Family Practice
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Vol. 13, No. 2
Printed in Great Britain

Antihypertensive therapy in older patients with isolated systolic hypertension: the Syst-Eur experience in general practice

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Celis H, Yodfat Y, Thijs L, Clement D, Cozic J, De Cort P, Forette F, Grégoire M, Heyrman J, Stibbe G, Van den Haute M, Staessen J and Fagard R. Antihypertensive therapy in older patients with isolated systolic hypertension: the Syst-Eur experience in general practice. *Family Practice* 1996; **13**: 138–143.

Background and objective. This interim report from the Syst-Eur trial investigated the level of blood pressure control achieved during the double-blind period in patients followed in general practices.

Methods. In the Syst-Eur trial elderly patients (60 years or older) with isolated systolic hypertension were randomized to either active or placebo treatment. Active treatment consisted of nitrendipine combined with enalapril and/or hydrochlorothiazide to reduce systolic pressure to <150 mmHg and by ≥ 20 mmHg. Matching placebos were used in the control group.

Results. This analysis was restricted to patients of general practitioners who had been followed for at least 12 months. The placebo ($N = 204$) and active treatment ($N = 217$) groups had similar characteristics at randomization. At one year, the difference in sitting pressure between the two treatment groups was 10 mmHg systolic and 4 mmHg diastolic. Fewer patients remained on monotherapy in the placebo than in the active treatment group and on placebo the second and third line medications were started earlier. Nitrendipine tablets were discontinued in 10 patients on placebo and in 21 patients assigned to active treatment ($P < 0.001$ for all comparisons).

Conclusions. A significant blood pressure reduction can be achieved and maintained in older patients with isolated systolic hypertension followed by general practitioners. Whether this blood pressure reduction results in a clinically meaningful decrease of cardiovascular complications is under investigation.

Keywords. Antihypertensive treatment, general practice, isolated systolic hypertension, randomized clinical trial.

Introduction

Several major intervention trials on the treatment of hypertension have been published during the last two decades. In most of these trials patients have been recruited in specialized university hospitals.[1-3] Few trials were community-based[4,5] or involved general practitioners.[6,7]

Syst-Eur is a double-blind placebo-controlled outcome trial in older patients with isolated systolic hypertension, which the European Working Party on High Blood Pressure in the Elderly is currently conducting in Western and Eastern Europe and Israel.[8] The Syst-Eur centres recruiting patients into the trial are in part university hospitals and community centres, but include also general practices, especially in Belgium, France and Israel. Progress reports on the Syst-Eur trial have been published previously.[9-11] The aim of the present paper was to investigate the level of blood pressure control achieved during the double-blind period in patients followed by general practitioners.

Received 25 October 1995; Accepted 9 November 1995.
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Methods

Study design

The protocol of the Syst-Eur trial has been published elsewhere.[8] Patients were eligible, 1) if they were at least 60 years old, 2) if on a placebo during the run-in phase their sitting systolic pressure ranged from 160 to 219 mmHg with a diastolic pressure below 95 mmHg, and 3) if their standing systolic pressure was 140 mmHg or more. These blood pressure criteria were based on the averages of six sitting and six standing readings, i.e. two in each position at three baseline visits one month apart.

Eligible patients were stratified by gender and the presence or absence of cardiovascular complications and randomized to double-blind treatment with active medication or placebo. Active treatment consisted of nitrendipine (10–40 mg per day), combined with enalapril (5–20 mg per day) and/or hydrochlorothiazide (12.5–25 mg per day). The patients of the control group received matching placebos. The study medication was step-wise titrated and combined in an attempt to reduce the sitting systolic pressure by 20 mmHg or more to a level of less than 150 mmHg.[8]

Blood pressure measurement

On each visit blood pressure (phase V diastolic pressure) was measured to the nearest 2 mmHg following the guidelines of the British Hypertension Society,[12] twice after 2 minutes rest in the supine position, twice after 5 minutes rest sitting, and finally twice after 2 minutes standing.

Statistical analysis

The serial measurements of BP and pulse rate in the two treatment groups of the trial were analysed according to the per-protocol principle, i.e. the analyses covered all 3-monthly measurements which were obtained on randomized treatment.

Blood pressure at one year was calculated according to both a per-protocol and an intention-to-treat analysis. The per-protocol analysis only included the patients who were followed at least 1 year on double-blind treatment. For patients in whom randomized treatment had been discontinued prior to the 1-year visit, the intention-to-treat analysis included, where available, measurements obtained after discontinuation of the double-blind medication, regardless of the treatment the patient was actually receiving. If the patient died or stopped regular follow-up before the 12-month visit, the last available measurement was retained.

