Systolic and Diastolic Blood Pressure Lowering as Determinants of Cardiovascular Outcome

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Abstract—Based on individual patient data, we performed a quantitative overview of trials in hypertension to investigate to what extent lowering of systolic blood pressure (SBP) and diastolic blood pressure (DBP) contributed to cardiovascular prevention. We selected trials that tested active antihypertensive drugs against placebo or no treatment. Our analyses included 12 903 young (30 to 49 years of age) patients randomized in 3 trials and 14 324 old (60 to 79 years of age) and 1209 very old (≥80 years of age) patients enrolled in 8 trials. Antihypertensive treatment reduced SBP/DBP by 8.3/4.6 mm Hg in young patients, by 10.7/4.2 mm Hg in old patients, and by 9.4/3.2 mm Hg in very old patients, respectively, resulting in ratios of DBP to SBP lowering of 0.55, 0.39, and 0.32, respectively ($P=0.004$ for trend with age). In spite of the differential lowering of SBP and DBP, antihypertensive treatment reduced the risk of all cardiovascular events, stroke and myocardial infarction in the 3 age strata to a similar extent. Absolute benefit increased with age and with lower ratio of DBP to SBP lowering. Furthermore, in patients with a larger-than-median reduction in SBP, active treatment consistently reduced the risk of all outcomes irrespective of the decrease in DBP or the achieved DBP. These findings remained consistent if the achieved DBP averaged <70 mm Hg. In conclusion, our overview suggests that antihypertensive drug treatment improves outcome mainly through lowering of SBP. **(*Hypertension*. 2005; 45:907-913.)**

Key Words: clinical trials ■ blood pressure ■ meta-analysis

Systolic blood pressure (SBP) increases with age until the eighth or ninth decade of life.[1–3] In contrast, diastolic blood pressure (DBP) rises only until middle age and then either levels off or slightly decreases. In the Framingham cohort, with increasing age, there was a gradual shift from DBP to SBP as predictors of cardiovascular risk.[4] In patients <50 years of age, DBP was the strongest predictor. Age 50 to 59 years was a transition period when SBP and DBP were comparable predictors. From 60 years of age onward, coronary heart disease risk was positively correlated with SBP but was inversely related to DBP. Several other studies[5–9] confirmed the superiority of SBP over DBP as predictor of cardiovascular morbidity and mortality.

Cruikshank was the first to raise the hypothesis that a too low DBP on antihypertensive treatment might cause rather than prevent mortality from coronary heart disease.[10] Whether or not the J-curve phenomenon is attributable to antihypertensive treatment has been debated vigorously over the past 20 years. Recent observations from the Framingham Study[11] and from the Systolic Hypertension in the Elderly Program (SHEP) trial[12] revived the controversy. Despite the overwhelming evidence highlighting the risk of systolic hypertension in the elderly[13] and the risk possibly associated with a forced reduction of a normal DBP,[12] regulators still insist that SBP and DBP be lowered for a new drug to be approved. In view of the ongoing debate, we performed a quantitative overview of trials in hypertension. In an age-stratified analysis, we first evaluated whether cardiovascular outcome was associated with differential reductions in SBP and DBP in young, old, and very old patients. Subsequently, we assessed to what extent DBP reduction or achieved DBP contributed to cardiovascular outcome in patients with a larger-than-median decrease in SBP on antihypertensive drug treatment.

Methods

Selection of Trials and Patients

Because our analyses required access to individual patient data, we used the trials available in the INdividual Data ANalysis of Antihypertensive intervention trials (INDANA) data set[14] or at the Study Coordinating Centre in Leuven (Belgium).[15–17] From the INDANA data set, we excluded 1 intervention trial of multiple risk factors[18] and 1 small pilot trial, with a 4:1 randomization to active antihypertensive treatment.[19] Thus, our analysis included 10 trials (Table 1): the Australian Trial in Mild Hypertension (ATMH),[20] the study conducted by the European Working Party on High Blood Pressure in the Elderly (EWPHE),[15] the Hypertension Detection and

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TABLE 1. Characteristics of the Trials

