Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials

Theodora Bejan-Angoulvant[a,b,c], Mitra Saadatian-Elahi[a], James M. Wright[d], Eleanor B. Schron[e], Lars H. Lindholm[f], Robert Fagard[g], Jan A. Staessen[g] and François Gueyffier[a,b,c]

Background **Results of randomized controlled trials are consistent in showing reduced rates of stroke, heart failure and cardiovascular events in very old patients treated with antihypertensive drugs. However, inconsistencies exist with regard to the effect of these drugs on total mortality.**

Methods **We performed a meta-analysis of available data on hypertensive patients 80 years and older by selecting total mortality as the main outcome. Secondary outcomes were coronary events, stroke, cardiovascular events, heart failure and cause-specific mortality. The common relative risk (RR) of active treatment versus placebo or no treatment was assessed using a random-effect model. Linear meta-regression was performed to explore the relationship between intensity of antihypertensive therapy and blood pressure (BP) reduction and the log-transformed value of total mortality odds ratios (ORs).**

Results **The overall RR for total mortality was 1.06 (95% confidence interval 0.89–1.25), with significant heterogeneity between hypertension in the very elderly trial (HYVET) and the other trials. This heterogeneity was not explained by differences in the follow-up duration between trials. The meta-regression suggested that a reduction in mortality was achieved in trials with the least BP reductions and the lowest intensity of therapy. Antihypertensive therapy significantly reduced ($P<0.001$) the risk of stroke (35%), cardiovascular events (27%) and heart failure (50%). Cause-specific mortality was not different between treated and untreated patients.**

Conclusion **Treating hypertension in very old patients reduces stroke and heart failure with no effect on total mortality. The most reasonable strategy is the one associated with significant mortality reduction; thiazides as first-line drugs with a maximum of two drugs.** ***J Hypertens*** **28:1366–1372 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: 80 and over, aged, antihypertensive therapy, heart failure, hypertension, intensity of therapy, meta-analysis, mortality, stroke

Abbreviations: BP, blood pressure; CI, confidence interval; HDL cholesterol, high density lipoprotein cholesterol; HR, hazard ratio; OR, odds ratio; RR, relative risk; SBP, systolic blood pressure; SR, slow release

[a]Department of Clinical Pharmacology, Hospices Civils de Lyon, Lyon, [b]UMR 5558, CNRS, Villeurbanne, [c]Université Claude Bernard Lyon1, Lyon, France, [d]Departments of Anesthesiology, Pharmacology & Therapeutics and Medicine, University of British Columbia, Vancouver, British Columbia, Canada, [e]formerly at National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA, [f]Department of Public Health and Clinical Medicine, Umeå University, SE 901 85 Umeå, Sweden and [g]Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Belgium

Correspondence to Theodora Bejan-Angoulvant, Centre d'Investigations Cliniques, Hôpital Cardiologique L. Pradel, 28 avenue Doyen Lépine, 69677 BRON Cedex, France
Tel: +334 7235 7231; fax: +334 7212 9419;
e-mail: theodora.bejan-angoulvant@chu-lyon.fr

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Introduction

The use of antihypertensive treatment has been shown to have clear beneficial effects in terms of reducing stroke, cardiovascular events and mortality in middle-aged and older patients [1,2]. However, until recently, the benefits of this treatment have not been proven in patients over 80 years of age [3–5].

The hypothesis that antihypertensive drugs might be less efficient and even harmful in very old patients, over 80 years old, was first pointed-out by Amery *et al.* [6] more than 20 years ago. The first meta-analysis of subgroups of 80 years and older from published papers reinforced the evidence that treating elderly patients with antihypertensive drugs reduces the rate of fatal and nonfatal stroke [relative risk (RR) 0.66, 95% confidence interval (CI) 0.48–0.92], major cardiovascular events (relative risk 0.78, 95%CI 0.64–0.94) and heart failure (relative risk 0.61, 95%CI 0.42–0.88) but leads to a borderline increase in the overall mortality (relative risk 1.06, 95%CI 0.95–1.18). This subgroup meta-analysis did not find an impact on other measured outcomes, that is cardiovascular death and major coronary events [1].

