

# Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials

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## Summary

**Background** Previous meta-analysis of outcome trials in hypertension have not specifically focused on isolated systolic hypertension or they have explained treatment benefit mainly in function of the achieved diastolic blood pressure reduction. We therefore undertook a quantitative overview of the trials to further evaluate the risks associated with systolic blood pressure in treated and untreated older patients with isolated systolic hypertension

**Methods** Patients were 60 years old or more. Systolic blood pressure was 160 mm Hg or greater and diastolic blood pressure was less than 95 mm Hg. We used non-parametric methods and Cox regression to model the risks associated with blood pressure and to correct for regression dilution bias. We calculated pooled effects of treatment from stratified 2 × 2 contingency tables after application of Zelen's test of heterogeneity.

**Findings** In eight trials 15 693 patients with isolated systolic hypertension were followed up for 3·8 years (median). After correction for regression dilution bias, sex, age, and diastolic blood pressure, the relative hazard rates associated with a 10 mm Hg higher initial systolic blood pressure were 1·26 (p=0·0001) for total mortality, 1·22 (p=0·02) for stroke, but only 1·07 (p=0·37) for coronary events. Independent of systolic blood pressure, diastolic blood pressure was inversely correlated with total mortality, highlighting the role of pulse pressure as risk factor.

Active treatment reduced total mortality by 13% (95% CI

2–22, p=0·02), cardiovascular mortality by 18%, all cardiovascular complications by 26%, stroke by 30%, and coronary events by 23%. The number of patients to treat for 5 years to prevent one major cardiovascular event was lower in men (18 vs 38), at or above age 70 (19 vs 39), and in patients with previous cardiovascular complications (16 vs 37).

**Interpretation** Drug treatment is justified in older patients with isolated systolic hypertension whose systolic blood pressure is 160 mm Hg or higher. Absolute benefit is larger in men, in patients aged 70 or more and in those with previous cardiovascular complications or wider pulse pressure. Treatment prevented stroke more effectively than coronary events. However, the absence of a relation between coronary events and systolic blood pressure in untreated patients suggests that the coronary protection may have been underestimated.

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## Introduction

The prevalence of isolated systolic hypertension rises curvilinearly with age, averaging 8% in sexagenarians and exceeding 25% beyond 80 years.<sup>1</sup> Isolated systolic hypertension is a distinct pathophysiological entity, in which the rise in systolic blood pressure is mainly due to a decreased elasticity of the large arteries and is not necessarily accompanied by a rise in mean arterial blood pressure or in peripheral resistance.<sup>1</sup>

Among the cardiovascular risk factors amenable to prevention in the elderly, systolic hypertension is of major importance.<sup>1</sup> The past decade witnessed the publication of three outcome trials,<sup>2–4</sup> which specifically addressed the question whether in the elderly the cardiovascular risk conferred by isolated systolic hypertension is reversible by antihypertensive drug treatment. Earlier published trials also included groups of older patients with isolated systolic hypertension.<sup>5–9</sup> Previous meta-analyses of outcome trials in hypertension<sup>10–21</sup> did not provide specific estimates of the risks in treated and untreated older patients with isolated systolic hypertension or explained treatment benefit mainly in function of the achieved diastolic blood pressure. We therefore reanalysed the evidence from the published trials. In untreated control patients we first evaluated the risk conferred by systolic and diastolic blood pressure at baseline both before and after correction for regression dilution bias.<sup>22,23</sup> We then calculated pooled estimates of relative and absolute benefit of antihypertensive drug treatment with and without stratification for the risk at baseline.

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## Methods

### Acquisition and selection

We defined isolated systolic hypertension as it was in two published trials.<sup>3,4</sup> Systolic blood pressure had to be 160 mm Hg or higher with diastolic blood pressure below 95 mm Hg. As in other studies,<sup>2-5</sup> we set the lower boundary of old age at 60 years without an upper limit. We screened published overviews<sup>10-13, 16-21</sup> and reports on collaborations between trialists<sup>14,15</sup> for outcome studies in hypertension, in which older patients with isolated systolic hypertension had been enrolled. Among the trials with eligible patients, we excluded seven: the outcome results in patients with isolated systolic hypertension were not separately available in two small studies,<sup>24, 25</sup> one study was done in stroke survivors,<sup>26</sup> one large trial compared specialised with routine antihypertensive care,<sup>27</sup> and one trial<sup>28</sup> done had a 4:1 randomisation to active treatment and was the pilot run of a landmark trial,<sup>2</sup> which we did include.

We incorporated in our overview three trials that exclusively involved older patients with isolated systolic hypertension (table 1): the Systolic Hypertension in the Elderly Program (SHEP),<sup>2</sup> the Systolic Hypertension in Europe trial (Syst-Eur),<sup>3</sup> and the Systolic Hypertension in China trial (Syst-China).<sup>4</sup> We also included elderly patients with isolated systolic hypertension enrolled in five other trials (table 1): the study conducted by the European Working Party on High Blood Pressure in the Elderly (EWPHE)<sup>5</sup> the trial on Hypertension in Elderly Patients in Primary Care (HEP),<sup>6</sup> the Swedish Trial in Old Patients with Hypertension (STOP),<sup>7</sup> and the Medical Research Council trials in mild hypertension (MRC1)<sup>9</sup> and in older adults (MRC2).<sup>8</sup> The study coordinating office in Leuven, Belgium, created and managed the databases of the EWPHE,<sup>5</sup> Syst-Eur,<sup>3</sup> and Syst-China<sup>4</sup> trials; the statistics of the other trials<sup>2,6-9</sup> were generated from the INDANA dataset.<sup>14</sup>

### Outcomes

We studied total and cardiovascular mortality, all cardiovascular complications, fatal and non-fatal stroke, and fatal and non-fatal coronary events. We defined these outcomes as in the INDANA database.<sup>14</sup> Stroke did not comprise transient ischaemic attacks. Coronary heart disease included fatal and non-fatal myocardial infarction and sudden death. All cardiovascular complications consisted of fatal and non-fatal stroke, fatal and non-fatal coronary heart disease, and other fatal and non-fatal vascular disorders as defined in each trial.<sup>2-9</sup>

### Statistical analysis

Database management and most statistical analyses were done with SAS software, version 6.12. Measurements of blood pressure at baseline are insufficient to estimate a patient's usual blood pressure, because readings are subject to large random variation.<sup>22</sup> Reliance on only baseline measurements leads to a systematic underestimation of the slope of the association between disease risk and a patient's usual blood pressure.<sup>22,23</sup> We

estimated the correction for regression dilution bias,<sup>22,23</sup> in a cohort of patients randomised to no treatment, who accumulated an event-free survival of 2 years.