Trials	Blinding	No. Patients†	Main Selection Criteria: Age, years	SBP, mm Hg	DBP, mm Hg	Goal SBP/DBP, mm Hg‡	Antihypertensive Treatment: First-line Agent(s)	Add-on Drugs
Trials excluding elderly ISH patients								
ATMH[20]	single	3427		<200	95–110	../≤90 (initially); ../≤80 (after 2 years)	thiazide	α-methyldopa, β-blocker, hydralazine, clonidine
HDFP[21]	none	10940		any	≥90	../≤90 (DBP ≥100 or treated); ../↓ 10 (DBP 90–99)	thiazide or triamterene or spironolactone	reserpine, α-methyldopa, hydralazine, guanethidine
Trials including only ISH patients								
SHEP[25]	double	4736		160–219	<90	<160/.. (SBP ≥180); ↓ 20/.. (SBP 160–179)	thiazide	β-blocker or reserpine
Syst-Eur[16]	double	4695		160–219	<95	<150/..	DHP	enalapril, thiazide
Syst-China[17]	single	2394		160–219	<95	<150/..	DHP	captopril, thiazide
Trials including a subgroup of elderly ISH patients								
EWPHE[15]	double	840		160–239	90–119	none	thiazide and triamterene	α-methyldopa
HEP*[22]	none	884		≥170	≥105	<170/<105	β-blocker	thiazide, α-methyldopa, DHP
STOP*[26]	double	1627		≥180	≥90	<160/<95	thiazide or β-blocker	β-blocker or thiazide
MRC1[23]	single	17354		>200	90–109	../<90	thiazide or β-blocker	α-methyldopa, guanethidine
MRC2[24]	single	4396		160–209	<115	≤150/.. (SBP <180); ≥160/.. (SBP ≥180)	thiazide or β-blocker	β -blocker or thiazide, DHP

ISH indicates isolated systolic hypertension; DHP, dihydropyridine calcium-channel blocker.

*In HEP[22] and STOP,[26] eligible patients had to comply either with the systolic or the diastolic entry criteria; †total No. of patients enrolled into each trial; ‡goal of treatment depended on blood pressure[21,24,25] or status of treatment[21] at entry, as given between the parentheses.

For ATMH,[20] the target pressure level was initially defined as a DBP of ≤90 mm Hg, but after 2 years, lowered to 80 mm Hg.

Follow-Up Program (HDFP),[21] the trial on Hypertension in Elderly Patients in Primary Care (HEP),[22] the Medical Research Council trials in mild hypertension (MRC1)[23] and in older adults (MRC2),[24] the SHEP,[25] the Swedish Trial in Old Patients With Hypertension (STOP),[26] the Systolic Hypertension in China trial (Syst-China),[17] and the Systolic Hypertension in Europe trial (Syst-Eur).[16]

To examine the effects of differential reductions in SBP and DBP by age stratum, we included in our analysis young (30 to 49 years of age) patients with systolic or diastolic hypertension (SBP ≥160 mm Hg or DBP ≥95 mm Hg) and old (60 to 79 years of age) and very old (≥80 years) patients with isolated systolic hypertension (SBP ≥160 mm Hg and DBP <95 mm Hg).[16,17,25]

Outcomes

We studied total and cardiovascular mortality, all cardiovascular events, fatal and nonfatal stroke, and fatal and nonfatal coronary heart disease, as defined in the INDANA database.[14] Stroke did not comprise transient ischemic attacks. Coronary heart disease included fatal and nonfatal myocardial infarction and sudden death. All cardiovascular events consisted of stroke, coronary heart disease, and other fatal and nonfatal vascular disorders as defined in each trial.[15–17,20–26]

Statistical Methods

We used the SAS statistical package (SAS Institute) version 8.1 for database management and statistical analysis. All reported *P* values are 2 sided. The achieved blood pressure was the last available measurement during follow-up, which, in some patients, was obtained before an end point. Net treatment effects on blood pressure were determined by subtracting the mean blood pressure changes from baseline to the last available measurement in the control group from the corresponding mean changes in the active treatment group.

To obtain pooled estimates across trials by age stratum, we computed relative risks with 95% confidence intervals (CIs) for active treatment versus control using Cox regression with stratification for trial. We tested heterogeneity of relative risks using the χ^2 test. We computed relative benefit as the percentage reduction in the outcome rate in the active treatment group compared with the rate in the control group.[15] Absolute benefit, expressed as the number of events prevented by treating 1000 patients for 5 years, was calculated from the rate in the control patients and the relative benefit of treatment.

