Office versus ambulatory recordings of blood pressure (OvA): a European multicenter study

Denis L. Clement on behalf of the Steering Committee*

The long-term prognostic value of ambulatory blood pressure recordings in essential hypertension is poorly documented. A European Multicenter study has been set up to evaluate office versus ambulatory (OvA) recordings during a follow-up period of 5 years in a minimum of 2000 patients. The end-point of the study is the question of whether ambulatory blood pressure measurements are better correlated with patient morbidity and mortality than office recordings. In a specific substudy, short-term evolution (6 months) of left ventricular hypertrophy will be followed in untreated hypertensives with randomly allocated treatment. A number of readaptations of the primary protocol are discussed.

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Keywords: Ambulatory blood pressure monitoring, essential hypertension, left ventricular hypertrophy, office blood pressure.

Introduction

The value of ambulatory blood pressure recording in determining the prognosis of hypertensive patients is not clear at present. Several studies have shown a better correlation between blood pressure and organ damage when blood pressure was measured under ambulatory conditions compared to blood pressure measured at the consultation [1–5] but there is only one study on the correlation between long-term prognosis and ambulatory blood pressure [6].

The techniques used in that study are no longer up to date and the treatment used in those patients is quite different from the present-day treatment of hypertension. Therefore, a prospective long-term study was set up to correlate blood pressure with long-term prognosis, and to compare office and ambulatory blood pressure data [7,8]. This paper discusses the results of a feasibility study and suggestions for readaptation of the primary protocol.

Comments on the questions being posed

The protocol was presented at different meetings, and the questions being posed were clearly accepted as being the key questions to be answered about ambulatory blood pressure recordings by a multicenter prospective study. There was some suggestion of a different study protocol for each aim. Any study of a possible correlation between blood pressure measurement and the long-term prognosis of hypertension requires a long-term protocol with as many patients as possible. A comparison between office and ambulatory blood pressure to determine which is more useful for treatment decisions is better served by a protocol where patients are randomly allocated either to office or to ambulatory blood pressure measurement.

Division of the patients into two groups according to the difference between office and ambulatory blood pressure

In the original protocol, the patients were to be divided into two groups according to whether they showed a large or a small difference between office and ambulatory measurements. Initial experience in many centers has shown that this protocol excludes a large number of patients who are, in fact, suitable for the study. Therefore it was suggested that all patients within certain blood pressure limits be considered for the study, irrespective

From The Study Coordinating Center at the University Hospital, Department of Cardiovascular Diseases, Gent, Belgium.

*Steering Committee: D.L. Clement (Chairman), A. Coats, J. Conway, G. Mancia, P.E. Nielsen, E. O'Brien, G. Parati and P. Sleight.

Requests for reprints to: Prof. D.L. Clement, University Hospital, Department of Cardiovascular Diseases, De Pintelaan 185, 9000 Gent, Belgium.

of the difference between office and ambulatory blood pressure.

Study of the evolution of left ventricular hypertrophy

Many investigators and clinicians felt that in the evaluation of organ damage the degree and evolution of left ventricular hypertrophy is a major item. However, left ventricular hypertrophy is known to be strongly influenced by treatment. Therefore a specific study arm was suggested to follow untreated patients over a short period of time with a randomly allocated treatment schedule. Within the protocol, β-blockers, calcium antagonists and angiotensin converting enzyme inhibitors will be compared and where the need for treatment is not clear-cut, a placebo will be included. Left ventricular hypertrophy will be assessed by ECG and echocardiography and compared with office and ambulatory blood pressure measurements. For the first 6 months every effort will be made to maintain the patients with monotherapy so that the evolution of left ventricular hypertrophy can be assessed during randomly allocated treatment, the evolution to be correlated with office and ambulatory blood pressure.

In patients who are already being treated the treatment will be kept as constant as possible in the early part of the study. There will be no attempt to specify treatment in those patients as the major question is long-term prognosis in correlation with office or ambulatory blood pressure measurements. After 1–3 months, the office–ambulatory difference and possible organ damage will be re-evaluated for reproducibility of the data. After 6 months of treatment the group of untreated patients will join the group of the treated patients in one large study protocol.