For both the per-protocol and the intention-to-treat analysis, all patients who were randomized less than 1 year ago and were still being followed at the moment of the analysis were excluded.

Data base management and statistical analyses were performed using the Statistical Analysis System (The SAS Institute Inc., Cary, NC, USA).

Results

Recruitment

On 1 October 1994 a total of 2243 patients from 19 countries had been randomized into the Syst-Eur trial. Of these, 421 patients (193 in Belgium, 75 in France and 153 in Israel) had been recruited in primary care and were followed by general practitioners.

The characteristics at entry of these 421 patients, of whom 217 were randomized to active treatment and 204 to placebo treatment, are reported in Table 1. Median age was 73 years and ranged from 60–93 years. At entry 16% of patients showed cardiovascular complications. The sitting blood pressure at randomization averaged $175 \pm 10/87 \pm 6$ mmHg.

TABLE 1 *Patient characteristics at randomization according to the treatment group*

	Placebo	Active treatment
Number	204	217
Male sex (%)	37	30
Age (years)	72 (62–86)	73 (61–88)
Weight (kg)	70 ± 11	68 ± 12
Height (cm)	163 ± 9	162 ± 9
BMI (kg/m-b^2-)	27 ± 4	26 ± 4
SBP sitting (mmHg)	175 ± 10	175 ± 9
DBP sitting (mmHg)	86 ± 6	87 ± 6
Pulse rate (beats/min)	76 ± 8	76 ± 8
CV complications (%)	14	18
Previously treated (%)	53	50

Values are means ± SD (except age = median and 5th and 95th percentile).

Blood pressure

The period of follow-up varied widely because the patients had been entered into the trial over a period of several years (up to 5 years). Three hundred and eighty-five patients had been followed for at least 3 months and in 261 patients a follow-up of at least 12 months was attained. The number of accumulated patient-years was 344 in the active treatment group and 337 on placebo.

In the active treatment group the sitting systolic blood pressure fell by 23 ± 14 mmHg and the sitting diastolic blood pressure by 5 ± 7 mmHg during the first year of double-blind treatment. On placebo treatment the corresponding reductions were 14 ± 16 mmHg for systolic and 1 ± 6 mmHg for diastolic pressure ($P < 0.001$ for all comparisons). At 1 year the per-protocol analysis showed a difference in sitting pressure between the two treatment groups of 10 mmHg systolic and 4 mmHg diastolic ($P < 0.001$) (Figure 1). These results were confirmed by the intention-to-treat analysis. In this analysis the differences between the active and placebo

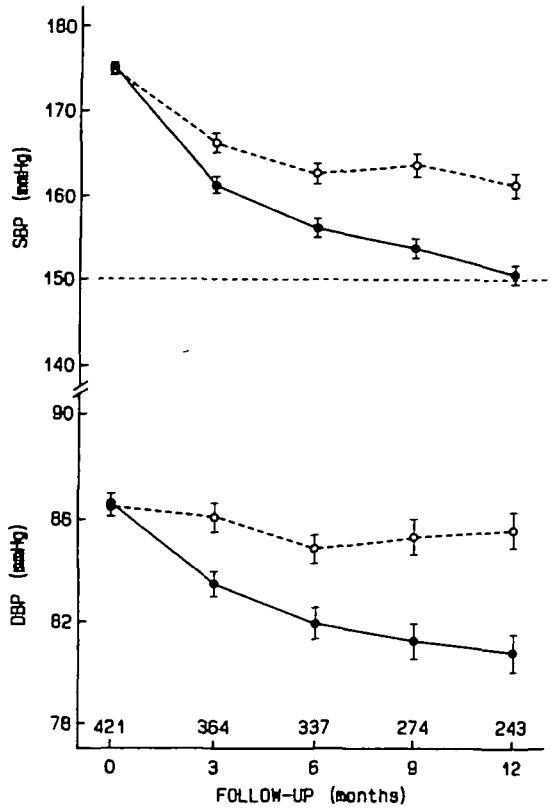

FIGURE 1 *Sitting systolic and diastolic blood pressures at randomization and at various follow-up visits on double-blind treatment (per-protocol analysis). Placebo (○—○); active treatment (●—●). The number of patients with blood pressure readings at a particular follow-up visit is given at the bottom of the Figure for the two treatment groups combined. The difference between the two treatment groups became significant at three months (P < 0.001) and a significant difference was maintained thereafter. Values are means ± SE*