Lack of confidence about the harms and benefits of antihypertension therapy in people over 80 led to the hypertension in the very elderly trial (HYVET). The pilot trial included three groups in an open label design; no treatment, bendrofluazide (diuretic) and lisinopril (angiotensin-converting enzyme inhibitor) [7]. Consistent with

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results of the subgroup meta-analysis, the trial found a significant decrease in fatal and nonfatal strokes with active treatment (relative hazard rate 0.31, 95%CI 0.12–0.79) and a non-significant increase in total mortality (relative hazard rate 1.23, 95%CI 0.75–2.01). This led to an up-dated 1.15 estimate of the pooled relative risk of death reaching statistical significance (95% CI 1.01–1.31) [7].

The results of the main HYVET, the largest double-blind, placebo-controlled trial to date, provided further evidence on the efficacy of antihypertensive treatment on fatal and nonfatal stroke (unadjusted hazard ratio 0.70, 95%CI 0.49–1.01), cardiovascular events (unadjusted hazard ratio 0.66, 95%CI 0.53–0.82) and heart failure (unadjusted hazard ratio 0.36, 95%CI 0.22–0.58). However, contrary to the earlier trials, HYVET found a statistically significant decrease in the overall mortality (unadjusted hazard ratio 0.79, 95%CI 0.65–0.95) associated with antihypertensive treatment [3].

We, therefore, aimed to update the published subgroup meta-analysis by adding new evidence from randomized clinical trials (HYVET pilot and HYVETs) that evaluated the effect of antihypertensive treatment compared with placebo or no treatment in patients 80 years and older. The primary outcome was total mortality. Secondary outcomes were coronary events, stroke, cardiovascular events, heart failure and cause specific mortality (coronary, stroke and cardiovascular).

Methods

Identification of trials

The flow diagram of the trial selection process is available in the appendix, http://links.lww.com/HJH/A24. Included in this meta-analysis were available data from randomized controlled trials comparing an antihypertensive treatment to placebo or no treatment in patients 80 years and older within the following trials systolic hypertension in the elderly program (SHEP)-Pilot [8], SHEP [9], the European Working Party on High blood pressure in the Elderly (EWPHE) [10], Coope and Warrender [11], Swedish Trial in Old Patients (STOP) [12], the Systolic Hypertension in Europe (Syst-Eur) [13], HYVET-Pilot [7] and HYVET [3]. The database was already available for studies included in the subgroup meta-analysis [1]. For the remaining studies [3,7] data were extracted from the published papers. To our knowledge, these data represent all the available information on mortality and morbidity related to the treatment of hypertension versus placebo or no treatment in randomized controlled trials in very elderly patients. The cardiovascular study of the elderly (CASTEL) trial [14], initially included in the subgroup meta-analysis [1] was excluded because the trial compared two strategies, 'special care' versus 'free therapy'.

Two other potential trials, the study on cognition and prognosis in the elderly (SCOPE) [15] and the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS) [16], were retrieved by search in the *Medline* database using the following keywords: blood pressure (BP) or hypertension, mortality, over 80 and randomized controlled trial, with no language restriction. These trials were excluded from the meta-analysis because almost all control patients were treated in the SCOPE trial and the JATOS trial compared two active strategies, intensive versus mild.

Outcomes

In order to explore the observed heterogeneity between earlier trials [1,7] and HYVET [3], total mortality was chosen as the primary outcome measure.

Secondary outcomes were coronary events, cardiovascular events, stroke, heart failure and cause specific mortality (coronary, stroke and cardiovascular).

Statistical analysis

The meta-analysis was based on aggregate data. The subgroup meta-analysis and the two additional trials [3,7] provided absolute number of events. RR and bilateral 95%CIs were calculated for every trial. The effect of active treatment versus placebo or no treatment was assessed using a random-effect model with measures of between-trial variance and inconsistency between all trials (tau^2 and I^2). For trials that reported zero events in one or both arms, a continuity correction using the pseudo-count method was applied by adding 0.25 events to all cells [17]. We also performed the meta-analysis of the trials excluding HYVET and assessed the heterogeneity between this subgroup of 'others' and HYVET. A P value of less than 0.10 was considered as significant for the heterogeneity between groups test. The calculations used EasyMA www.spc.univ-lyon1.fr/EasyMa and the 'meta' package from R software [18,19].

