Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials

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Summary

Background Beneficial clinical effects of treatment with antihypertensive drugs have been shown in middle-aged patients and in those hypertensive patients over 60 years old, but whether treatment is beneficial in patients over 80 years old is not known.

Methods We collected data from all participants aged 80 years and over in randomised controlled trials of antihypertensive drugs through direct contact with study investigators. Our primary outcome was fatal and non-fatal stroke. Secondary outcomes were death from all causes, cardiovascular death, fatal and non-fatal major coronary and cardiovascular events, and heart failure.

Findings There were 57 strokes and 34 deaths among 874 actively treated patients, compared with 77 strokes and 28 stroke deaths among 796 controls, representing 1 non-fatal stroke prevented for about 100 patients treated each year. The meta-analysis of data from 1670 participants aged 80 years or older suggested that treatment prevented 34% (95% CI 8–52) of strokes. Rates of major cardiovascular events and heart failure were significantly decreased, by 22% and 39%, respectively. However, there was no treatment benefit for cardiovascular death, and a non-significant 6% (–5 to 18) relative excess of death from all causes.

Interpretations The inconclusive findings for mortality contrast with the benefit of treatment for non-fatal events. Results of a large-scale specific trial are needed for definite conclusion that antihypertensive treatment is beneficial in very elderly hypertensive patients. Meanwhile, an age threshold beyond which hypertension should not be treated cannot be justified.

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Introduction

Randomised controlled trials have clearly shown the clinical benefit of treating even mildly hypertensive people with drugs to lower blood pressure, either through strategy comparison[1] or in placebo-controlled trials,[2,3] mainly based on diuretics or β-blockers. The effect of treatment is beneficial in elderly hypertensive patients with systolic and diastolic hypertension[4] or with isolated systolic hypertension.[5,6] The effect of treatment is greater in hypertensive people over 60 or 65 years old if expressed as an absolute risk reduction,[7] because elderly people have a greater risk of cardiovascular disease without treatment than younger people.

However, Amery and colleagues[8] used a trend analysis in their trial to suggest that the treatment might be less effective or even harmful above the age of 80 years. Given lack of certainty about the efficacy of such treatment in very elderly people, a specific trial was started in 1994.[9,10] The results of that trial are not yet available, so we have collected data from subgroups of randomised controlled trials to assess the evidence for and against antihypertensive treatment in people over age 80.

Methods

Trials

In our analysis, we included all available subgroup data from randomised controlled clinical trials to give a non-biased estimate of the effect of treatment in hypertensive people of 80 years or older compared with that of placebo, no treatment, or lower dosage. We identified trials by use of a literature review, contacts with the principal investigators of published trials or the authors of meta-analyses, and the results of a systematic review by Mulrow and colleagues[11] for the Cochrane Collaboration.

Outcomes

We used fatal and non-fatal stroke, excluding transient ischaemic attack, as the primary outcome, since stroke is most commonly used as the main outcome in clinical trials of antihypertensive drug treatment. Secondary outcomes were death from all causes, cardiovascular death, fatal and non-fatal major coronary and cardiovascular events, and congestive heart failure. Major cardiovascular events comprised stroke, major coronary events, and cardiovascular deaths. Sudden death was included with coronary events and cardiovascular deaths. Angina pectoris or coronary revascularisation alone were not classified as major coronary events. Deaths from pulmonary thrombo-embolism were included with cardiovascular deaths.

Statistical analyses

We calculated the relative risk of each outcome between treatment groups for each trial, and we expressed the summary estimate as a weighted average, by weighting each trial estimate by the inverse of its variance.[12] We used the heterogeneity test to assess the extent to which the differences among trial results were due to random fluctuations.[12] Calculations used EasyMA software (version 97b). Sensitivity analyses excluded the data from two trials with open-label design, to assess the possible influence of those trials' data on the overall results. One of those