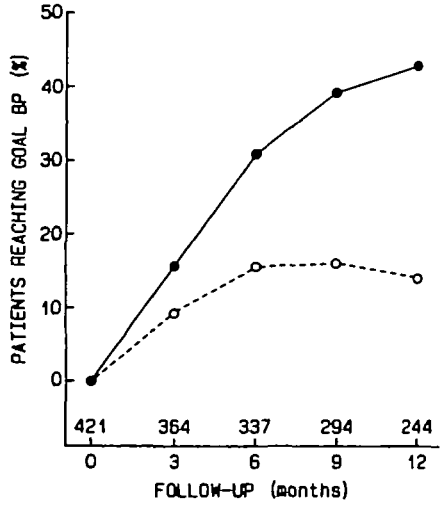

FIGURE 2 *Percentages of patients on double-blind treatment reaching the goal pressure at various follow-up visits (per-protocol analysis). Placebo (○—○); active treatment (●—●). Goal pressure was defined as a sitting systolic pressure < 150 mmHg with a reduction following randomization by at least 20 mmHg. The number of patients with blood pressure readings at a particular follow-up visit is given at the bottom of the figure for the two treatment groups combined. The difference between the two groups was significant at the 0.1% level*

treatment group were 8 and 4 mmHg, respectively ($P < 0.001$).

The percentage of patients reaching the goal blood pressure during follow-up was significantly greater with active than with placebo treatment ($P < 0.001$). At one year of follow-up, 43% of patients on active treatment and 14% on placebo treatment had reached the goal blood pressure (Figure 2).

Treatment during double-blind period

Fewer patients remained on monotherapy in the placebo than in the active treatment group ($P < 0.001$) and in the placebo group the second and third line medication were started more frequently ($P < 0.001$) (Figure 3).

The number of study drugs taken by the patients at the one-year visit, according to the achievement of goal blood pressure, is given in Table 2. In the active treatment group the daily dose of nitrendipine averaged 29 ± 12 mg ($N = 110$), the dose of enalapril was 13 ± 6 mg ($N = 48$) and the dose of hydrochlorothiazide 18 ± 7 mg ($N = 5$). Patients randomized to placebo took a number of tablets corresponding to a daily dose of 33 ± 11 mg ($N = 118$) nitrendipine, 16 ± 5 mg ($N = 67$) enalapril, and 24 ± 7mg ($N = 28$) hydrochlorothiazide.

TABLE 2 *Study medication at one year according to treatment group*

	Placebo	Active treatment
Patients reaching goal pressure		
patients on 1 drug	13	30
patients on 2 or 3 drugs	3	22
total	16	52
Patients not reaching goal pressure		
patients on 1 drug	41	43
patients on 2 or 3 drugs	64	27
total	105	70
Total	121	122

Reasons for discontinuation of first line medication

The first line medication (nitrendipine or placebo) was definitely interrupted in 31 of 421 patients in whom at least one follow-up visit following randomization was available. This happened in 10 patients assigned to placebo and in 21 on active treatment ($P < 0.001$). The reasons for discontinuation of nitrendipine or placebo were: suspected side-effects (25 patients), misinterpretation of the protocol by the investigator (three patients), refusal to take the double-blind medication (one patient), unknown (two patients).

Discussion

There is now considerable evidence that lowering blood pressure using antihypertensive therapy in patients with combined systolic and diastolic hypertension decreases