Title of the study

In the original protocol HOME BP was given as the title of the study, i.e. Home versus Office Monitoring of blood pressure: a European multicenter study on high Blood Pressure. Several clinicians felt that this title could be misleading in many countries because HOME BP is considered the technique whereby patients record their own pressure. Therefore the title was changed to OvA, Office versus Ambulatory recordings of pressure.

Instruments

Only fully validated instruments will be used, according to the United States Association for the Advancement of Medical Instrumentation or equivalent national standards. Dr E. O'Brien's experience in this area will be used to evaluate all newer instruments that are used regularly. At the time of writing only the SpaceLabs and the Oxford Medilog had been fully validated by these rules but it is expected that several other instruments will be evaluated.

Follow-up of patients on the basis of ambulatory recordings only

In one center the ethical committee considered it unsafe to follow-up patients only on the basis of ambulatory recordings. The reasoning was that there are no data available to prove that this is the better way of measuring blood pressure. This is, of course, the basic question in the present study. The study protocol will therefore be adapted so that all patients can be followed up on the basis of office blood pressure measurements, but all will undergo ambulatory recording as well, so that the question of which blood pressure is best correlated with the long-term prognosis can be answered. This protocol will also eliminate the need for a 'neutral' person, a requirement that presented practical problems in some centers. Further, the objection of the ethical committee will be met.

Conclusion

The different comments and experiences outlined here, which came from several centers carrying out a pilot and feasibility trial, were considered positive and worthwhile by the protocol committee. The protocol is now being adapted to take care of all these comments and will shortly be finalized and distributed to the different participating centers throughout Europe. Since this study is considered to be of the highest importance all delegates to the meeting were asked to take an active part in the study and to recruit as many patients as possible. Preliminary figures suggest that a minimum of 2000 patients will be followed over a period of 5 years. It is hoped that this study protocol will be feasible in all the different European centers so that the basic questions that are most relevant for day-to-day hypertension treatment can be answered.

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Age-related effects of placebo and active treatment in patients beyond the age of 60 years: the need for a proper control group

Lutgarde Thijs, Antoon Amery, Willem Birkenhäger, Christopher J. Bulpitt, Denis Clement, Peter de Leeuw, André De Schaepdryver, Colin Dollery, Françoise Forette, Jean-François Henry, Allan Koistinen, Gastone Leonetti, Aulikki Nissinen, Eoin O'Brien, Kevin O'Malley, Jan Staessen, Jaakko Tuomilehto, John Webster, Brian Williams and Alberto Zanchetti

The age-related response to placebo and active antihypertensive treatment was evaluated in 742 elderly hypertensive patients who were followed in the double-blind placebo-controlled trial conducted by the European Working Party on High blood pressure in the Elderly (EWPHE). In the two treatment groups, the fall in systolic and diastolic blood pressures after 3 months was negatively correlated with age ($P < 0.02$), indicating that the hypotensive effect of placebo and active treatment was more pronounced in older patients. Further comparison of the two treatment groups failed to demonstrate any statistical differences in the slopes of the hypotensive effect on age. These conclusions were not altered by cumulative adjustments for baseline blood pressure, pulse rate, serum creatinine and the presence of cardiovascular complications at entry. In conclusion, in the present study, a similar blood-pressure-lowering action which increased with age was observed on active and placebo treatment; thus, proof that an observed age-related hypotensive effect is caused by a particular drug requires comparison with a control group on placebo.

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Introduction

An age-oriented strategy for prescribing antihypertensive agents is an appealing concept since it translates certain physiological and pharmacological principles into clinical practice. Examples are the decrease with age in plasma renin activity [1], the increment with age in postjunctional α-adrenoceptor-mediated and calcium-influx-dependent vasoconstriction [2], and the enhanced serotonin-mediated vasoconstrictor tone in older patients with atherosclerotic endothelial lesions [3]. During the last two decades, diuretics [4,5], β-blockers [6,7], converting-enzyme inhibitors [8,9], calcium entry blockers [2,10], serotonin antagonists [3,11,12] and other antihypertensive agents, have variously been reported to show or not to show age-dependent efficacy. However,

From the European Working Party on High blood pressure in the Elderly (EWPHE) trial (see Appendix).