To further assess the role of the reduction in DBP in cardiovascular prevention, we performed a matched-pair analysis with stratification by trial. Within each trial, we first selected actively treated patients with a larger-than-median treatment-induced decrease in SBP. These actively treated patients were matched with untreated controls from the same trial by gender, age (within 10 years), smoking, previous cardiovascular complications, and SBP and DBP at entry (within 5 mm Hg). We then subdivided the patients into quartiles according to the decrease in DBP in the actively treated patients. With stratification for trial and respecting the randomization within each trial, we then calculated the relative risks for active treatment versus control, while controlling for age and SBP and DBP at baseline, using multiple Cox regression. We repeated the matched-pair analysis according to quartiles of achieved DBP and for patients whose achieved DBP blood pressure at the last follow-up visit was below the 10th percentile.

Results

Characteristics of Trials and Patients

The main characteristics of the trials appear in Table 1. In ATMH, HDFP, SHEP, Syst-Eur, Syst-China, EWPHE, and MRC1, the stratification criteria included center,[16,17,21,23,25] gender,[15–17,20,23] age,[20,23] baseline blood pressure,[21] previous cardiovascular complications,[15–17] or antihypertensive drug treatment at initial contact.[25] No stratification was applied in HEP, STOP, and MRC2. The ATMH, HDFP, SHEP, Syst-Eur, EWPHE, HEP, and STOP trials relied on balanced

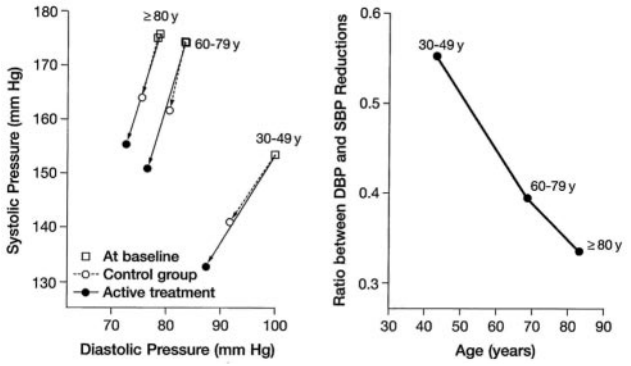

Figure 1. SBP and DBP at baseline and during follow-up in 3 age groups by randomization group (left), and the ratio of SBP to DBP lowering by age group (right). y indicates years.

randomization to active medication or to a control group. In the MRC1 and MRC2 studies, patients were randomized into 4 groups, in whom treatment was started with a diuretic, a β-blocker, or 1 of 2 matching placebos. In the Syst-China trial, patients were sequentially assigned placebo or active medication but remained unaware of the nature of their treatment.[17]

Various antihypertensive drug regimens were tested (Table 1). In general, to reach the goal blood pressure, a stepped-care approach was used, which consisted of increasing the dose of the first-line medication and introducing the second-line and third-line drugs as necessary. The goal blood pressure was defined based on SBP in MRC2, SHEP, Syst-China, and Syst-Eur, on DBP in ATMH, HDFP, and MRC1, and on both blood pressure components in HEP and STOP.

The numbers of young, old, and very old patients were 12 903 (ATMH, HDFP, and MRC1), 14 324 (EWPHE, HEP, STOP, MRC1, MRC2, SHEP, Syst-Eur, and Syst-China), and 1209 (EWPHE, HEP, STOP, SHEP, Syst-Eur and Syst-China), respectively. At baseline, their SBP/DBP averaged 154/100, 174/83, and 176/78 mm Hg. The characteristics of the patients by age stratum are described in detail in a supplemental Table, available online at http://www.hypertensionaha.org. Median follow-up was 5.0 years in the young patients, and 3.9 and 3.8 years in the old and very old patients, respectively.