In individual control patients, we used Cox regression with stratification for trial and with adjustments for sex, age, and other confounders to investigate the relationship between outcome and blood pressure. This parametric approach rested on the assumption of a common log-linear relationship across the control groups. We also used a non-parametric approach.<sup>22</sup> First, in all control patients combined, we divided the distributions of the baseline blood pressure into fifths. From one overall logistic-regression model adjusted for sex, age, and study, we then computed the risk of an adverse outcome in each blood-pressure fifth relative to the common risk in all patients,<sup>22</sup> by the use of the deviation-from-means coding approach.<sup>29</sup> We plotted these five risk estimates with 95% CI against the blood pressure in each fifth. This non-parametric approach avoids any assumption about the shape of the association between outcome and blood pressure.<sup>22</sup> We corrected the associations between the risk of an event and the baseline blood pressure for regression dilution bias, using the parametric and non-parametric approaches described by MacMahon and colleagues.<sup>22</sup>

Net treatment effects on blood pressure were determined by taking the mean blood-pressure changes from baseline to the last available measurement<sup>30</sup> in the control group and subtracting them from the corresponding mean changes in the active-treatment group. For each study and for pooled studies, we found benefit of active treatment from the odds ratios in stratified 2×2 contingency tables.<sup>10,31</sup> We used StatXact for Windows version 4.0 (CYTEL Software Corporation, Cambridge, MA) to check the homogeneity of the odds ratios by Zelen's test and to calculate exact 95% CIs.<sup>32</sup> To permit comparisons with other overviews,<sup>10-21</sup> we also derived the SDs of the pooled odds ratios by analogy with the asymptotic approach by dividing the logarithmically transformed CI by (2×1.96). All reported p-values are for two-sided hypotheses.

We calculated relative benefit as the percentage reduction in the outcome rate in the active-treatment group compared with the rate in the control group.<sup>3</sup> Absolute benefit with 95% CI, expressed as the number of patients to treat for 5 years to prevent one event, was calculated from the rate in the control patients, the difference in the rates between the control and active-treatment groups, and its SE.<sup>33</sup>

## Results

### Characteristics of trials

The main characteristics of the trials appear in table 1. In SHEP, Syst-Eur, Syst-China, EWPHE, and MRC1, the stratification criteria included centre,<sup>2-4,9</sup> sex,<sup>3-5,9</sup> age,<sup>9</sup> previous cardiovascular complications,<sup>3-5</sup> or anti-hypertensive drug treatment at initial contact.<sup>2</sup> No stratification was applied in HEP, STOP, and MRC2. The SHEP, Syst-Eur, EWPHE, HEP, and STOP trials

Characteristic	Trials including only ISH patients			Trials including subgroup of elderly ISH patients				
	SHEP <sup>2</sup>	Syst-Eur <sup>3</sup>	Syst-China <sup>4</sup>	EWPHE <sup>5</sup>	HEP* <sup>6</sup>	STOP* <sup>7</sup>	MRC1 <sup>9</sup>	MRC2 <sup>8</sup>
<b>Blinding</b>	Double	Double	Single	Double	None	Double	Single	Single
<b>Total number of patients</b>	4736	4695	2394	840	884	1627	17 354	4396
<b>Main selection criteria</b>								
Age (years)	≥60	≥60	≥60	≥60	60-79	70-84	35-64	65-74
Systolic pressure (mm Hg)	160-219	160-219	160-219	160-239	≥170	≥180	>200	160-209
Diastolic pressure (mm Hg)	<90	<95	<95	90-119	≥105	≥90	90-109	<115
<b>Antihypertensive treatment</b>								
First-line	Thiazide	DHP	DHP	Thiazide and triamterene	β-blocker	Thiazide and amiloride or β-blocker	Thiazide or β-blocker	Thiazide and amiloride or β-blocker
Add-on	β-blocker or reserpine	ACE inhibitor, thiazide	ACE inhibitor, thiazide	α-methyl dopa	Thiazide, methyl dopa, DHP	β-blocker or thiazide and amiloride	α-methyl dopa, guanethidine	β-blocker or thiazide and amiloride, DHP

ISH=isolated systolic hypertension; ACE=angiotensin-converting enzyme; DHP=dihydropyridine calcium-channel blocker.

\*In HEP and STOP patients complied with the entry criteria for either systolic or diastolic blood pressure.