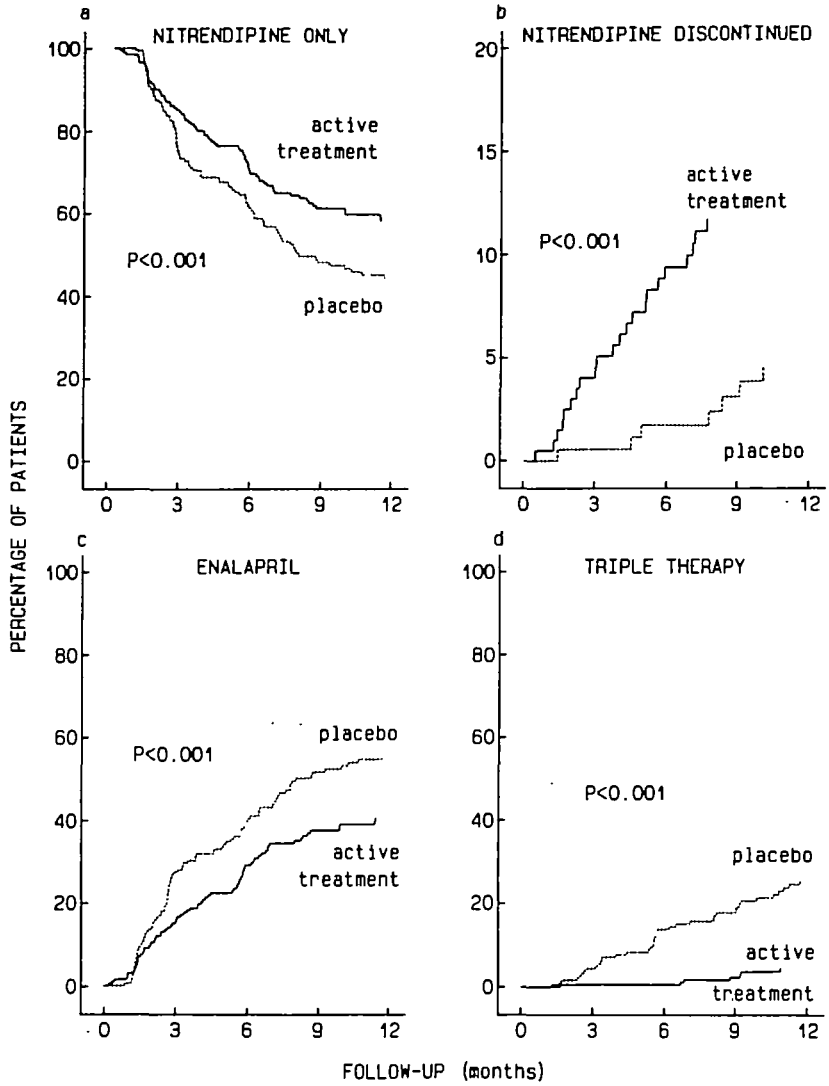

FIGURE 3 *The percentage of patients at a given follow-up visit in the two treatment groups, who remained on monotherapy with nitrendipine (a), in whom nitrendipine was discontinued (b), and in whom enalapril (c) or triple therapy with nitrendipine, enalapril and hydrochlorotiazide (d) was started. The differences between the two treatment groups were significant at the 0.1% level*

the incidence of cardiovascular events in patients up to 75 years of age.13 It is also firmly established that isolated systolic hypertension, which affects 15–20% of all subjects over the age of 60 years, constitutes a major cardiovascular risk factor. In the EWPHE-trial,[3] a placebo-controlled, double-blind inter-patient assessment of diuretic treatment in hypertensive patients aged 60 years or more, 840 patients were included of whom 247 had isolated systolic hypertension[14] (systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≤ 95 mmHg). In this subgroup the data on morbidity and mortality were insufficient to draw firm conclusions. In the active treatment group trends towards a lower cardiac mortality, lower incidence of terminating non-fatal events and lower incidence of fatal and non-fatal cardiovascular events was observed, but none of the differences between active and placebo treatment achieved statistical significance. However, up to now only one intervention trial in elderly patients with isolated systolic hypertension, i.e. the SHEP-trial,[15] has reported its results. In the SHEP-trial patients were recruited by mass mailing and community screening. The SHEP-patients on active treatment showed significant reductions in non-fatal stroke by 37% (95% CI 18–51%), non-fatal myocardial infarction by 33% (95% CI 4–53%) and non-fatal congestive heart failure by 54% (95% CI 35–67%). However, in contrast to previous intervention studies in elderly patients with combined systolic and diastolic hypertension[3,5,6] the SHEP-trial did not demonstrate a significant beneficial effect of antihypertensive therapy on any of the mortality endpoints. Some concerns have been raised on the generalizability of the SHEP-results and whether these are sufficient to establish a minimum worthwhile benefit with a high level of certainty.[16] The results of the Syst-China[17] and the Syst-Eur trials[8] are therefore awaited to confirm or refute the findings of the SHEP-investigators.