	Coope and Warrender[23]*	EWPHE[22]	SHEP-P[24]	SHEP[5]	STOP[25]	Syst-Eur[6]	CASTEL[13]†	Total
Trial characteristics								
Number of patients	7	155	85	650	235	441	97	1670
% of trial total	1	18	15	14	14	9	13	13
First-line treatment	BB	T	T	T	T or BB	CA	T/BB or others	..
Blood pressure inclusion criteria								
Systolic (mm Hg)	>170	160–239	160	160–219	180–230	160–200	>160	..
Diastolic (mm Hg)	105–120	90–119	<90	<90	>90 or 105–120	<95	>95	..
Follow-up (years)	3·8	3·1	2·8	4·2	2·1	2·9	6·8	3·5
Loss to follow-up (%)	0	0	0	1	0	9	3	3
Baseline characteristics								
Mean (SD) age (years)	80 (0)	85 (4)	83 (3)	83 (3)	82 (1)	84 (4)	83 (2)	83 (3)
Maximum age (years)	81	97	99	96	85	98	89	99
M/F (%)	57/43	10/90	26/74	36/64	32/68	27/73	NA	30/70
Mean (SD) systolic blood pressure (mm Hg)	204 (18)	190 (17)	NA	173 (11)	197 (14)	177 (11)	186 (22)	180 (13)
Mean (SD) diastolic blood pressure (mm Hg)	85 (17)	99 (7)	NA	73 (9)	101 (7)	84 (7)	96 (12)	84 (8)
Mean (SD) serum cholesterol (mmol/L)	6·8 (1·5)	5·9 (1·2)	NA	5·9 (1·0)	6·3 (1·2)	5·9 (1·2)	5·8 (1·0)	6·0 (1·2)
Clinical history								
Smokers (%)	0	6	NA	6	6	11	6	7
Diabetes (%)	0	14	NA	8	12	24	16	14
Myocardial infarction (%)	0	0	NA	4	4	9	3	5
Stroke (%)	0	10	NA	3	4	3	3	4

NA=data not available; BB=β-blockers; T=thiazide; CA=calcium antagonist, α2 antagonist. Trials were double-blind placebo controlled except *open-label untreated control and †open-label referred-care control.

Table 1: **Trial characteristics**

trials, the CASTEL trial,[13] compared a group of patients who received specific antihypertensive drug treatment with a group of referred-care patients, and did not show a net blood-pressure reduction in the more systematic intervention group.

We tested the robustness of our results by estimation of the number of additional trials with no treatment effect that would be needed to give a non-significant overall result in an updated meta-analysis.[14] These dummy trials were characterised according to the sample size of the continuing Hypertension in the Very Elderly (HYVET) trial, which was 2100 patients in three groups. We assumed a similar risk of disease to that observed on average in the control groups of the trials' subgroups. Such analysis of robustness allowed us to assess the extent to which publication bias might affect results of the meta-analysis.

Results

Six of the trials that are included in most meta-analyses on drugs to lower blood pressure in older people did not recruit patients over 80 years old.[1,15–19] The data from the Kuramoto trial[20] were not available by subgroup. To our knowledge, that trial is the only eligible one that we were not able to include in our analysis. The data from five trials[5,22–25] that included people over 80 were available from the INDANA database of individual patients.[21] These five trials were the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial,[22] the Coope and Warrender trial,[23] the Systolic Hypertension in the Elderly Program Pilot (SHEP-P) trial,[24] the Systolic Hypertension in the Elderly Program (SHEP) trial,[5] and the Swedish Trial in Old Patients with Hypertension (STOP).[25] Data from the Cardiovascular Study in the Elderly (CASTEL) trial[13] and from the Syst-Eur trial[6] were obtained through direct contacts with the principal investigators. Except for Coope and Warrender's trial,[23] which included only a few participants of 80 years of age, the subgroups of patients aged 80 years and over made up about 15% of the total number of participants in the trials. Our analysis includes 1670 participants, of whom 1132 (68%) took part in trials included in the INDANA database. 76% of participants were women, and there were small percentages of smokers, and people with diabetes or a history of stroke or myocardial infarction (table 1). The maximum age at baseline was 99 years.

Data on non-fatal outcomes from the EWPHE trial have not been included in our analysis, since these data are subject to a censoring bias.[21] Table 2 gives the number of patients and of events by treatment groups in each trial. The risk of fatal events among trial participants was high, with a mortality rate of more than 20% after a mean follow-up of 3·5 years. Less than 10% of patients were lost to follow-up in all trials.