Table 1: Characteristics of trials

Characteristic	Trials							
	SHEP <sup>2</sup>	Syst-Eur <sup>3</sup>	Syst-China <sup>4</sup>	EWPHE <sup>5</sup>	HEP <sup>6</sup>	STOP <sup>7</sup>	MRC1 <sup>8</sup>	MRC2 <sup>8</sup>
<b>Number of patients</b>								
Total	4736	4695	2394	172	349	268	428	2651
Control group	2371	2297	1141	82	199	131	199	1337
Assigned active treatment	2365	2398	1253	90	150	137	229	1314
<b>Mean (SD) age (years)</b>	72 (7)	70 (7)	67 (6)	73 (8)	70 (5)	76 (4)	62 (1)	70 (3)
<b>Mean (SD) blood pressure (mm Hg)</b>								
Systolic	170 (9)	174 (10)	170 (11)	178 (15)	191 (17)	194 (12)	174 (11)	182 (13)
Diastolic	77 (9)	85 (5)	86 (7)	92 (2)	85 (8)	91 (3)	92 (2)	83 (9)
Pulse pressure	94 (13)	88 (11)	84 (12)	86 (15)	105 (19)	103 (12)	82 (11)	99 (13)
<b>Patients with characteristic at baseline</b>								
Women	56.8%	66.8%	35.6%	76.7%	64.8%	74.3%	58.6%	58.5%
Cardiovascular complications	42.7%	29.9%	11.2%	30.8%	39.5%	9.0%	28.3%	30.9%
Previous treatment	33.3%	46.6%	69.6%	52.9%	0	..	0	0
Smoking	12.7%	7.3%	30.8%	13.4%	18.9%	7.8%	25.5%	21.6%
<b>Follow-up duration (years)</b>	4.4	2.0	3.0	4.3	3.6	1.9	5.2	6.1
<b>Mean (SE) effect of treatment on blood pressure (mm Hg)*</b>								
Systolic	11.5 (0.6)	10.2 (0.5)	6.9 (0.7)	12.7 (3.2)	13.2 (2.6)	18.2 (2.5)	13.8 (1.8)	10.6 (0.9)
Diastolic	4.1 (0.3)	3.5 (0.2)	2.3 (0.4)	6.0 (1.3)	8.3 (1.4)	6.4 (1.1)	5.9 (0.9)	5.6 (0.5)
<b>Number of major events</b>								
Deaths	455	260	143	61	55	11	28	377
Cardiovascular events	521	323	168	50	56	12	30	322

\*Baseline minus last available blood-pressure measurement corrected for control.

Table 2: Characteristics of patients with isolated systolic hypertension

relied on balanced randomisation to active medication or a control group. In MRC1 and MRC2 the patients were randomised into four groups, in whom treatment was started with a diuretic, a  $\beta$ -blocker, or one of two matching placebos. In the Syst-China trial, the patients were alternately assigned placebo or active medication, but were unaware of the nature of their treatment.<sup>4</sup>

Various antihypertensive drug regimens were tested (table 1). In general, to reach the target 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. In four trials<sup>2-4,8</sup> the target was a systolic blood pressure below 160 mm Hg<sup>2,8</sup> or 150 mm Hg,<sup>3,4</sup> and for patients with an entry systolic pressure in the range 160–179 mm Hg, a decrease in the systolic level by at

least 20 mm Hg<sup>2-4</sup> or 30 mm Hg.<sup>8</sup> In MRC1 the target for patients randomised to active treatment was a diastolic blood pressure below 90 mm Hg. In HEP,<sup>6</sup> treatment was intensified if blood pressure exceeded 170 mm Hg systolic or 105 mm Hg diastolic; in STOP these thresholds were 160 mm Hg or 95 mm Hg.

#### Characteristics of patients

In all studies except for Syst-China, most patients were female (table 2). Mean age of the selected patients ranged from 62<sup>9</sup> to 76<sup>7</sup> years, but in most trials it was about 70. The overall prevalence of smoking at baseline was 15.8% (range 7.3–30.8%).

4848 patients (30.9% of all patients) had one or more cardiovascular complication at baseline. 217 patients (4.5% of those with cardiovascular complications) had a history of stroke and 357 (7.4%) had a history of myocardial infarction. 689 (14.2%) patients had symptoms suggestive of angina pectoris and 64 (1.3%) had symptoms of other vascular diseases. Electrocardiographic changes compatible with left ventricular hypertrophy were seen in 1602 (33.0%) patients, Q-wave changes suggestive of definite or probable myocardial infarction according to the Minnesota classification<sup>34</sup> in 465 (9.6%) patients, changes of the ST-segment (classes 1–3<sup>34</sup>) in 822 (17.0%), and T-wave alterations (classes 1–3<sup>34</sup>) in 2150 (44.4%) patients.

#### Blood pressure as risk factor

In multiple Cox regression with stratification for trial we introduced sex, age, and systolic and diastolic blood pressures at baseline as explanatory variables (table 3). Total mortality was positively correlated with systolic blood pressure at entry ( $p=0.0001$ ), whereas the association with diastolic blood pressure was negative ( $p=0.05$ ). These findings highlight the importance of pulse pressure as a risk factor. Indeed, at any given level of systolic blood pressure, a lower diastolic blood pressure was associated with a higher death rate (figure 1).

By the use of the same stratified and adjusted Cox model as for total mortality, the relative hazard rates associated with a 10 mm Hg increase in the baseline

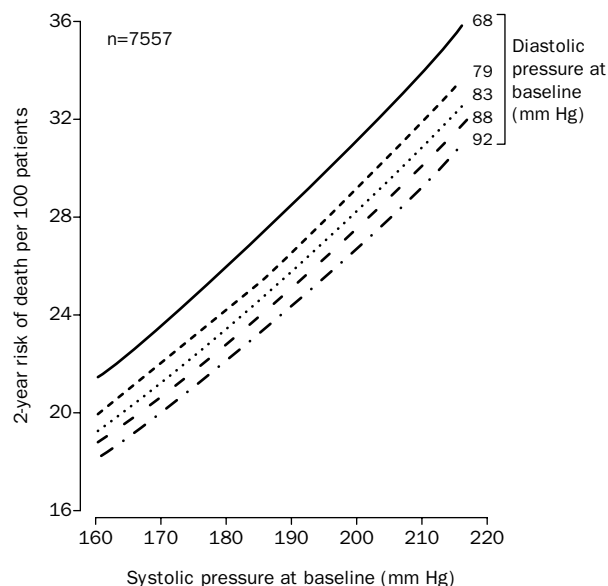


Figure 1: Risk of death associated in control patients with systolic pressure at baseline at fixed levels of diastolic pressure

The 2-year probability of death was standardised to female sex, mean age (70 years), no previous cardiovascular complications, and non-smoking.