Sponsorship: The trial was carried out in consultation with the World Health Organization and supported by the Belgian National Research Foundation (NFWO) and the Belgian Hypertension Committee through grants from Merck, Sharp and Dohme and Smith, Kline and French. These companies prepared Aldomet® tablets (500 mg methyldopa) and Dyazide® capsules (25 mg hydrochlorothiazide and 50 mg triamterene), and matching placebos. The drugs were processed under the supervision of A. De Maesschalck, pharmacist, with the advice of G. Van Herpe. Yearly meetings of the EWPHE were also sponsored by the European Economic Community, ICI and Astra Pharmaceuticals; J. Vanhollenbeke from Boehringer Pharma, Brussels, Belgium, collaborated in performing the quality control.

Requests for reprints to: L. Thijs, Klinisch Laboratorium Hypertensie, Inwendige Geneeskunde-Cardiologie, U.Z. Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.

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until now, the scientific community remained divided over age-dependent efficacy and, therefore, over the desirability of age-oriented drug prescription [1–11]. This is due mainly to the statistical difficulties in proving an age-dependent antihypertensive action, and not least because many published studies lack a proper control series [13,14].

This article is based on the double-blind trial conducted by the European Working Party on High blood pressure in the Elderly (EWPHE) [15–17]. It examines whether an age-related antihypertensive effect could be demonstrated in elderly hypertensive patients on treatment with a thiazide diuretic, when the hypothesis was tested by comparison with a placebo.

Subjects and methods

Study protocol

The protocol of the EWPHE trial has been described in detail elsewhere [15]. Patients of at least 60 years of age, with sitting blood pressure averaging 160–239/90–119 mmHg during the placebo run-in period, were randomized into the trial. After stratification by sex, age, and the presence or absence of cardiovascular complications, the patients (n = 840) were randomized into active treatment or placebo. Active treatment was initiated with 25 mg hydrochlorothiazide in combination with 50 mg triamterene. If the blood pressure remained elevated, the dose of the diuretics could be doubled and α-methyldopa added in a starting daily dose of 250 mg which could, in further steps, be increased to 2 g. For the control patients, placebo tablets matching the active diuretics and α-methyldopa were available and treatment was adjusted following similar dosing steps as in the actively treated patients [15].

Entry and treated blood pressures

Blood pressure readings were obtained after 3 min in the sitting position at three different visits during the placebo run-in period and then at 3-monthly follow-up visits after randomization into the trial.

The entry blood pressure was defined as the average of the pressure readings at the three run-in visits. The effects of placebo and active treatment were calculated by subtracting the entry blood pressure from the blood pressure at 3 months. In the present analysis, treatment response was defined as successful when diastolic blood pressure simultaneously decreased by at least 10 mmHg and reached a level below 90 mmHg. If the follow-up blood pressure was not available, the patient was excluded from the analysis.

Statistical methods

Means were compared by Student's t-test. Baseline blood pressure, blood pressure at 3 months and changes in blood pressure were correlated with age by single and multiple linear regression [18] while the relationship between successful treatment responses and age was investigated by logistic regression [19]. As suggested by Murray and Lesaffre [13], the divergence between the regression lines in the two treatment groups was tested by including an interaction term in the regression models.

Results

Characteristics of the patients at entry

Follow-up blood pressure measurements at 3 months on double-blind treatment were available in 377 of the 424 patients randomized to placebo, and in 365 of the 416 patients allocated to active treatment, leaving a total of 742 subjects for the present analysis.

The two treatment groups included in the present analysis were similar at randomization in their sex ratio, age, sitting blood pressure, pulse rate, body weight and percentage of patients with cardiovascular complications (Table 1). At randomization, systolic pressure was positively related to age while diastolic blood pressure decreased with age (Table 2).

Table 1. Characteristics of the patients at randomization.