Only few outcome studies on the treatment of hypertension involved patients recruited or followed by general practitioners.[6,7] Coope and Warrender[6] conducted a randomized open trial in 884 elderly (60–79 years) patients of 13 general practices in England and Wales. Patients with blood pressures at entry from 170–280 mmHg systolic and below 120 mmHg diastolic or with systolic pressure below 280 mmHg and diastolic pressure from 105–120 mmHg could be included. The first-line antihypertensive agents used were atenolol and bendrofluazide. The mean follow-up was 4.4 years. Active treatment reduced the rate of fatal stroke by 70% and of all strokes by 42%. The incidence of fatal myocardial infarction as well as the total mortality was however unaffected by active treatment. Although 23% of the patients admitted to the Coope and Warrender trial had isolated systolic hypertension, the main publication[6] did not report separate results for this subpopulation. A post-trial analysis[18] however revealed that in patients with a diastolic pressure of at least 90 mmHg, mortality tended to be lower in the subgroup on active treatment than in the patients on placebo (16 versus 24 deaths per 1000 patient-years). However in the patients with isolated systolic hypertension (diastolic pressure <90 mmHg) the opposite tendency was observed (30 versus 21 deaths per 1000 patient-years).

The MRC trial[7] also included patients recruited from (but not followed in) general practices. The patients were between 65 and 74 years and had a systolic blood pressure from 160 to 209 mmHg and a diastolic blood pressure below 115 mmHg at entry. In this randomized, placebo-controlled, single-blind study active treatment consisted of hydrochlorothiazide plus amiloride or atenolol. Four thousand three hundred and ninety-six patients were randomized and the mean follow-up time was 5.8 years. In the active treatment group (diuretic and beta-blocker combined), stroke was reduced by 25%, coronary events by 19% (not significant) and all cardiovascular events by 17%. These reductions were however only due to a reduction in the number of strokes (31%), coronary events (44%) and all cardiovascular events (35%) in the patients treated with diuretics, since the beta-blocker treated group showed no reductions in these endpoints. The MRC-trial included 1879 (43%) patients with isolated systolic hypertension defined as a systolic pressure of at least 160 mmHg and a diastolic pressure below 90 mmHg. The MRC investigators reported that there is no reason to doubt that the overall trial results would also be applicable to the patients with isolated systolic hypertension. However, to the best of our knowledge, separate incidence rates on the patients with isolated systolic hypertension have never been reported in the literature.

In the present analysis 19% of all patients randomized before 1 October 1994 were recruited and followed by general practitioners. In these patients the blood pressure difference between the active and the placebo treatment group after 1 year of randomized treatment was 10 mmHg systolic and 4 mmHg diastolic. This value is comparable to the 12/5 mmHg difference in pressure after 2 years of double-blind treatment reported in the third progress report of the Syst-Eur trial.[11] The present blood pressure results are also similar to those observed in the remainder of this trial population who were not followed in general practices (unpublished data). This reduction in blood pressure is comparable to, although slightly smaller than, that reported in the two previously mentioned trials on older people with systolic and diastolic hypertension in general practice. In the trial conducted by Coope and Warrander[6] the difference in blood pressure between the control group and the active treatment group after 1 year of treatment was nearly 16/10 mmHg. In the MRC trial[7] this difference was 16/7 mmHg. The smaller difference in blood pressure in the present analysis may be due to the type of hypertension, as the latter two trials[6,7] included mainly patients with diastolic or combined diastolic and systolic hypertension. Whether the reduction in blood pressure observed in the Syst-Eur trial will also lead to a decreased number of cardiovascular complications, in particular strokes, remains to be elucidated.

Acknowledgements

The Syst-Eur Trial is a concerted action of the European Union's Medical and Health Research Programme. The Syst-Eur Trial is carried out in consultation with the World Health Organization, the International Society of Hypertension, the European Society of Hypertension and the World Hypertension League. The trial is supported by Bayer AG (Wuppertal, Germany) and the National Fund for Scientific Research (Brussels, Belgium). Study medication is donated by Bayer AG and Merck Sharpe and Dohme Inc. (West Point, Pennsylvania, USA).

Centres. On 31 May 1995, the following general practitioners took part in the Syst-Eur trial: *in Belgium:* G Adriaens (Neerwinden), B Aertgeerts (Wilsele), C Agten (Peer-Wijchmaal), R André (Naast), JM Berthot (Pepingen), G Beuken (Bruxelles), F Bolly (Burdinne), W Bos (Emblem), E Bourdon (Dinant), J Buffels (Anderlecht), E Buts (Mechelen), J Claus (Manage), K Cornelli (Oostende), G Decadt (Ruddervoorde), P De Cort (Tienen), E De Graef (Humbeek), L Devriendt (Maldegem), F Dewaele (Tienen), E Dierckx (Westouter), H Dieu (Kraainem), M Dobbeleir (Mortsel), H Duprez (Tielt), R Duyck (Lennik), F Francis (Ham), P Gilbert (Nivelles), M Glibert-Walgraffe (Genappe), J Gremling (Virton), W Holsters (Duffel), JB Lafontaine (Namur), B Langhoor (Froidmont), V Leyssens (Hasselt), F Libaut (Opwijk), PA Lourtie (Ottignies), W Onsea (Kasterlee), H Proost (Turnhout),