Primary outcome

There was no heterogeneity in terms of primary outcome between trials (p=0·37) or between the subgroups of trials of different designs (p=0·59). For the primary outcome of stroke, treatment gave a relative risk of 0·66 (95% CI 0·48–0·92, p=0·014)—on average, treatment was associated with a 34% lower rate of fatal and non-fatal stroke (figure 1). If data from the two open-label

	Coope and Warrender		EWPHE		SHEP-P		SHEP		STOP		Syst-Eur		CASTEL		Total	
	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control
Number of patients	3	4	70	85	70	15	331	319	122	113	231	210	47	50	874	796
Stroke	0	1	NA	NA	3	3	21	38	10	8	17	20	6	7	57*	77*
Stroke death	0	0	11	9	0	0	3	4	4	1	10	9	6	5	34	28
Heart failure	0	0	NA	NA	4	0	12	33	3	2	14	15	9	14	42*	64*
Coronary events	0	0	NA	NA	3	0	19	26	0	1	17	14	4	10	43*	51*
Coronary death	0	0	9	8	3	0	14	18	2	1	14	11	2	9	44	47
Cardiovascular events	0	1	NA	NA	9	3	45	65	12	16	42	40	25	33	133*	158*
Cardiovascular death	0	0	34	34	6	0	25	29	7	3	32	27	23	30	127	123
Total mortality	0	0	58	60	10	0	57	59	11	8	72	53	37	43	245	223

NA=data not available. *Excludes data from EWPHE.

Table 2: **Outcomes (number of patients) by treatment group**

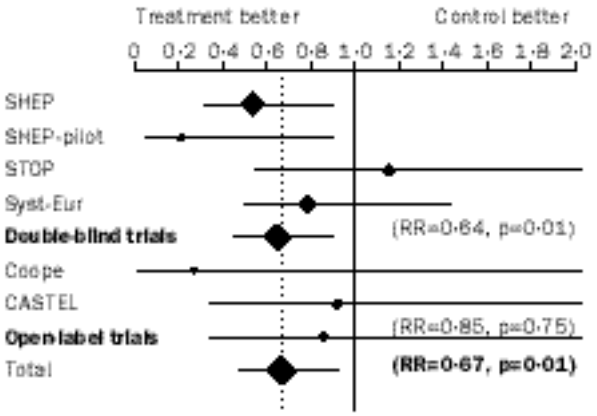

Figure 1: **Treatment effect on relative risk of stroke**
RR=relative risk. Area of symbols is proportional to the amount of information provided; error bars=95% CIs.

trials were excluded (sensitivity analysis), the significance of the results did not change. Our tests of the robustness of results showed that only one hypothetical negative trial with 700 participants per group and a mean stroke rate of 3% per year would be needed to make the overall results non-significant (p=0·10).

Secondary outcomes

There was no heterogeneity in secondary outcomes between trials. The only two secondary outcomes that showed a significant difference between treatment and control were major cardiovascular events and heart failure (figure 2). Results were similar in the sensitivity analysis. Addition of the data of one trial of the size of HYVET, with a mean rate of 6% per year for cardiovascular events or 2% per year for heart failure, and no effect of treatment, would make the overall results non-significant (p=0·054, p=0·073 for cardiovascular events and heart failure, respectively).

Results for major coronary events showed a non-significant trend towards treatment benefit. Treatment effect was not significant for fatal outcomes, but there was a non-significant trend of increased total mortality, with a 6% relative excess of death from all causes (95% CI –5 to 18, figure 2). This trend became stronger if analysis was limited to double-blind trials: there was a mean increase of 11% for cardiovascular deaths (95% CI –13 to 41, p=0·41) and 14% for total mortality: (0–31, p=0·05).