	Placebo	Active
n	377	365
Gender (% women)	70	68
Age (years)	72 ± 8	72 ± 8
Systolic blood pressure (mmHg)	182 ± 16	183 ± 16
Diastolic blood pressure (mmHg)	101 ± 7	101 ± 7
Pulse rate (beats per min)	79 ± 10	81 ± 10
Body weight (kg)	67 ± 13	67 ± 13
Cardiovascular complications (% without complications)	65	65

Means ± s.d. None of the differences between the placebo and active treatment groups are significant.

Blood pressure 3 months after randomization

Three months after randomization, sitting blood pressure averaged 175 ± 22/98 ± 11 mmHg (mean ± s.d.) in the placebo group and 160 ± 20/92 ± 11 mmHg in the active treatment group ($P < 0.001$).

As shown in Table 2, diastolic blood pressure at 3 months was negatively correlated with age in both treatment groups.

In single regression analysis, the relationship between systolic blood pressure at 3 months and age was not significant in the placebo, nor in the active treated patients. However, when baseline pressure was taken into account, systolic blood pressure at 3 months was negatively correlated with age in the placebo group. Thus, systolic blood pressure during placebo treatment was lower in older patients independent of the blood pressure at randomization. In the active treatment group, the correlation between systolic blood pressure and age was not sig-

Table 2. Linear regression models relating blood pressure (BP) to age.

	R^2	*P*	Intercept	Age	BP at baseline
Placebo					
SBP at baseline	0.101	<0.001	137.7***	0.62***	
SBP at 3 months	0.008	0.08	157.4***	0.24	
	0.291	<0.001	37.2***		0.76***
	0.298	<0.001	47.6***	−0.25*	0.80***
DBP at baseline	0.026	0.002	110.8***	−0.14**	
DBP at 3 months	0.041	<0.001	118.4***	−0.29***	
	0.301	<0.001	9.4		0.88***
	0.315	<0.001	24.5**	−0.17**	0.85***
Active					
SBP at baseline	0.113	<0.001	132.8***	0.70***	
SBP at 3 months	0.008	0.09	144.3***	0.22	
	0.146	<0.001	76.2***		0.46***
	0.148	<0.001	80.9***	−0.11	0.48***
DBP at baseline	0.016	0.02	108.4***	−0.11*	
DBP at 3 months	0.076	<0.001	118.0***	−0.37***	
	0.176	<0.001	25.3***		0.66***
	0.227	<0.001	51.5***	−0.31***	0.61***

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. R, multiple partial correlation coefficient; SBP, systolic blood pressure; DBP, diastolic blood pressure.

nificant when baseline pressure was accounted for (Table 2).

Is the blood pressure fall on double-blind treatment related to age?

The decrease in systolic and diastolic blood pressure in the active treatment group (−22 and −9 mmHg) was more pronounced ($P < 0.001$) than the decrease in the placebo group (−7 and −3 mmHg).

In the two treatment groups, the changes in systolic and diastolic blood pressures, expressed in mmHg, were negatively correlated with age (Fig. 1; $P < 0.02$), indicating that blood pressure falls were more pronounced in older patients. The slope of the change in blood pressure on age in the actively treated patients was −0.47 mmHg/year (95% confidence interval from −0.74 to −0.22 mmHg/year) for systolic and −0.26 mmHg/year (−0.39 to −0.14 mmHg/year) for diastolic blood pressure. In the placebo-treated patients, the slopes for systolic and diastolic pressures were −0.37 (−0.61 to −0.14 mmHg/year) and −0.15 (−0.27 to −0.03 mmHg/year), respectively.

The age-related hypotensive action of placebo and active treatment has been investigated by evaluating the relationship between the probability of a successful treatment response and age. Using this rather arbitrary way of analysing data, in the group on active treatment, 122 patients (34%) showed a successful treatment response as did 49 patients (13%) in the group on placebo ($P < 0.001$). Logistic regression demonstrated that, in the two treatment groups, the probability of a successful treatment response increased with age (Fig. 2).