Event	Number of events	Relative hazard rates* associated with blood pressure		
		Baseline	Usual†	p
<b>Systolic pressure (+10 mm Hg)</b>				
All-cause mortality	734	1.14 (1.07–1.21)	1.26 (1.13–1.40)	0.0001
Cardiovascular deaths	392	1.12 (1.03–1.21)	1.22 (1.06–1.40)	0.007
Cardiovascular events	835	1.08 (1.02–1.15)	1.15 (1.04–1.28)	0.01
Stroke	387	1.12 (1.02–1.21)	1.22 (1.04–1.40)	0.02
Coronary events	373	1.04 (0.95–1.14)	1.07 (0.91–1.26)	0.37
<b>Diastolic pressure (+5 mm Hg)</b>				
All-cause mortality	734	0.96 (0.92–1.00)	0.95 (0.89–1.00)	0.05
Cardiovascular deaths	392	0.95 (0.89–1.01)	0.93 (0.86–1.01)	0.08
Cardiovascular events	835	0.99 (0.95–1.03)	0.98 (0.93–1.04)	0.54
Stroke	387	0.99 (0.93–1.05)	0.98 (0.90–1.06)	0.66
Coronary events	373	1.00 (0.94–1.07)	1.00 (0.91–1.09)	0.99

\*The Cox regression models were stratified for trial. The relationships between outcome and systolic or diastolic blood pressure were adjusted for each other and in addition also for sex and age.

†Correction for regression dilution bias (see table 4) increased the slopes of the outcomes on systolic and diastolic blood pressures by 90% and 40%, respectively.

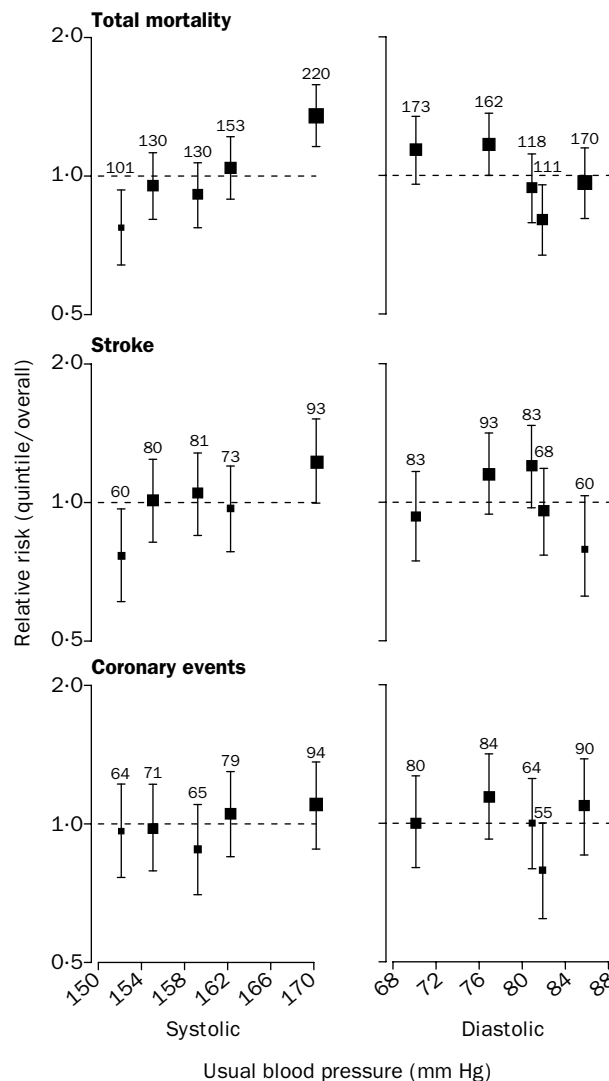
**Table 3: Relative hazard rates associated in 7757 control patients with baseline and usual blood pressures**

Quintiles of blood pressure at entry	Number of patients	Mean blood pressure (mm Hg) in each category* (cumulative difference with lowest category)		
		Entry	1 year	2 years
<b>Systolic pressure</b>				
<164	1050	161.0	152.5	152.2
164–168	1127	166.0 (5.0)	155.7 (3.2)	154.4 (2.2)
169–174	1089	171.5 (10.5)	159.4 (6.9)	158.0 (5.8)
175–183	1087	178.7 (17.7)	162.7 (10.2)	161.7 (9.5)
>183	1136	193.8 (32.8)	171.4 (18.6)	169.8 (17.6)
<b>Diastolic pressure</b>				
<76	1086	68.3	70.4	69.8
76–80	1092	78.6 (10.3)	77.7 (7.3)	77.4 (7.6)
81–85	1043	83.5 (15.2)	80.9 (10.5)	80.5 (10.7)
86–89	1044	87.7 (19.4)	83.6 (13.2)	81.8 (12.0)
>90	1224	92.1 (23.8)	87.3 (16.9)	86.3 (16.5)

**Table 4: Mean blood pressures in 5489 control patients followed up for 2 years**

systolic blood pressure were 1.12 ( $p=0.02$ ) for stroke, but only 1.04 ( $p=0.37$ ) for coronary events. Diastolic blood pressure at baseline tended to be inversely correlated with cardiovascular mortality; the relative hazard rate associated with a 5 mm Hg increase was 0.95 ( $p=0.08$ ). However, diastolic blood pressure was not significantly associated with outcome, if fatal and non-fatal events were combined (table 3). Further adjustments for previous cardiovascular complications and smoking did not materially alter the hazard rates reported in table 3.