Three possible sources of heterogeneity between the HYVET and 'others' have been explored further as the achieved BP reductions, the intensity of antihypertensive therapy allowed in the trials and the changes of treatment effect over time.

Intensity of antihypertensive therapy for each trial was determined by giving a value of 1 for drugs given at the recommended starting dose, 2 for twice the starting dose and 3 for four times the starting dose. The same values applied for second and third-line drugs. The overall intensity for each trial was the maximum dose of all antihypertensive drugs allowed for that trial. For example the HYVET gets an intensity value of 2 because indapamide was first-line at the recommended starting dose and perindopril could be added at one-half the recommended starting dose and increased to the recommended starting dose as a maximum. The recommended starting doses for hypertension treatment were taken from the Physicians' Desk Reference, USA. Linear fixed-effect

meta-regression model with trial weights corresponding to the inverse of the variance was performed to explore the relationship between the intensity of antihypertensive therapy and the log-transformed value of the odds ratios (ORs). We chose the log-transformed value of the ORs because of its properties of symmetry around zero. A similar model was used to explore the relationship between SBP reductions (mean differences between active and control groups during follow-up) and the log-transformed value of the ORs. Only trials, for which information about BP reductions and total mortality outcome was available, were included in this analysis [3,7,9,10,12,13]. Random-effect Poisson model was used to compute cumulative hazard ratio at the end of each year of follow-up up to 5 years. Trials included in this analysis were those for which individual patient data were already available in our database [8–12]. All analyses were performed using the R software version 2.10.1 [18].

Results

Baseline characteristics of trials included in the meta-analysis are summarized in Table 1. The analysis was based on 6701 patients, of whom 3617 have been treated with at least one antihypertensive drug (active group). With the exception of two trials carried out in the United States [8,9] and with the exception of HYVET, all other trials were performed in European countries [7,10–13]. HYVET trial recruited also patients from China, Australasia and Tunisia [3]. Mean SBP at entry was 173 mmHg in the HYVET population and about 180 mmHg in the remaining trials. The mean follow-up was 3.5 years in the subgroup meta-analysis, 1.1 year in the HYVET pilot and 1.8 years in the HYVET main. Percentage of patients with history of diabetes was lower, and previous stroke and previous hypertension treatment were more frequent in the HYVET.

Primary outcome

The overall relative mortality risk was 1.06 (95%CI 0.89–1.25, $P = 0.54$) with significant heterogeneity [$P = 0.07$, $\text{tau}^2 = 0.0236$, $I^2 = 45.7\%$ (0%–75.9%)], confirming the previous meta-analyses [4,5] (Fig. 1). Likewise, highly statistically significant heterogeneity was observed when comparing HYVET to the 'others' ($P = 0.003$, $\text{tau}^2 = 0.0504$, $I^2 = 88.8\%$). Between trials heterogeneity in the random-effect model disappeared when the results from HYVET were removed [$P = 0.79$, $\text{tau}^2 = 0$, $I^2 = 0\%$ (0%–44.4%)].

Secondary outcomes

There was no heterogeneity between trials for secondary endpoints in the random-effect meta-analysis (Fig. 2). Furthermore, when comparing HYVET with the 'others', no heterogeneity was observed for coronary events ($P = 0.78$, $\text{tau}^2 = 0.00$, $I^2 = 0\%$), stroke ($P = 0.43$, $\text{tau}^2 = 0.00$, $I^2 = 0\%$), cardiovascular events ($P = 0.64$, $\text{tau}^2 = 0.00$, $I^2 = 0\%$) heart failure ($P = 0.23$, $\text{tau}^2 = 0.03$, $I^2 = 32.3\%$), and cause-specific mortality: coronary death ($P = 0.70$, $\text{tau}^2 = 0.00$, $I^2 = 0\%$), stroke death ($P = 0.21$, $\text{tau}^2 = 0.03$, $I^2 = 37.6\%$), except for cardiovascular death ($P = 0.06$, $\text{tau}^2 = 0.04$, $I^2 = 71.5\%$).

