exclusion of these patients did not modify the overall results.

## DISCUSSION

A plethora of reports have described the shape of the relationship between blood pressure and risk. Some re-

*Table 3.* **Nadir Estimates and Statistical Evidence of a Quadratic Relationship between Last-Obtained Blood Pressure and Risk for Death***

| Blood Pressure | Total Mortality | | Cardiovascular Mortality | | Noncardiovascular Mortality | |
|---|---|---|---|---|---|---|
| | Nadir Blood Pressure (95% CI) | *P* Value | Nadir Blood Pressure (95% CI) | *P* Value | Nadir Blood Pressure (95% CI) | *P* Value |
| | *mm Hg* | | *mm Hg* | | *mm Hg* | |
| Diastolic blood pressure | | | | | | |
| Control group | 94 (87–102) | 0.001 | 84 (72–91) | 0.001 | –† | |
| Active treatment group | 84 (76–91) | 0.001 | 80 (67–89) | 0.001 | 89 (77–114) | 0.014 |
| Systolic blood pressure | | | | | | |
| Control group | 169 (157–181) | 0.001 | 156 (132–168) | 0.001 | –† | |
| Active treatment group | 156 (145–166) | 0.001 | –† | | 164 (154–177) | 0.001 |

* Adjusted for age, sex, smoking status; history of diabetes, stroke, and myocardial infarction; and coronary events during follow-up.
† Data not shown because the values provide no evidence of a J-shaped relationship.

*Table 4.* **Risk for Total Mortality in Six Categories of Achieved Diastolic Blood Pressure, according to Diastolic Blood Pressure at Study Entry and Treatment Group**

| Baseline Diastolic Blood Pressure | Risk for Total Mortality (95% CI), according to Achieved Diastolic Blood Pressure | | | | | |
|---|---|---|---|---|---|---|
| | ≤65 mm Hg | 66–75 mm Hg | 76–85 mm Hg | 86–95 mm Hg | 96–105 mm Hg | >105 mm Hg |
| | ← ×1000 patient-years → | | | | | |
| <90 mm Hg | | | | | | |
| Control group | 15.8 (9.8–25.2) | 11.0 (7.1–17.0) | 10.9 (7.2–16.4) | 10.2 (6.4–16.3) | 12.8 (6.5–25.2) | 25.8 (9.7–68.6) |
| Active treatment group | 8.7 (5.3–14.0) | 6.4 (4.0–10.2) | 4.8 (2.8–8.0) | 8.2 (4.4–15.2) | 23.6 (10.3–54.2) | –* |
| ≥90 mm Hg | | | | | | |
| Control group | 30.3 (18.3–50.4) | 15.9 (11.0–23.2) | 13.7 (10.2–18.4) | 9.8 (7.3–13.1) | 11.2 (8.2–15.1) | 14.9 (10.6–20.9) |
| Active treatment group | 21.1 (13.4–33.1) | 17.3 (12.7–23.6) | 12.9 (9.7–17.2) | 12.9 (9.5–17.4) | 14.6 (10.2–21.0) | 27.8 (17.7–43.7) |

* The available data were insufficient for analysis.

ports have shown this relationship to be continuous and positive, while others have demonstrated an increased risk in participants with low blood pressure. Because many such investigations studied cohorts drawn from the general population, they could not investigate whether drugs that reduce blood pressure have harmed hypertensive patients when blood pressure is reduced below a certain level. Some studies focused specifically on cohorts of treated hypertensive patients who were followed for several years. However, these studies lacked control patients; thus, comparison with similar but untreated patients was impossible. Hence, several authors have criticized the conclusions drawn from the results of these studies, arguing that there may have been uncontrolled confounding factors, such as comorbid conditions, that exposed the patients with low blood pressure to a high risk for events (16, 32).

The INDANA database offered the opportunity to assess the shape of the relationship between risk for events and level of blood pressure in both treated and initially untreated hypertensive patients, with a power greater than those of the few clinical trials that have reanalyzed their data to explore this issue (12, 13). We believe that this database provides the best set of existing data from which new insights in the discussion on the J-shaped curve can be generated.

In the population of hypertensive patients included in our meta-analysis, the risk for fatal events was increased at lower blood pressures; we noted this observation in treated and untreated patients and for both cardiovascular and noncardiovascular deaths. Hence, our data support the conclusion that the J-shaped curve is at least partly independent of treatment and may be explained by patients with poor health conditions in the lowest categories of blood pressure. As a result of randomization, such patients were found in both treatment groups and therefore partly contribute to the J-shaped relationship observed in the active treatment group. The EWPHE trial investigators found similar results, in which patients with low blood pressure had decreased values for body mass index and hemoglobin—two indicators of poor health (12). Unfortunately, the INDANA database did not contain measurements of such markers over time. Results remained unchanged when we excluded patients with nonfatal coronary heart disease during follow-up or those with a history of myocardial infarction.