Effects of Differential Lowering of SBP and DBP

In young patients, on average, active treatment reduced blood pressure by 8.3 (95% CI, 5.7 to 11.0) mm Hg SBP and 4.6 (95% CI, 2.6 to 6.6) mm Hg DBP (Figure 1). The corresponding reductions in old and very old patients were 10.7 (95% CI, 8.3 to 13.0) mm Hg and 9.4 (95% CI, 4.4 to 14.3) mm Hg SBP, and 4.2 (95% CI, 2.4 to 6.0) mm Hg and 3.2 (95% CI, −1.0 to 7.3) mm Hg DBP, respectively. Thus, with increasing age, the ratio of DBP to SBP lowering significantly decreased from 0.55 (95% CI, 0.46 to 0.64) in the young patients to 0.39 (95% CI, 0.29 to 0.49) and 0.32 (95% CI, 0.01 to 0.63) in the old and very old patients, respectively (Figure 1; $P=0.004$ for trend).

In old patients with an intermediate ratio of DBP to SBP lowering, active treatment reduced total mortality by 17% (95% CI, 6% to 26%; $P=0.003$) and cardiovascular mortality by 21% (95% CI, 7% to 33%; $P=0.004$), whereas this was not the case in young and very old patients ($P\geq0.28$; Figure 2). Despite the differential lowering in DBP, antihypertensive treatment reduced all cardiovascular events and the risk of stroke and coronary events to a similar extent in the 3 age strata (Figure 3). Moreover, for fatal and nonfatal end points combined, absolute benefit increased with higher age and with lower ratio of DBP to SBP lowering (Figure 4).

Matched-Pair Analysis

The characteristics of the patients enrolled in the matched-pair analysis appear in Table 2 by degree of DBP reductions. In this analysis, which was stratified by trial, the median decrease in SBP ranged from 18.0 to 29.5 mm Hg (weighted

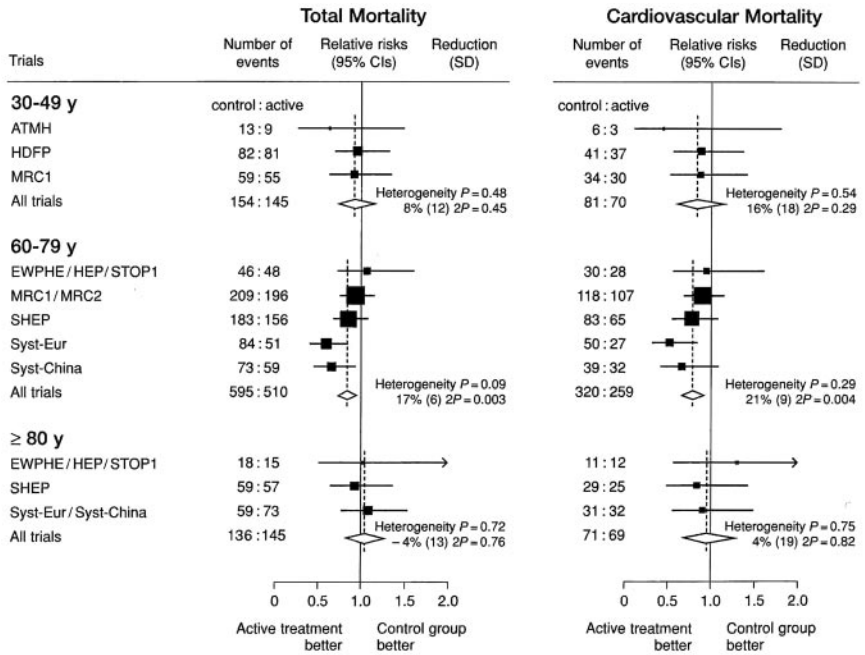

Figure 2. Effects of treatment on total and cardiovascular mortality in 3 age strata. Solid squares (■) represent treatment-to-control odds ratios in trials and have a size proportional to number of events. The 95% CIs for individual trials are denoted by lines and those for pooled odds ratios by diamonds. y indicates years.