Comparison of the age-related effects between the two treatment groups

The fall in diastolic blood pressure with advancing age seemed to be more pronounced in the actively-treated patients compared with the placebo-treated patients (−0.26 versus −0.15 mmHg/year). However, the difference in slope between the two treatment groups was not significant for diastolic blood pressure (95% confidence limits from −0.29 to +0.06 mmHg/year), nor for systolic blood pressure (−0.45 to +0.25 mmHg/year). Similarly, the rise with age in the probability of a successful treatment response was not different between the two treatment groups (chi-square for testing the treatment–age interaction = 0.29; $P = 0.59$). These findings were not altered after adjusting treatment responses for baseline blood pressure, pulse rate, serum creatinine and the presence of cardiovascular complications at entry.

At 3 months, only 25 patients (7%) in the active treatment group received α-methyldopa with 49 patients (13%) in the placebo group taking placebo tablets matching α-methyldopa. Excluding these patients from the two treatment groups did not materially alter the present results.

Discussion

The present study shows that the hypotensive effects of diuretics, and of placebo, increase with advancing age. For diastolic pressure, this age-related hypotensive effect tended to be more pronounced in the active treatment group compared with the placebo group. The age-re-

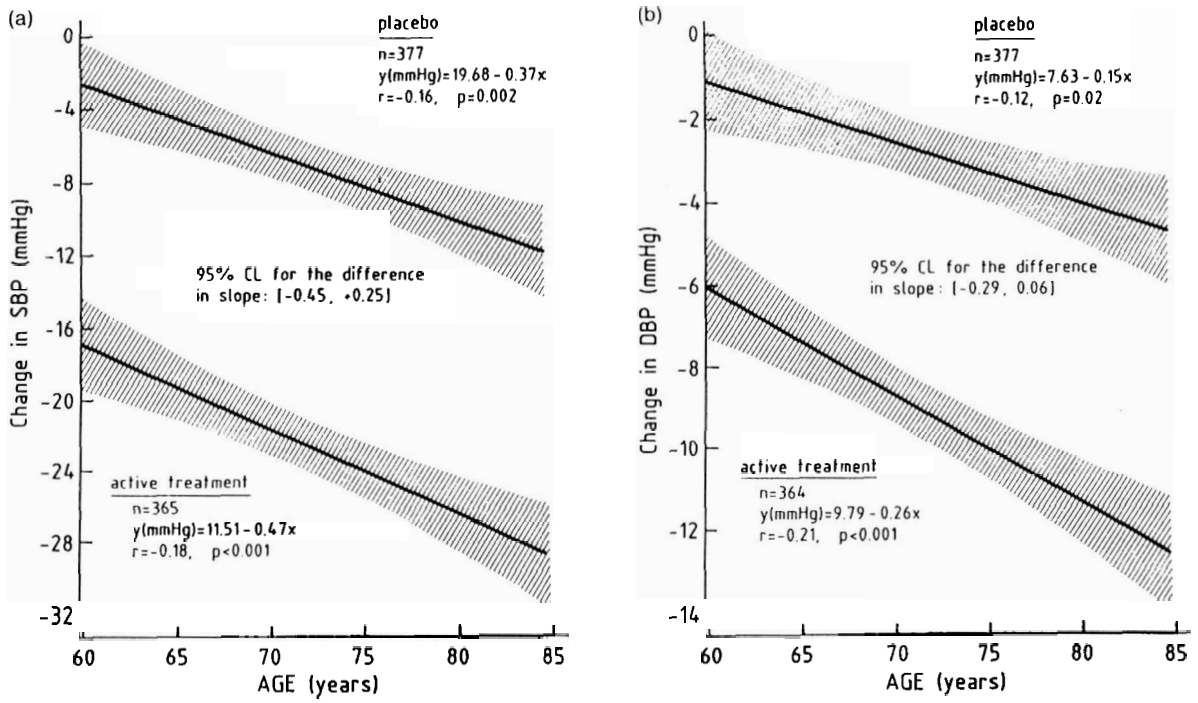

Fig. 1. Relationship between the changes in (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP) and age in patients on active and placebo treatment. For each relationship the 95% confidence limits for the prediction of the mean are presented, as well as the correlation coefficient and the regression equation.