Baseline blood pressure is obviously an important consideration in determining whether the observed increase in mortality at decreasing blood pressures is primarily the result of the magnitude of change in pressure or the actual achieved blood pressure. However, an analysis involving baseline blood pressures of patients selected above or below some threshold (depending on the trial entry criteria) would introduce statistical problems (for example, because of misclassification or regression to the mean) (33) that are likely to bias the estimates of the relationship with risk. Despite these limitations, we analyzed patient data according to baseline diastolic blood pressure of less than or at least 90 mm Hg, and our findings illustrated a J-shaped curve for both these subgroups within the active treatment and control groups. Therefore, the magnitude of decrease in diastolic blood pressure from baseline did not influence the overall finding that the risk for death was increased in patients with a lower achieved diastolic blood pressure.

Increased death rates in untreated patients with low diastolic blood pressure could also be explained by the

fact that most of these patients had isolated systolic hypertension (provided mainly by the SHEP and the MRC2 studies) and, hence, wide pulse pressure, which is associated with bad prognosis (17, 34, 35). However, after adjustment for pulse pressure, the death rates in patients with low achieved diastolic blood pressure increased, even for fixed levels of pulse pressure. The results of this analysis are similar to those of Somes (36), who entered diastolic blood pressure and systolic blood pressure jointly in the model. Somes found an increased risk for death with decreasing diastolic blood pressure in the active treatment group only. However, we have observed this relationship among the control patients as well. Age may be another important confounding factor, as the SHEP and the MRC2 studies contributed older patients in the lower categories of diastolic blood pressure. We believe that our adjustment for age in the model should have adequately controlled for this potential bias. In addition, we found evidence in subgroup analyses of a J-shaped curve (for total mortality) among patients with a pulse pressure less than 70 mm Hg and in patients younger than 70 years of age.

We determined the blood pressure at which the risk was lowest; we found that this value was lower in treated patients than in untreated patients. Let us assume that the J-shaped relationship observed in the untreated patients results from the following two factors: 1) a monotonic continuous positive relationship between blood pressure and risk, as reported by McMahon and colleagues (37) and 2) the presence of high-risk patients in the low blood pressure categories for reasons of reverse causality (ill heath causing low blood pressure). According to this hypothesis, patients receiving active treatment should be shifted downwards in terms of blood pressure and risk. Consequently, this should decrease the proportion of high-risk patients in the lower categories of blood pressure and hence shift the nadir in the treated group downward, as we observed. Below that point, the effect of high-risk patients with comorbid illness would predominate and invert the relationship with risk.

We used updated blood pressure measurements over time to relate blood pressure to the risk for events occurring during the following year. This modeling approach for analysis of the short-term effect of blood pressure was also used to examine data from the Framingham (15), HDFP (11), and Hypertension Optimal Treatment (HOT) (38) studies, and all these studies found some evidence of a J-shaped curve. However, the confounding effect of subclinical comorbid diseases in patients with low blood pressure is probably more pronounced over the short term than over the long term. Reanalyses of the cohort initially screened for the MR-FIT study produced a J-shaped curve, in which events occurred during the first 2 years of follow-up, but a positive relationship was maintained thereafter (up to 16 years of follow-up) (39). Similarly, a J-shaped curve was observed only during the first 3 years of follow-up of a population-based cohort older than 65 years of age (16).

Our findings for systolic blood pressure were similar to those for diastolic blood pressure: We found no evidence of an increased risk for cardiovascular deaths with decreasing systolic blood pressure in treated patients. This observation may be related to the observation in a few studies (40, 41) that systolic blood pressure is more closely positively related than diastolic blood pressure to the risk for cardiovascular events, especially in elderly persons (42). Therefore, the relative effect of other confounding factors should be attenuated with systolic blood pressure. Moreover, because the HDFP data on ongoing systolic blood pressure were unavailable, we could not include this trial; consequently, the omission of the 98 cardiovascular deaths from the HDFP trial (of 415 overall in INDANA) decreased the power of our analysis.

Many researchers had expected the HOT trial to definitively determine the optimal blood pressure target for treating hypertensive patients. Unfortunately, direct comparison in that study of the three randomly allocated groups—with diastolic blood pressure targets of 80, 85, and 90 mm Hg—showed no significant difference in the risk for events, except for myocardial infarction, which showed a trend of decreased risk at lower blood pressure targets. Despite its inclusion of 18 790 patients, the HOT trial observed only 589 deaths—that is, 25% of the fatal events in our study. Hence, the secondary analysis of the HOT data (modeling the relationship between blood pressure and risk in patients receiving active treatment) was much less powerful than the current meta-analysis.

In conclusion, our findings indicate an increased risk for death among both treated and untreated hypertensive patients with low blood pressure, and this increased risk was apparent for cardiovascular deaths as

well as for non–blood pressure–related events (noncardiovascular deaths). The blood pressure at which the risk for total mortality was lowest was 169/94 mm Hg in the control group and 156/84 mm Hg in the active treatment group. These results support the idea that the J-shaped curve is independent of treatment and is explained by other factors, such as poor health associated with low blood pressure.

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