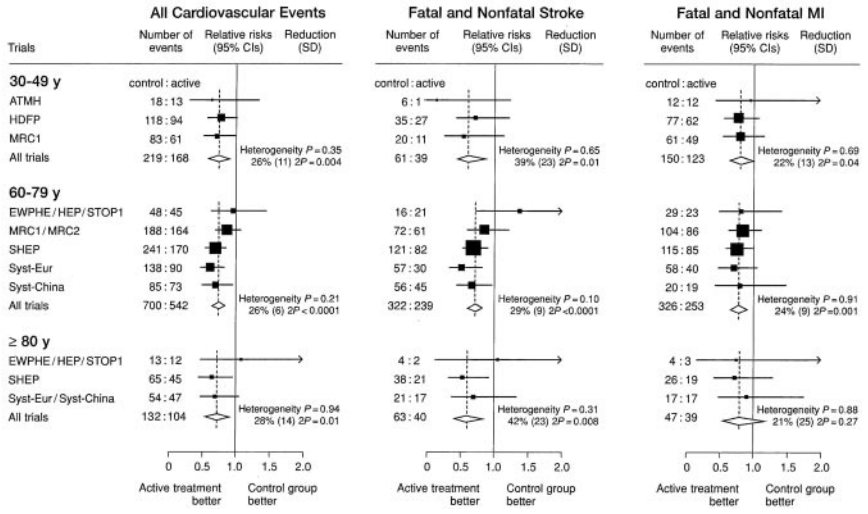

Figure 3. Effects of treatment on all cardiovascular events, stroke, and myocardial infarction. y indicates years. For further explanation, see Figure 2.

mean 21.9 mm Hg). The 25th, 50th, and 75th percentiles used to define the quartiles of DBP change, across trials, ranged from 3.3 to 13.0 mm Hg (8.2 mm Hg), from 8.3 to 19.0 mm Hg (13.7 mm Hg), and from 13.3 to 26.0 mm Hg (19.5 mm Hg). Despite the between-quartile differences in DBP reduction, active treatment tended to reduce the risk of any outcome to a similar extent (Figure 5). In particular, in quartile 1 with the least reduction in DBP, benefits were observed for all end points ($P \leq 0.09$).

Sensitivity analyses based on quartiles of the achieved DBP at the last follow-up visit were confirmatory (detailed results are available in the online supplement). We also matched actively treated patients with a greater-than-median fall in SBP and an achieved DBP below the 10th percentile with control patients with a similar cardiovascular risk profile (571 pairs). The achieved blood pressure in the actively treated patients averaged 123.6 mm Hg SBP and 62.1 mm Hg DBP. The corresponding levels in the matched controls were 153.5 mm Hg SBP and 83.8 mm Hg DBP. In this stratum, the relative hazard ratios were 0.46 (95% CI, 0.27 to 0.80; $P=0.006$) for total mortality, 0.34 (95% CI, 0.16 to 0.74; $P=0.007$) for cardiovascular mortality, 0.59 (95% CI, 0.37 to 0.94; $P=0.02$) for all cardiovascular events, 0.35 (95% CI, 0.14 to 0.85; $P=0.02$) for stroke, and 0.86 (95% CI, 0.47 to 1.56; $P=0.61$) for myocardial infarction.

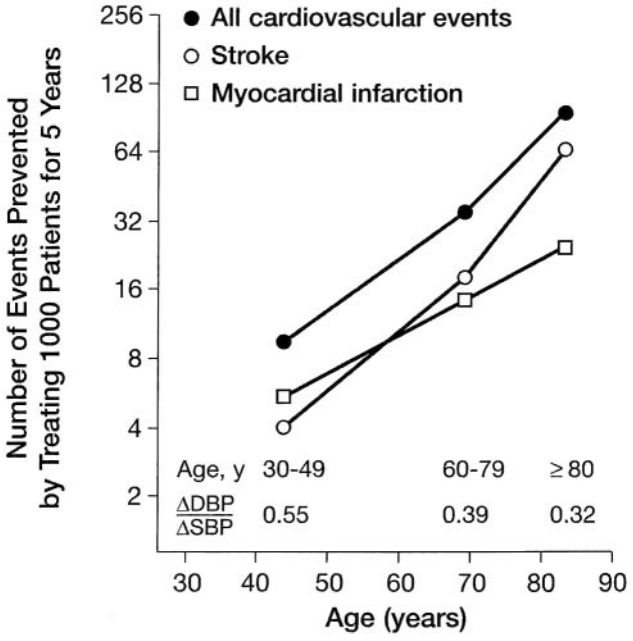

Figure 4. Absolute benefits in the prevention of fatal and nonfatal cardiovascular events, stroke, and myocardial infarction in 3 age groups. Symbols represent the number of events that can be prevented by treating 1000 patients for 5 years. ΔSBP/ΔDBP refers to the mean ratio of DBP-to-SBP lowering; y, years.