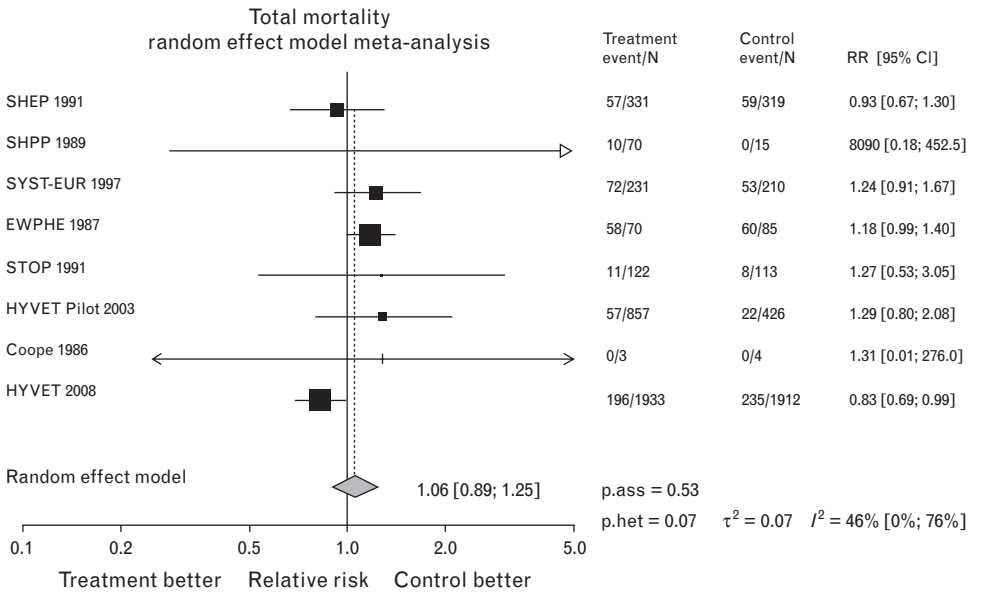
Antihypertensive therapy was associated with statistically significant reduction in stroke (35%, $P < 0.001$), cardiovascular events (27%, $P < 0.001$) and heart failure (50%, $P = 0.001$). On the contrary, coronary events and cause-specific mortality were not different between treated and nontreated patients (Fig. 2). Considering a population who would experience an annual incidence of 1.8% for stroke in untreated patients, as reported by the HYVET, the observed benefit on stroke prevention can be estimated as an absolute risk reduction of 3% over 5 years, meaning that one stroke is prevented for every 33 patients treated for 5 years.

Table 1 Baseline characteristics of trials (subgroups and full trials) involved in the meta-analysis

	Subgroup meta-analysis ($N = 1573$)	HYVET Pilot ($N = 1283$)	HYVET ($N = 3845$)
	5 double-blind and 1 open label	Open label	Double-blind
N per arm	Active ($N = 827$) Control ($N = 746$)	Active ($N = 857$) Control ($N = 426$)	Active ($N = 1933$) Control ($N = 1912$)
Population	West-Europe (4 trials), United States (2 trials)	East Europe (91%)	East Europe (56%) + China (40%)
Active medication (first line)	D[a] or BB[b] or CA[c]	D[a] or ACEI[d]	D[a]
Mean (SD) age (years)	83 (3)	83.8 (3)	83.6 (3.2)
Men/women (%)	30/70	37/63	40/60
Mean (SD) blood pressure (mmHg)	180/84 (13/8)	182/100 (11/3)	173/91 (9/9)
Range SBP	160–232	160–217	160–199
Range DBP	<120	90–114	<110
Current smokers (%)	7	4.2	6.5
Diabetes (%)	14.0	NA	6.9
Previous MI (%)	5.0	3.0	3.1
Previous stroke (%)	4.0	4.5	6.8
Previous HT treatment (%)	34[e]	48	65
Mean follow-up (range)	3.5 (0–11.6)[e]	1.1 (NA)	2.1 (0–6.5)