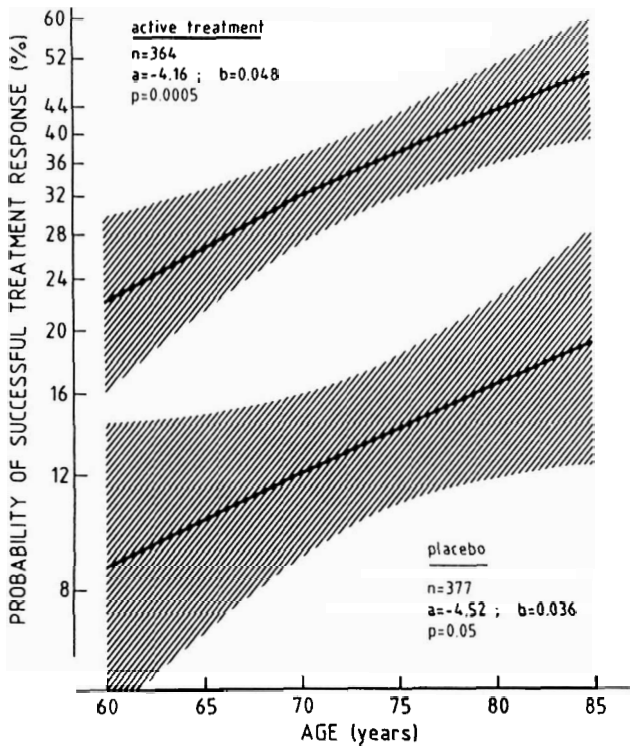

Fig. 2. Relationship between the probability of a successful treatment response [diastolic blood pressure (DBP) < 90 mmHg and $\Delta DBP \leq -10$ mmHg] and age in the placebo and active treatment groups. The predicted probability together with the 95% confidence limits are shown. The parameters a and b are the intercept and the regression coefficient of age in the logistic regression model [19].

lated fall in systolic blood pressure was very similar in the two treatment groups. However, the age distribution of the present patients was truncated at 60 years and it is possible that the age-dependent blood-pressure-lowering effect would have been different in the two treatment groups had the age range been wider. In addition, the EWPHE study was not designed to look at age-related effects in the two treatment groups, the statistical power to demonstrate a significant interaction between the regression lines of the two treatment groups being, therefore, rather low; a difference in slope of 0.15 mmHg/year for diastolic blood pressure and of 0.35 mmHg/year for systolic blood pressure could be detected with a power of about 50%. On the other hand, the present study does illustrate the need for a proper control series when age-dependent effects are investigated [13,14]. Indeed, had the active-treatment group been analyzed without knowledge of the age-dependent effects observed in the placebo group, it is likely that one would have concluded erroneously that diuretics, due to their pharmacological characteristics, lower blood pressure more with advancing age in elderly hypertensives.

The hypotensive response to placebo and active treatment was evaluated 3 months after randomization into the trial. Later follow-up visits on double-blind treatment were not considered for the present study, primarily to keep in the analysis a maximum number of patients on monotherapy with diuretics, but also because most published studies on age-dependent antihypertensive drug effects [2–12] have not extended follow-up beyond 3

months. The conclusions of the present article were not altered when the response to treatment was evaluated 1 year after randomization into the trial.

Why the decrease in blood pressure in the placebo group was age-related remains to be elucidated. In the present elderly hypertensive patients, systolic blood pressure at baseline rose with age. One could, therefore, propose that the hypotensive effect of placebo was higher in older patients because of their higher pressure at entry. However, the relationship persisted when adjustment was made for the baseline pressure. Moreover, age dependency was also observed for diastolic pressure which, in the present elderly hypertensives, declined with advancing age as in the population above 50 years of age at large [20]. An alternative possibility is that the older patients were physically and psychologically more stressed by the initial visits during the placebo run-in period and that, therefore, during subsequent follow-up, they showed a greater fall in blood pressure. Indeed, several investigators [21,22] have reported that, at older age, blood pressure becomes more variable, possibly through a decrease in the sensitivity of the baroreflex arch [23]. Finally, it is also possible that older and younger patients were selected for entry into the study from different populations and that, therefore, they showed an age-related placebo effect; older patients were predominantly recruited from the more dependent residents of old people's homes. However, the present findings were not altered when adjustments were made for cardiovascular complications at entry, for pulse rate at entry as a crude index of cardiovascular sympathetic tone, and for baseline serum creatinine as a crude measure of renal function.