Discussion

The key finding of our analysis was that differential lowering of DBP had little influence on the benefit of antihypertensive treatment, which was similar in young, old, and very old hypertensive patients. Our matched-pair analysis further corroborated the hypothesis that the degree of DBP reduction or the achieved DBP did not lead to differences in cardiovascular outcome as long as SBP pressure substantially decreased. Furthermore, lowering of DBP to levels averaging <70 mm Hg did not cause harm. Our null findings with regard to mortality in young and very old patients were expected because 4 to 5 years of follow-up might be insufficient to reveal any effect on fatal outcomes in young patients but too long in very old patients.

Our study confirmed Koch-Weser's early finding that the wider the pulse pressure, the smaller the ratio of DBP to SBP lowering with antihypertensive therapy.[27] These results are consistent with well-known hemodynamic principles. Indeed, DBP rises with increased peripheral arterial resistance but falls with increased stiffness of the large conduit arteries.[3,28] Whereas increased arterial resistance is the hallmark of combined systolic and diastolic hypertension in the young, increased arterial stiffness becomes the dominant hemodynamic factor and overrides resistance in elderly hypertensive patients, leading to a fall in DBP, widening of pulse pressure, and hence isolated systolic hypertension.[3,28] Therefore, antihypertensive therapy will maximize the decrease in SBP and

TABLE 2. Characteristics of Patients Included in the Matched-Pair Analysis*

Characteristic	Quartile 1		Quartile 2		Quartile 3		Quartile 4	
	Control (n=1522)	Active (n=1522)	Control (n=1602)	Active (n=1602)	Control (n=1697)	Active (n=1697)	Control (n=1697)	Active (n=1697)
Age, years	57.7±14.3	57.6±14.1	57.4±13.9	57.3±14.0	57.7±14.2	57.7±14.1	57.5±14.2	57.5±14.2
SBP at baseline, mm Hg	167.5±15.5	167.5±15.4	166.9±15.4	166.9±15.3	167.4±15.6	167.4±15.7	170.0±15.3	170.1±15.3
DBP at baseline, mm Hg	88.3±10.7	87.8±10.4	90.6±10.1	90.6±9.8	91.9±10.6	92.1±10.5	94.9±11.8	95.4±11.9
Change in SBP during follow-up, mm Hg	−14.1±18.6	−31.1±8.7	−13.7±18.7	−33.4±10.3	−14.1±19.3	−36.0±10.6	−16.5±21.1	−42.4±13.9
Change in DBP during follow-up, mm Hg	−4.0±10.0	−3.1±5.4	−5.1±10.4	−10.7±3.8	−6.0±11.0	−16.1±4.2	−8.3±11.4	−25.0±7.2
ΔSBP/ΔDBP reduction, mm Hg†	17.1/−0.9		19.7/5.7		22.0/10.0		25.9/16.7	

Values are mean±SD.

*The matched-pair analysis was stratified by trial. Across trials, the average decrease in SBP exceeded 21.9 mm Hg. The 25th, 50th and 75th percentiles of the reductions in DBP, used to define the quartiles, averaged 8.2, 13.7, and 19.5 mm Hg, respectively. For further details, see Methods.

†ΔSBP/ΔDBP represent the within-quartile differences in DBP reduction between patients allocated active treatment or control. A negative value indicates lesser blood pressure reduction in the active treatment group.

minimize the reduction in DBP in direct proportion to the age-related stiffening of large arteries.