HT, hypertension; NA, not available. [a] Diuretics: hydrochlorothiazide plus triamterene or amiloride in respectively EWPHE and STOP trials; chlorthalidone in SHEP-P and SHEP trials; bendrofluazide in HYVET-Pilot trials; indapamide SR in HYVET trials. [b] Beta-Blockers: atenolol in the Coope and Warrender trial as first line treatment, atenolol or metoprolol or pindolol as first line treatment in 3 out of 4 active groups in the STOP trial. [c] Calcium antagonists: nitrendipine in the Syst-Eur trial. [d] Angiotensin-converting enzyme inhibitors: lisinopril in HYVET Pilot trial. [e] Value obtained without Syst-Eur, SHEP-Pilot and STOP trials.

Fig. 1

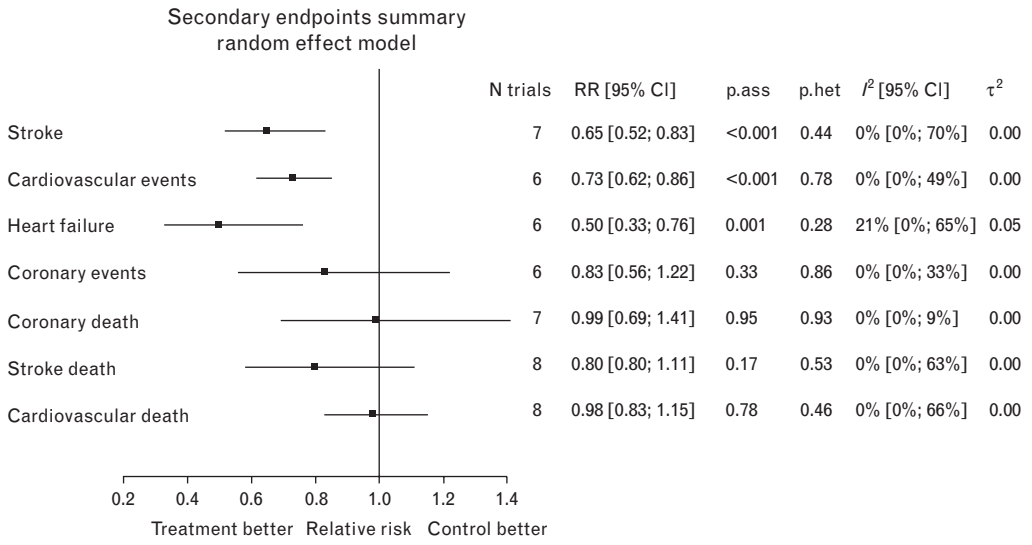


Random-effect meta-analysis for total mortality. The figure provides number of events, number of patients in treatment and control groups, relative risks (RR) and 95% confidence interval (CI) for each trial, overall RR estimate with 95% CI and *P* value for association test, *P* value for heterogeneity test, between trial variance (tau^2) and inconsistency (I^2) measures.

Intensity of antihypertensive therapy and risk of death

The information regarding intensity of antihypertensive therapy and risk of death was available for all eight trials. Nevertheless, the subgroup of patients in Coope and Warrender trial was not included in the analysis, as there were no events observed in either group (Table 2). The linear meta-regression showed an inverse relationship between the maximum treatment units allowed in each trial and the benefit of treatment on total mortality expressed as the log-transformed value of the OR (slope = 0.2, standard error (SE) = 0.024, $P < 0.01$) (Fig. 3).

Fig. 2



Secondary endpoints estimates from random-effect meta-analysis. The figure provides number of trials used for each endpoint meta-analysis, common relative risk (RR) estimates from random-effect model with 95% confidence interval (CI), *P* value for association test, *P* value for heterogeneity test, between-trial variance (tau^2) and inconsistency (I^2) measures.