To correct for regression dilution bias,<sup>22,23</sup> the usual blood pressure level was measured in 5489 control patients with an event-free survival of 2 years (table 4). The distributions of their baseline systolic and diastolic blood pressures were subdivided into fifths. At baseline, the differences between the blood pressure means of the lowest and highest fifths were 32.8 mm Hg systolic and 23.8 mm Hg diastolic. At 2 years of untreated follow-up, these differences had decreased to 17.6 mm Hg and 16.5 mm Hg, respectively. For systolic blood pressure these findings suggested that the relationships between disease outcomes and blood pressure were about 1.9 times (32.8/17.6) steeper for usual compared with baseline levels. For diastolic blood pressure this ratio was 1.4 (23.8/16.5). After parametric<sup>22</sup> correction for regression dilution bias, the relative hazard rates associated with a 10 mm Hg increase in systolic blood pressure were 1.26 ( $p=0.0001$ ) for total mortality, 1.22 ( $p=0.02$ ) for stroke, but only 1.07 ( $p=0.37$ ) for coronary events. The non-parametric approach<sup>22</sup> confirmed the latter findings (figure 2).



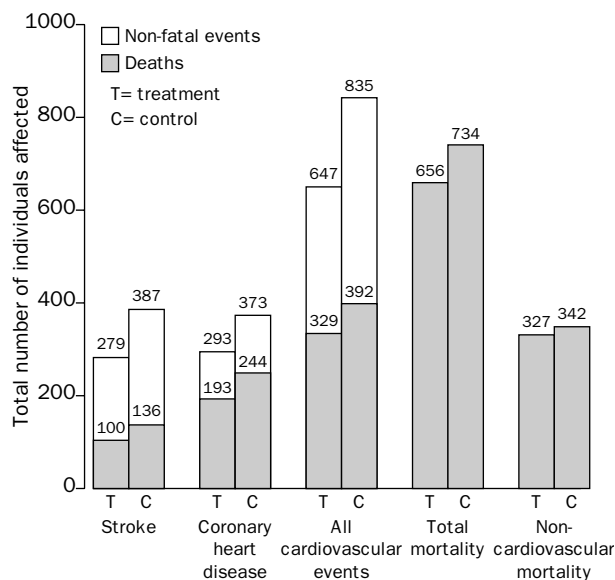
**Figure 2: Associations between total mortality, stroke, and coronary events and usual blood pressure in 7757 control patients**

Solid squares represent risks in fifths of blood pressure distribution relative to common risk in all patients. Sizes of the squares are proportional to number of events in each quintile. Vertical lines denote 95% CIs. Relative risk adjusted for sex, age, and trial. 220 under total mortality is number of events per quintile.

#### Overall effects of antihypertensive treatment

In all 15 693 patients blood pressure at enrollment averaged 174 (SD 12) mm Hg systolic and 83 (9) mm Hg diastolic. The mean baseline-corrected differences in systolic and diastolic blood pressures between patients assigned control or active treatment were 10.4 (95% CI 9.8–11.0) mm Hg and 4.1 (3.8–4.4) mm Hg. Among individual trials the blood pressure differences ranged from 6.9<sup>4</sup> to 18.2<sup>7</sup> mm Hg systolic and from 2.3<sup>4</sup> to 8.3<sup>6</sup> mm Hg diastolic (table 2). Overall, the net reductions in systolic and diastolic blood pressures expressed as a percentage of the values at baseline averaged 5.96 (5.63–6.28) and 4.91 (4.44–5.38), respectively.

Among 7757 control patients, 734 deaths and 835 major cardiovascular complications occurred; in 7936 patients allocated active treatment, these numbers were 656 and 647, respectively (figure 3). To avoid unstable contributions from smaller groups with few events,<sup>10</sup> the EWPHE, HEP, and STOP patients were combined as well as the patients enrolled in the MRC1 and MRC2



**Figure 3: Summarised results in older patients with isolated systolic hypertension enrolled in 8 trials of antihypertensive drug treatment**

Analysis included 15 693 patients. Blood pressure at entry averaged 174 mm Hg systolic and 83 mm Hg diastolic. During follow-up (median 3·8 years), mean difference in blood pressure between treated and control patients was 10·4 mm Hg systolic and 4·1 mm Hg diastolic.

studies. In the former three trials<sup>5-7</sup> older patients had been recruited, mainly on the basis of their diastolic blood pressure, while the latter two trials<sup>8,9</sup> had a similar design and were both done via the Medical Research Council's general practice research network.<sup>8</sup> Zelen's test for heterogeneity did not reach significance for any outcome, irrespective of whether the pooled estimates excluded or included the Syst-China results. Thus, the hypothesis of a common treatment effect across the trials was not rejected.

Across all trials active treatment reduced total mortality (figure 4) by 13% (2-22,  $p=0\cdot02$ ) and cardiovascular deaths by 18% (4-29,  $p=0\cdot01$ ). The pooled reduction in fatal combined with non-fatal events (figure 5) was 26% (17-34,  $p<0\cdot0001$ ) for all cardiovascular complications, 30% (18-41,  $p<0\cdot0001$ ) for stroke and 23% (10-34,  $p=0\cdot001$ ) for coronary events. If, in view of the alternating treatment allocation,<sup>4</sup> Syst-China is excluded, the pooled

estimates of relative benefit are 10% (-2 to 22,  $p=0\cdot09$ ) for all-cause mortality, 16% (1-28,  $p=0\cdot04$ ) for cardiovascular mortality, 25% (16-33,  $p<0\cdot0001$ ) for cardiovascular events, 30% (17-41,  $p<0\cdot0001$ ) for stroke and 23% (10-35,  $p=0\cdot002$ ) for coronary events. Furthermore, if only the three trials<sup>2-4</sup> that specifically focused on isolated systolic hypertension were considered, active treatment decreased total mortality by 17% (5-28,  $p=0\cdot008$ ), cardiovascular mortality by 25% (8-39,  $p=0\cdot005$ ), all cardiovascular complications by 32% (13-41,  $p<0\cdot001$ ), stroke by 37% (24-48,  $p<0\cdot001$ ) and coronary events by 25% (9-39,  $p<0\cdot001$ ).