JP Rijckaert (Naninne), C Van Cauwenberge (Zottegem), H Vandenabbeele (Hansbeke), S Van der Vliet (Eppegem), A Vandenbroeck (Wezembeek-Oppem), J Vanlint (Arendonk), D Vantroyen (Hasselt), W Vanverrewegen (Kumtich), P Verhaert (Antwerpen), A Vlaeminck (Brugge); *in France*: J A Cozic (Nantes), P Berger (Paris), L Boucher (Murs Erigne), G Etchegaray (Niort), A Campagne (Tours), C Copere (Roanne), E De Sainte Lorette (Paris), M Gregoire (Tallard), H Feuillette (La Regrippière), G Meridjen (Mallemort), R Gorlier (La Seyne), S Houdry-Pavie (Paris), M Masieri (Besle sur Vilaine), CH Mercier (La Montagne), LM Pommier (Esvres); *in Israel*: J Fidel (Jerusalem), A Goldhaber (Raanana), A Margalit (Kibbutz Ramat Hashofet), I Moran (D.N. H'ela), Y Yodfat (Jerusalem)

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References

1 Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. *Circulation* 1972; **45**: 991–1004.

2 Hypertension-Stroke Cooperative Study Group. Effect of antihypertensive treatment on stroke recurrence. *JAMA* 1974; **229**: 409–418.

3 Amery A, Birkenhäger W, Brixko R, *et al*. Mortality and morbidity results from the European Working Party on High Blood pressure in the Elderly trial. *Lancet* 1985; **i**: 1349–1354.

4 Management Committee. Treatment of mild hypertension in the elderly. A study initiated by the National Heart Foundation of Australia. *Med J Aust* 1981; **2**: 398–402.

5 Dahlof B, Lindholm L, Hausson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedisch Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991; **338**: 1281–1285.

6 Coope J,Warrender TS. Randomized trial of treatment of hypertension in elderly patients in primary care. *Br Med J* 1986; **293**: 1145–1151.

7 MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *Br Med J* 1992; **304**: 405–412.

8 Amery A, Birkenhäger W, Bulpitt CJ, *et al*. Syst-Eur a multicentre trial on the treatment of isolated systolic hypertension in the elderly : objectives, protocol and organisation. *Aging* 1991; **3**: 287–302.

9 Staessen JA, Amery A, Birkenhäger W, *et al*. Syst-Eur: A multicentre trial on the treatment of isolated systolic hypertension in the elderly: First interim report. *J Cardiovasc Pharmacol* 1992; **19**: 120–125.

10 Staessen J, Bert P, Bulpitt CJ, *et al*. Nitrendipine in older patients with isolated systolic hypertension: second progress report on the Syst-Eur Trial. *J Human Hypertens* 1993; **7**: 265–271.

11 Thijs L, Amery A, Antikainen R, *et al*. Antihypertensive therapy in eldery patients with isolated systolic hypertension: third progress report of the Syst-Eur Trial. *Clin and Exper Hypertens* 1993; **15**: 953–966.

12 Petrie JC, O'Brien ET, Littler WA, de Swiet M. Blood pressure measurement. *Br Med J* 1987.

13 Thijs L, Fagard R, Lijnen P, Staessen J, Van Hoof R, Amery A. A meta-analysis of out-come trials in elderly hypertensives. *J Hypertens* 1992; **10**: 1103–1109.

14 O'Malley K, McCormack P, O'Brien E. Isolated systolic hypertension: data from the European Working Party on High blood Pressure in the Elderly. *J Hypertens* 1988; **6 (Suppl 1)**: S105–S108.

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

16 Fletcher A, Spiegelhalter D, Staessen J, Thijs L, Bulpitt C. Implications for trials in progress of publication of positive results. *Lancet* 1993; **342**: 653–657.

17 Systolic Hypertension in the Elderly's Collaborative Group Coordinating Centre. Systolic hypertension in the elderly: chinese trial (Syst-China)—Interim report. *Chinese J Cardiol* 1992; **20**: 270–275.

18 Staessen J, Amery A, Fagard R. Editorial review. Isolated systolic hypertension in the elderly. *J Hypertens* 1990; **8**: 393–405.