The drugs currently in use for treatment of hypertension reduce SBP and DBP.[29] No clinical trial ever investigated the effects of selective lowering of SBP or DBP on cardiovascular risk. Our meta-analysis addresses this question while respecting initial randomization within trials. Five trials compared tight with usual blood pressure control[30–34] but produced divergent results. In all 5 trials,[30–34] regardless of randomization group, the achieved DBP consistently averaged <90 mm Hg. This increases the likelihood that differential reductions in SBP might have been the main determinant of outcome. However, most of these trials were not designed or powered to detect differences in outcome attributable to small gradients in SBP. This might explain the null findings in the Hypertension Optimal Trial (HOT)[30] and the Appropriate Blood Pressure Control in Diabetes (ABCD) trial in hypertensive patients.[32] When a pronounced SBP reduction was achieved, such as in the United Kingdom Prospective Diabetes Study-Hypertension in Diabetes Study (UKPDS; 10 mm Hg; UKPDS–HDS)[31] or in the ABCD trial in normotensive patients (9 mm Hg),[33] tight compared with usual blood pressure control significantly decreased the risk of stroke. In the African American Study of Kidney disease and hypertension (AASK),[34] the difference in achieved SBP was 13 mm Hg, but the incidence of all cardiovascular events was only slightly reduced by 15%. It is noteworthy that the primary end point consisted of microvascular complications in the AASK,[34] ABCD,[32,33] and UKPDS-HDS trials.[31]

We based the present meta-analysis on comparisons between actively treated and control patients enrolled in randomized clinical trials. This approach is different from that used in previous overviews of observational cohort studies addressing the predictive value of SBP and DBP components or investigating the J-curve issue.[10,35,36] SBP and DBP are closely related. Without appropriate adjustment for SBP, the direct relationship between the risks of stroke and coronary heart disease and DBP might be confounded by SBP. On the other hand, the J- or U-shaped association between cardiovascular risk and DBP might not be treatment induced. It might reflect the age-related stiffening of the large arteries, leading to increased SBP, lower DBP, wider pulse pressure, and hence higher cardiovascular risk.[3] It might also be the consequence of ill health with lower levels of blood pressure as a consequence of immobilization.[10,36]

In our analysis, we used a large database of individual patient data, which allowed us to run a matched-pair analysis. Within each trial, the actively treated patients were matched with control subjects. At entry, matched patients had a similar risk profile in terms of gender, age, smoking habits, previous cardiovascular complications, antihypertensive treatment before enrollment, and SBP and DBP. On the other hand, our analysis has also limitations. The results were obtained retrospectively and cannot be compared with evidence from a

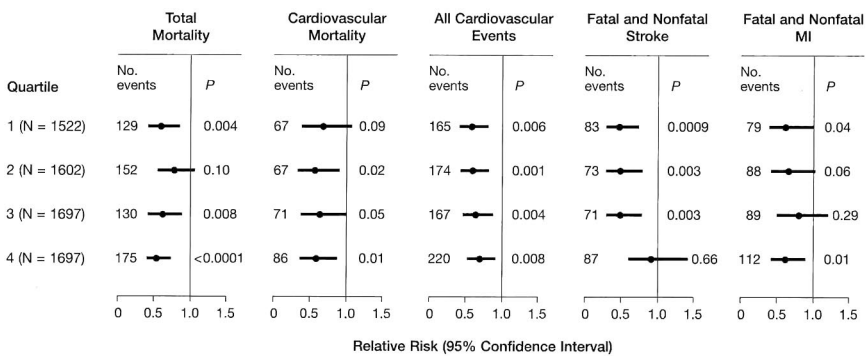

Figure 5. Effects of active treatment on outcome in the matched-pair analysis. For the definition of quartiles, see Methods and Table 2. MI indicates myocardial infarction. N indicates the number of pairs in each stratum.

dedicated prospective outcome trial. Furthermore, our conclusions are based partly on the comparisons of the outcomes between treated and untreated patients across different age strata. Because of the differences across the reviewed trials in the combinations of antihypertensive drugs, our results should not be viewed to provide any evidence for a selective benefit of a specific antihypertensive agent. Finally, we could not assess to what extent our results might be influenced by imprecision in the blood pressure readings. Measurement error is usually larger for DBP than SBP because of the greater variability in the auscultatory end point, which leaves the observer more room for interpretation.[37]

Perspectives

Our overview suggests that antihypertensive drug treatment might improve outcome mainly through lowering of SBP. The hypothesis that in older patients, selective lowering of SBP, for instance by long-acting nitrates[38] or drugs increasing total arterial compliance,[39] might improve prognosis more than the indiscriminate reduction of SBP and DBP should be further tested in randomized trials.

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