#### Cardiovascular risk at baseline

The patients were subdivided into lower-risk and higher-risk groups based on the following baseline characteristics: sex, age, systolic blood pressure, pulse pressure, the presence of previous cardiovascular complications, and current smoking (table 5). Relative benefit was similar across these strata, reflecting for all events the estimates of overall relative benefit presented in figures 4 and 5. The  $p$  values of Zelen's test of heterogeneity were consistently greater than 0·30.

In terms of absolute benefit active treatment was particularly effective in men, older patients, and patients with previous cardiovascular complications (table 5). To prevent one major fatal or non-fatal cardiovascular event, the number of patients to treat for 5 years was 18 in men versus 38 in women, 19 in patients aged 70 years or older versus 39 in those aged 60-69 years, and 16 in patients with previous cardiovascular complications versus 37 in those without such complications. The number of patients to treat to prevent one cardiovascular death was 63, if pulse pressure at baseline was 90 mm Hg or greater compared with 119 for patients with smaller pulse pressure. Finally, the number of patients to treat for 5 years to prevent one major fatal or non-fatal cardiovascular event was similar in smokers and non-smokers (30 *vs* 26), because of opposite trends for stroke (85 *vs* 45) and coronary events (43 *vs* 72).

#### Discussion

Previous meta-analyses focused on the role of diastolic blood pressure as cardiovascular risk factor<sup>17,22,31</sup> and studied the benefit of antihypertensive drug treatment

Characteristic	Number	Mortality (95% CI)		Fatal and non-fatal events combined (95% CI)		
		Total	Cardiovascular	Cardiovascular	Stroke	Coronary
<b>All patients</b>	15 693	59 (55-64)	79 (72-89)	26 (25-27)	48 (45-51)	64 (59-70)
<b>Sex</b>						
Male	6654	53 (50-58)	54 (50-59)	18 (17-19)	34 (32-35)	44 (42-47)
Female	9039	65 (60-72)	119 (102-143)	38 (36-40)	68 (62-75)	92 (82-106)
<b>Age (years)</b>						
60-69	7920	117 (100-141)	169 (137-222)	39 (36-41)	99 (87-115)	89 (79-102)
≥70	7773	39 (37-42)	52 (48-56)	19 (18-20)	32 (30-33)	50 (47-54)
<b>Systolic pressure (mm Hg)</b>						
160-179	10 998	82 (73-92)	92 (81-105)	24 (23-25)	44 (42-47)	64 (58-70)
≥180	4695	37 (35-39)	61 (56-67)	31 (29-32)	57 (52-62)	64 (58-70)
<b>Pulse pressure (mm Hg)</b>						
65-89	7825	63 (58-69)	119 (102-143)	25 (24-26)	44 (42-47)	75 (68-84)
≥90	7868	59 (54-64)	63 (58-70)	27 (26-28)	52 (48-56)	57 (53-62)
<b>Previous complications</b>						
Absent	10 845	75 (68-84)	141 (118-175)	37 (35-39)	59 (55-65)	89 (79-101)
Present	4848	41 (39-44)	41 (39-44)	16 (15-17)	34 (32-35)	40 (38-43)
<b>Smoking</b>						
Absent	13 220	60 (55-65)	99 (87-115)	26 (25-27)	45 (42-48)	72 (65-80)
Present	2473	72 (65-82)	42 (39-45)	30 (29-31)	85 (75-98)	43 (40-46)

Table 5: Number of patients to treat for 5 years to prevent one event

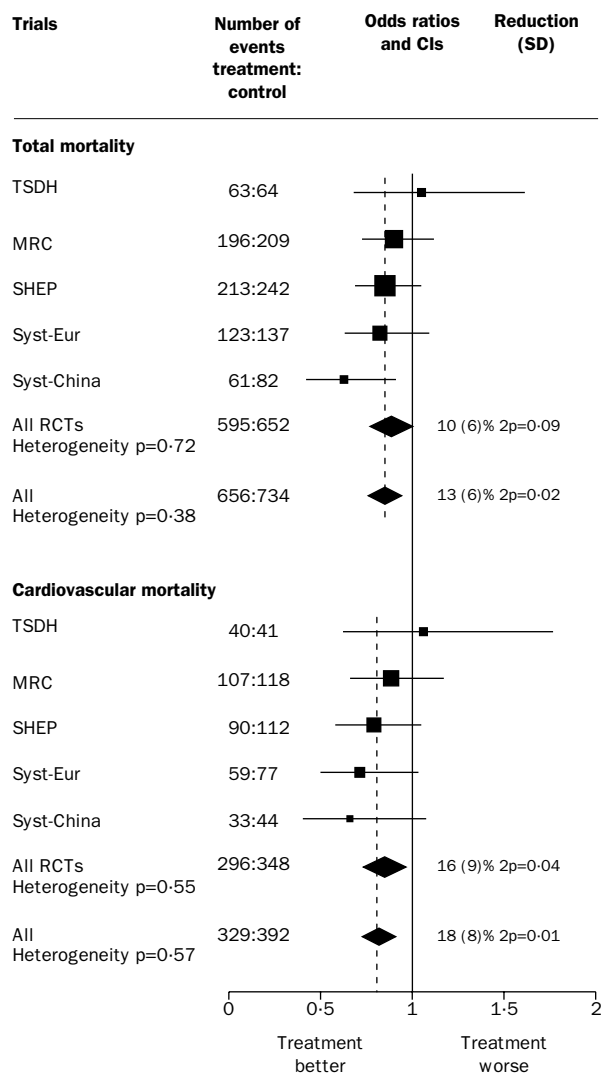


Figure 4: **Effects of treatment on total and cardiovascular mortality**

Solid squares represent treatment-to-control odds ratios in trials and have size proportional to number of events. 95% CI for individual trials are denoted by lines and those for pooled odds ratios by diamonds. Odds ratios presented for three smaller trials<sup>5-7</sup> in systolic and diastolic hypertension (TSDH), MRC trials in mild hypertension,<sup>9</sup> and in older adults,<sup>8</sup> SHEP,<sup>2</sup> Syst-Eur,<sup>3</sup> and Syst-China<sup>4</sup> Pooled estimates exclude (all randomised controlled trials [RCT]) or include (all) the Syst-China results.