In the present study, the correlation between observed blood pressure falls and the age of patients was highly significant but explained no more than 1–5% of the variance. Also, in most other reported studies, the correlation coefficients were generally weak and the explained variance was no greater than 10%.

An age-related increase of the hypotensive action has been described for several antihypertensive drugs: diuretics [4,5], calcium entry blockers [2,10] and ketanserin [3,11,12]. The question remains, which part of the age-related hypotensive effect of these drugs would exceed that of a placebo?

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Appendix

The following individuals and centres collaborated in the European Working Party on High blood pressure in the Elderly (EWPHE) trial: P. Lund-Johansen, O.J. Ohm, P. Omvik, University Hospital Haukeland, Bergen, Norway; A. Alasoini, A. Koistinen, A. Nissinen, P. Puska, J. Tuomilehto, R. Varis, North Karelia project, Helsinki, Finland; W. Birkenhäger, P. de Leeuw, P. Willemse, Zuiderziekenhuis, Rotterdam, The Netherlands; K. Beard, J.L.C. Dall, the late J.P.R. MacFarlane, B.O. Williams, Victoria Geriatric Unit, Glasgow, Scotland; T.A. Jeffers, J.C. Petrie, O.J. Robb, J. Webster, Aberdeen Royal Infirmary, Aberdeen, Scotland; M. Laher, P. McCormack, F. Meagher, E. O'Brien, W. O'Callaghan, K. O'Malley, Royal College of Surgeons, Dublin, Ireland; C.J. Bulpitt, C. Dollery, A.E. Fletcher, P. Lewis, M. Murphy, Hammersmith Hospital, London, England; R.C. Hamdy, N.H. Perera, St. John's Hospital, London, England; X. Chellappah, J. Morris, A.I. Suchett-Kaye, St. Charles' Hospital, London, England; H. Feltkamp, A. Konrads, U. Laaser, K. Meurer, University Hospital, Köln, West-Germany; A. Amery, R. Fagard, the late J. Hellemans, J.V. Joossens, P. Lijnen, W. Pelemans, J. Staessen, L. Thijs, R. Van Hoof, University Hospital Gasthuisberg, Leuven, Belgium; M. Bogaert, D. Clement, A. De Schaepdryver, University Hospital, Ghent, Belgium; R. Brixko, A. Ernould, A. Mutsers, Geriatric hospital Le Valdor, Liège, Belgium; J.F. De Plaen, Ch. van Ypersele, University Hospital St. Luc, Bruxelles, Belgium; M. Deruyttere, Medisch Centrum voor Huisartsen, Leuven, Belgium; P. Berthaux, F. Forette, J.F. Henry, Hôpital Charles Foix, Ivry, France; G. Leonetti, X. Tammaro, L. Terzoli, A. Zanchetti, Centro di Fisiologia Clinica e Ipertensione, Milano, Italy; F. de Padua, J. Forte, J.M. Pereira-Miguel, University Hospital Santa Maria, Lisboa, Portugal.

The EWPHE trial was coordinated by A. Amery, Leuven and A. De Schaepdryver, Ghent, Belgium.

The steering committee included A. Amery, A. De Schaepdryver, C. Dollery, J.V. Joossens and T. Strasser.

The publication committee included A. Amery, W. Birkenhäger, C.J. Bulpitt, A. De Schaepdryver and C. Dollery.

The advisors were E. Freis, the late F. Gross, M. Healy, S. Hoobler, P. Milliez and J. Willems.