Table 2 Intensity of antihypertensive therapy expressed as maximum treatments units and mean SBP reductions in the included trials

Trial	Maximum treatment units	Mean SBP reduction
SHEP	3	11 mmHg
SHEP-Pilot	5	NA
Syst-Eur	5	12 mmHg
EWPHE	6	17 mmHg
STOP	3.5	19 mmHg
HYVET-Pilot	4	23 mmHg
HYVET	2	12 mmHg
Total[a]	3	14 mmHg

NA, not available. [a]Average maximum treatment units and mean SBP reduction were obtained after weighting by trial size.

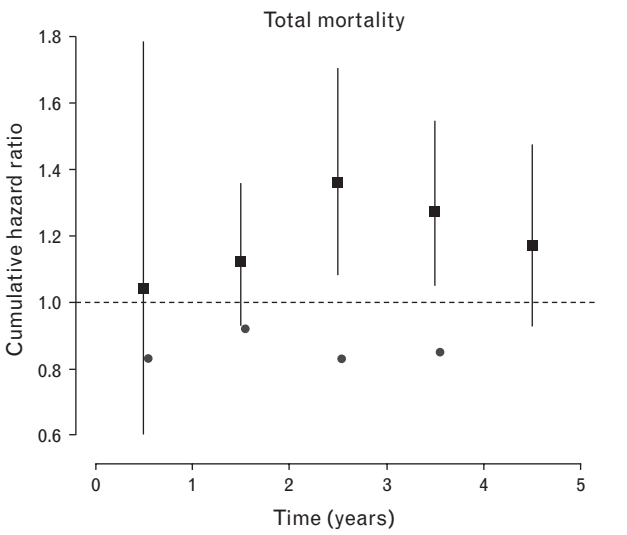
Mean differences in SBP during follow-up and risk of death

Mean differences in SBP during the follow-up period were available for six trials [3,7,9,10,12,13], ranging from 10.8 mmHg (SHEP) to 23 mmHg (HYVET-pilot). The linear meta-regression showed an inverse relationship between the extent of SBP reduction and benefits of treatment on total mortality expressed as the log-transformed value of the OR (slope = 0.04, SE = 0.029, $P = 0.23$) (Fig. 3).

Changes of treatment effect over time

The cumulative hazard ratio of total mortality over time in five trials [8–12] displayed a significant deleterious effect at the end of the third year [hazard ratio = 1.35 (1.08–1.70)] and reached a nonsignificant hazard ratio of 1.17 (0.93–1.47) at 5 years (Fig. 4). The relative risk extrapolated from the Kaplan–Meyer curves of the HYVET [3] showed a different pattern of treatment effect over time, reinforcing the contrast between the HYVET and other trials.

Fig. 4

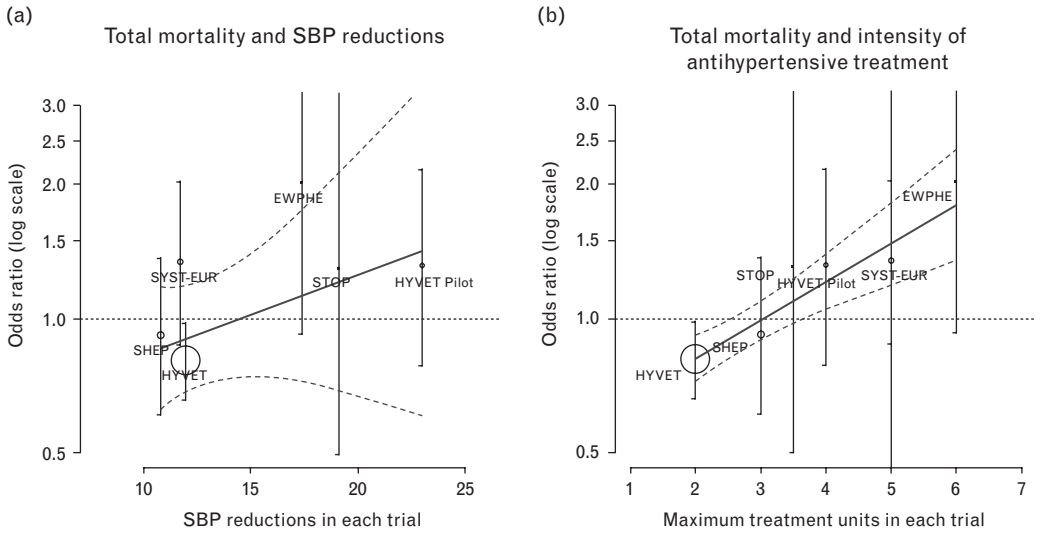


Cumulative hazard ratio (black squares) and 95% CI up to 5 years from random-effect Poisson model and extrapolated point estimate (black dots) hazard ratio for the HYVET.