relative to the achieved reduction in diastolic blood pressure.<sup>10,19</sup> In our overview we found that in untreated patients systolic blood pressure was a more accurate predictor of mortality and cardiovascular complications than diastolic blood pressure. After correction for regression dilution bias,<sup>22,23</sup> a 10 mm Hg increase in systolic blood pressure was significantly and independently correlated with increases by nearly 10% in the risk of all fatal and non-fatal complications, except for coronary events. Diastolic blood pressure, on the other hand, was inversely correlated with total and cardiovascular mortality. At any given level of systolic blood pressure, the risk of death rose with lower diastolic blood pressure and therefore also with greater pulse pressure. The correction that we and other investigators<sup>22</sup> have applied for regression dilution bias avoids underestimation of the slope between disease outcomes and a patient's blood pressure. However, it may also introduce bias from other sources. Indeed, patients with 2 years of follow-up in a trial or epidemiological survey<sup>22</sup> do

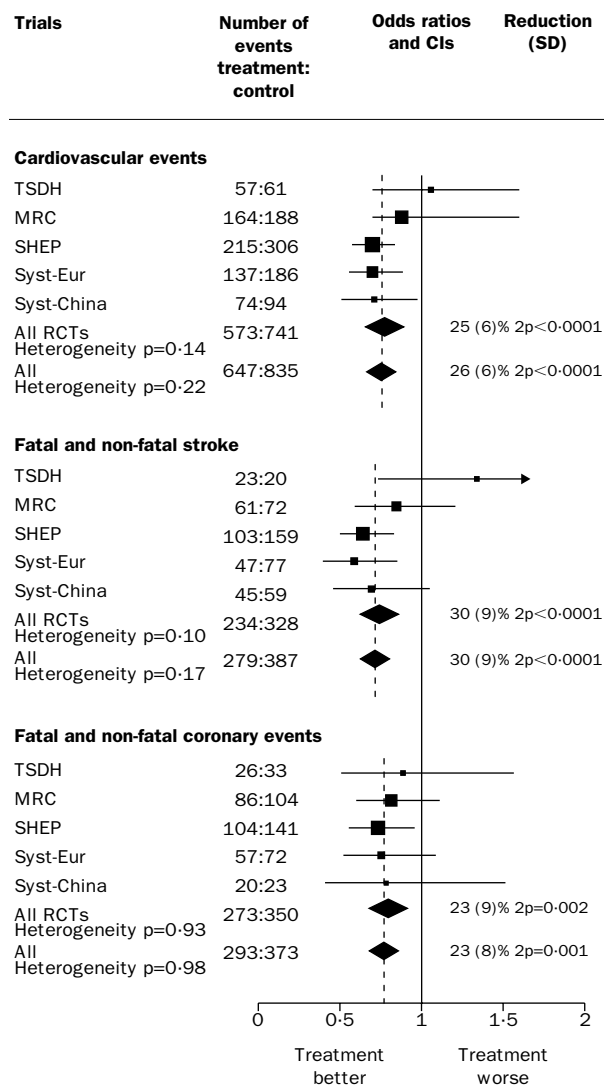


Figure 5: **Effects of treatment on fatal and non-fatal cardiovascular complications, stroke, and coronary events**  
Further explanation as in figure 4.

not represent a random sample of those enrolled. In our analysis we also excluded patients who experienced a non-fatal event, because major cardiovascular complications, such as stroke or myocardial infarction, may be preceded or followed by a fall in blood pressure.<sup>35</sup>

Our findings on the role of systolic blood pressure as a risk factor may have important clinical implications. The target level of blood pressure to be reached by antihypertensive drug treatment should, in older patients, be based on systolic rather than on diastolic blood pressure. The failure of HOT<sup>36</sup> to prove benefit with tighter diastolic blood pressure control, except in the patients with diabetes mellitus, may have been due to the fact that systolic blood pressure was not considered as modifiable risk factor. The observation in MRC1<sup>37</sup> (mean age 51.6 years<sup>9</sup>) that pulse pressure and systolic blood pressure predicted coronary risk is also in keeping with our findings. An editorial<sup>38</sup> recommended that, irrespective of age, systolic blood pressure should guide antihypertensive treatment, but did not recognise that diastolic blood pressure should be measured to calculate pulse pressure. We found that fewer patients had to be treated to prevent one cardiovascular death if pulse pressure at baseline was 90 mm Hg or more.