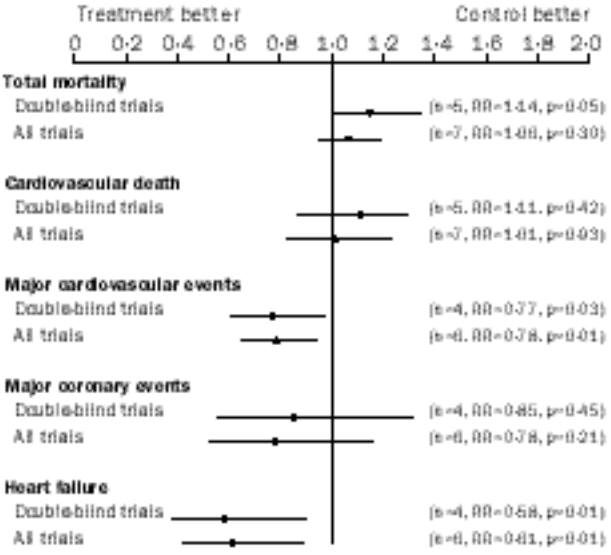

Figure 2: **Treatment effect on relative risk of secondary outcomes**
Format as for figure 1.

Discussion

Our review is based on several data sources, but we made no further attempt to identify any unpublished trial data that would cause potential publication bias. If any reader knows of completed trials for which data are not yet published, we would like them to contact us.

We analysed data from subgroups of trials that had not been specifically designed to test our hypothesis—that antihypertensive treatment is beneficial in hypertensive patients aged 80 years or older. Overall, our results suggest a significant benefit of treatment in these subgroups for our primary outcome of stroke, and for the two secondary outcomes of cardiovascular events and heart failure.

Stroke was chosen as the main outcome because it was the main outcome for most of the hypertension trials, which strengthens the results of our meta-analysis.[26] Comparison of the effects of treatment on fatal stroke and non-fatal stroke suggests that treatment benefit was restricted to non-fatal stroke.

The prevalence of heart failure increases with age,[27] and this disorder can severely affect quality of life. A previous subgroup analysis showed that in trials of elderly patients or in trials of severe hypertension, treatment had a significant effect on heart failure.[7] This outcome should be noted for current and future trials of patients with hypertension. Heart failure as an outcome has been neglected in many meta-analyses of antihypertensive drug treatment, probably because the rate of heart failure is more difficult to assess in a standardised and extensive way than the rate of stroke or myocardial infarction. In all trials, classification of outcomes was done by an ad-hoc committee. Thus, possible differences in the definition of outcomes does not introduce bias to our study, but makes a clear definition of the content of this outcome impossible in our meta-analysis. The notification of hospital admissions attributed to heart failure would overcome the difficulty of notification, as shown in trials of digoxin[28] and angiotensin-converting-enzyme inhibitors[29] in patients with heart failure.

Overall, the positive results from our meta-analysis were not robust: addition of data from only one hypothetical trial of proper design (ad hoc power) with no treatment effect would be enough to make the results non-significant. The results for fatal outcomes raise some concern about possible harmful effects of treatment, especially for total mortality. Stroke events may be so disabling that patients will take the risk of treatment that causes some reduction in overall survival. Survival must be adjusted for quality of life.[30] The HYVET trial will use a health status index based on the work of Fanshel and Bush.[31] The trial will collect information on the fact and date of death, and patients will be classified as bedridden, confined to the house, or disabled with major or minor disabilities.[32]

Confirmation of our results is needed through a properly and specifically designed trial.[9] Meanwhile, our results do not suggest that there is an age threshold above which hypertension should not be treated.

Contributors

The INDANA Group comprises John Coope, Jeffrey Cutler, Tord Ekbom, Robert Fagard, Lawrence Friedman, Karla Kerlikowske, Mitchell Perry, Stuart Pocock, Ronald Prineas, Eleanor Schron, François Gueyffier, Jean-Pierre Boissel, and Florent Boutitie. François Gueyffier constructed the INDANA database, established the collaboration, extracted and analysed data, and wrote the paper. Christopher Bulpitt proposed the systemic review. Jean-Pierre Boissel established the collaboration. Eleanor Schron provided SHEP trial data. Tord Ekbom provided STOP trial data. Robert Fagard provided EWPHE and SYST-EUR trial data. Edoardo Casiglia provided CASTEL trial data. Karla Kerlikowske provided SHEP pilot trial data. John Coope provided Coope and Warrender trial data. All authors reviewed the paper.

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