Discussion

Consistent with the finding of the previous subgroup meta-analysis and the HYVET, the results of this meta-analysis indicate significant reduction in the rates of stroke, heart failure and cardiovascular events in patients treated with antihypertensive drugs as compared with placebo or no treatment. On the contrary, our results do not support those of the HYVET with regard to the

Fig. 3



Linear meta-regression between the log transformed value of total mortality odds-ratio (OR) and: a – the mean SBP reductions; b – the intensity of antihypertensive therapy (maximum treatment units).

reduction, in the treated group, of death from all-cause mortality.

Methodological aspects, the study population, type and dose of antihypertensive therapy and the achieved differences in BP between groups could explain the observed discrepancy in the effect of antihypertensive therapy on total mortality.

The methodological strength of the HYVET due to its double-blind character could explain the observed heterogeneity. However, this is unlikely because limiting the analysis to double-blind trials involved in the subgroup meta-analysis displayed an even higher RR of 1.14 ($P = 0.05$).

Larger-than-expected treatment effect may result from analyzing data at a 'random-high', that is simply by chance when stopping randomized trials early because of an apparent benefit [20]. This should be remembered when making inferences to clinical practice from truncated trials. HYVET and STOP (full trial) are the only two trials that found a significant benefit on total mortality and were both stopped earlier then planned [3,12]. Time-trend analysis of treatment effect showed a steady effect over time in the HYVET, contrasting with the deleterious effect observed in other trials (Fig. 4). The differences in follow-up durations are, therefore, not likely to explain the observed heterogeneity with regard to total mortality.

More than one-third of the HYVET population was recruited in China. The baseline characteristics of this subgroup were recently compared with the rest of the study population [21]. The results showed that Chinese patients had significantly lower BMI, lower sitting DBP, lower total cholesterol, higher high-density lipoprotein (HDL) cholesterol and better renal function. Furthermore, previous episodes of myocardial infarction and congestive-heart failure were significantly lower among Chinese. However, better health condition of this population at study entry could hardly explain the benefit of antihypertensive treatment on total mortality. Indeed the estimated annual mortality rate in control groups varied from 3.4 [12] to 15.4% [10], HYVET being somewhere in the middle at approximately 6%.

The long-acting thiazide diuretics, chlorthalidone [22] and indapamide SR were used as first-line therapy in the two trials that reported decrease in total mortality in treated patients [3,9]. This observation suggests that these drugs may provide beneficial effects on total mortality. However, first-line thiazides were also used in a substantial proportion of patients in four of the other six trials, so this alone does not explain the heterogeneity.

The exploratory meta-regressions suggest possible association between the increase in total mortality and higher intensity of antihypertensive treatment. Similar association was observed between the increase in total mortality and the achieved SBP reductions. Both the intensity of antihypertensive treatment and the achieved SBP reduction represent a common motivation to further control BP. In the recent JATOS trial including patients 65–85 years old, the strict BP control did not provide further benefit in risk reduction as compared with the mild-BP control. Overall, 54 patients died in the strict BP arm versus 42 in the mild-BP arm. Even though not statistically significant ($P = 0.22$), this result suggests a deleterious effect of intensive-BP control in elderly [16] in keeping with our findings. The results are compelling enough to recommend a low-maximal intensity of antihypertensive therapy in individuals 80 years and over. It also suggests that other trials need to be carried out to determine whether there is a deleterious effect of more intensive-antihypertensive therapy in younger age groups as well.