In older patients with isolated systolic hypertension, pharmacological treatment reduced the stroke rate by one third and the incidence of coronary events by 23%. Collins and MacMahon published consecutive overviews of 14<sup>10</sup>–17<sup>17,19</sup> randomised trials of anti-hypertensive drug treatment in middle-aged and older hypertensive patients with predominantly diastolic hypertension. These investigators reported that 5–6 mm Hg mean decline in diastolic blood pressure for 5 years led to 38<sup>17,19</sup>–42%<sup>10</sup> reductions in stroke incidence, but only to 14<sup>10</sup>–16%<sup>17,19</sup> decreases in coronary events. Furthermore, a meta-analysis<sup>31</sup> limited to the fatal outcomes in six trials in older patients with predominantly diastolic hypertension,<sup>5–8,24,39</sup> showed that active treatment decreased cerebrovascular mortality by 33% and coronary deaths by 26%. We found that to prevent one stroke, overall, 48 patients had to be treated for 5 years, whereas to avert one coronary event this number rose to 64. Similarly, an overview of six trials<sup>2,5,7,8,28,39</sup> involving 12 732 patients aged 60 years or over, showed that these numbers were 43 and 61, respectively.<sup>16</sup>

Why antihypertensive treatment apparently provided less protection against coronary complications than against stroke remains unclear. A chance finding cannot be ruled out, because our meta-analysis shared part of the input data used by other reviewers.<sup>10,16,31</sup> In the early trials in hypertension, the metabolic side-effects of thiazides,<sup>40</sup> given at higher doses than currently recommended,<sup>41</sup> and those of non-cardioselective  $\beta$ -blockers,<sup>10</sup> may have counteracted the coronary protection due to blood pressure lowering. It usually takes several years for coronary heart disease to become clinically evident, so that a median follow-up of 3.8 years may have been too short to reveal in untreated patients the relationship between systolic blood pressure and coronary heart disease and hence to fully expose the coronary benefit of therapy. Furthermore, the association between systolic blood pressure and coronary heart disease may weaken with increasing age.<sup>42</sup> In very old patients an inverse association has even been described,<sup>43</sup> because low blood pressure may reflect immobility or ill health<sup>35</sup> or because of selective survival at middle age. Whatever the underlying mechanism, the absence of a correlation between the incidence of coronary events and initial systolic pressure in our control patients raises the possibility that the trials in hypertension might have underestimated the coronary protection achievable by treating hypertension, particularly in the elderly.

Relative treatment benefit is usually constant over a wide range of risk, whereas absolute benefit may vary widely and is positively associated with absolute risk, as exemplified by the disease rate in untreated control patients.<sup>11</sup> To facilitate the generalisation of our results, we investigated relative and absolute benefit of treatment in different strata. There was no heterogeneity of relative benefit according to sex, age, initial systolic blood pressure or pulse pressure, previous cardiovascular complications, or smoking habits. However, in terms of the number of patients to treat to prevent one event, antihypertensive therapy was particularly effective in men and in patients with previous cardiovascular complications and in patients aged 70 years or older. The latter observation is in keeping with a previous report<sup>13</sup> that showed that in patients aged 80 years or above antihypertensive treatment prevented 34% of strokes and 22% of major cardiovascular events. However, these positive results in very old patients were not strong

evidence and could disappear by the addition of just one hypothetical trial with adequate design and sample size and with no treatment effect.<sup>13</sup> Furthermore, the number of patients to treat for 5 years to prevent one major fatal or non-fatal cardiovascular event was similar in smokers and non-smokers because of opposite trends for stroke and coronary events. In several trials active treatment provided better protection against stroke in non-smokers compared with smokers; this occurred in the Syst-Eur trial,<sup>44</sup> in the MRC1 trial for patients allocated propranolol,<sup>9</sup> and in the MRC2 trial for patients randomised to bendrofluazide.<sup>8</sup>

Although the patients were selected to have a low diastolic blood pressure, further lowering of diastolic blood pressure did not produce harm without any evidence of a J-curve phenomenon.<sup>45</sup> The SHEP investigators<sup>46</sup> have reported that after controlling for confounders and after adjustment for systolic blood pressure as time-dependent covariate, a 5 mm Hg lower on-treatment diastolic blood pressure increased the risk of stroke and coronary heart disease in the active-treatment group, but not in the patients randomised to placebo. However, this report<sup>46</sup> did not provide any information on non-cardiovascular events and did not exclude the possibility that poor health<sup>35</sup> or greater pulse pressure already present at baseline<sup>47</sup> may explain the findings. In our analysis, active treatment reduced both systolic and diastolic blood pressure by about 5%. Because systolic blood pressure at entry was a positive risk factor, whereas diastolic was not, one may assume that the benefit of treatment was overwhelmingly due to the reduction of systolic blood pressure. However, to prove this hypothesis, antihypertensive agents could be used<sup>48</sup> which selectively decrease systolic blood pressure and actively increase the distensibility of the large arteries over and above the effect that is due to blood-pressure lowering. If such a trial, for which we have proposed a protocol,<sup>47</sup> was positive the current strategy of treating hypertension<sup>41</sup> could change drastically to account for pulse pressure as a reversible risk factor.

In conclusion, drug treatment is justified in older patients whose systolic blood pressure is 160 mm Hg or higher. Absolute benefit is greater in men, in older patients, and in those with previous cardiovascular complications or greater pulse pressure. In relative and absolute terms, treatment prevented stroke more effectively than it did coronary events. However, the absence of a relation between coronary events and systolic blood pressure in untreated patients suggests that the coronary protection achievable in elderly hypertensive patients might have been underestimated.

#### Contributors

Mitchell Perry and Jan Staessen had the idea for this quantitative overview. Jerzy Gasowski, Jan Staessen, and Ji Wang did the statistical calculations with the help of Elly Den Hond and Lutgarde Thijs. Jerzy Gasowski and Jan Staessen wrote the first draft of the paper; Jan Staessen prepared the final version. Lutgarde Thijs built the EWPHE and Syst-Eur databases. Lisheng Liu and Ji Wang provided and analysed the Syst-China data. Robert Fagard established the collaboration between the study coordinating centre in Leuven, Belgium, and the INDANA group. François Gueyffier and Jean-Pierre Boissel constructed the INDANA database (Lyon, France). The INDANA group includes John Coope, Jeffrey Cutler, Tord Ekblom, Robert Fagard, Lawrence Friedman, Karla Kerlikowske, Mitchell Perry, Stuart Pocock, Ronald Prineas, Eleanor Schron, François Gueyffier, Jean-Pierre Boissel, and Florent Boutiti. All authors read and commented on the paper.

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