In conclusion, particular attention should be given to hypertensive elderly patients who constitute a large, growing and vulnerable population. Treating hypertension in very old patients reduces stroke and heart failure. Despite this, the meta-analysis of the best available evidence showed no decrease in total mortality and the mortality results were heterogeneous. The heterogeneity was best explained by an increase in mortality in trials where the maximal allowable antihypertensive treatment and BP lowering were greater, although our results are not robust enough to definitively conclude that over treatment and excessive blood pressure lowering increase mortality. In patients over 80 years old the most reasonable strategy is the one proposed by the HYVET trial: a thiazide diuretic as first-line therapy and a maximalantihypertensive therapy with two drugs in low doses.

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There are no conflicts of interest.

References

1 Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard R, *et al.* Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. INDANA Group. *Lancet* 1999; **353**:793–796.

2 Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Heberlein KA, *et al.* Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990; **335**:827–838.

3 Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, *et al.* Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; **358**:1887–1898.

4 Therapeutics Initiative. Treatment of elevated blood pressure in the elderly: less is better. Therapeutics Letter 2008; 71:1–2. http://ti.ubc.ca/letter71. [Accessed October 2009]

5 Musini VM, Tejani A, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. Cochrane Database Syst Rev 2009. doi: 14651858.

6 Amery A, Birkenhäger W, Brixko P, Bulpitt C, Clement D, de Leeuw P, *et al.* Influence of antihypertensive drug treatment on morbidity and mortality in patients over the age of 60 years. European Working Party on High blood pressure in the Elderly (EWPHE) results: sub-group analysis on entry stratification. *J Hypertens Suppl* 1986; **4**:S642–S647.

7 Bulpitt CJ, Beckett NS, Cooke J, Dumitrascu DL, Gil-Extremera B, Nachev C, *et al.* Hypertension in the Very Elderly Trial Working Group. Results of the pilot trial for the Hypertension in the Very Elderly Trial. *J Hypertens* 2003; **21**:2409–2417.

8 Perry HM Jr, Smith WM, McDonald RH, Black D, Cutler JA, Furberg CD, *et al.* Morbidity and mortality in the Systolic Hypertension in the Elderly Program (SHEP) pilot trial. *Stroke* 1989; **20**:4–13.

9 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265**: 3255–3264.

10 Amery A, Birkenhäger W, Brixko P, Bulpitt C, Clement D, Deruyttere M, *et al.* Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet* 1985; **1**:1349–1354.

11 Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *BMJ* 1986; **293**:1145–1151.

12 Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991; **338**:1281–1285.

13 Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhäger WH, *et al.* Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997; **350**:757–764.

14 Casiglia E, Spolaore P, Mazza A, Ginocchio G, Colangeli G, Onesto C, *et al.* Effect of two different therapeutic approaches on total and cardiovascular mortality in a Cardiovascular Trial in the Elderly (CASTEL). *Jpn Heart J* 1994; **35**:589–600.

15 Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, *et al.*, SCOPE Trial Group. The Trial on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003; **21**:875–886.

16 JATOS Trial Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res.* 2008; **31**:2115–2127.

17 Hauck WW, Anderson S, Leahy FJI. Finite sample properties of some old and some new estimators of common odds-ratios from multiple 2x2 tables. *J Am Stat Assoc* 1982; **77**:145–152.

18 R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org. [Accessed December 2009]

19 Guido Schwarzer. meta: Meta-Analysis with R. R package version 1.1-5. http://CRAN.R-project.org/package=meta. [Accessed December 2009]s

20 Montori VM, Devereaux PJ, Adhikari NK, Burns KE, Eggert CH, Briel M, *et al.* Randomized trials stopped early for benefit: a systematic review. *JAMA* 2005; **294**:2203–2209.

21 Liu LS, Wang JG, Ma SP, Wang W, Lu FH, Zhang LQ, *et al.* Characteristics of the Chinese subjects entered the hypertension in the very elderly trial. *Chin Med J (Engl)* 2008; **121**:1509–1512.

22 Wing LM, West MJ, Graham JR, Chalmers JP. Long-acting and short-acting diuretics in mild essential hypertension. *Clin Exp Hypertens A* 1982; **4**:1429–1441.