Ambulatory blood pressure monitoring in elderly patients with isolated systolic hypertension

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Objectives: This study compared clinic and ambulatory blood pressure measurement and the reproducibility of these measurements in older patients with isolated systolic hypertension (ISH).

Patients: Eighty-seven patients aged ≥60 years with ISH on clinic measurement were followed in the placebo run-in phase of the Syst-Eur trial.

Methods: Clinic blood pressure was defined as the mean of two blood pressure readings on each of three clinic visits (six readings in total). Ambulatory blood pressure was measured over 24 h using non-invasive ambulatory blood pressure monitors.

Results: Daytime ambulatory systolic pressure was, on average, 21 mmHg lower than the clinic blood pressure, whereas diastolic pressure was, on average, similar with both techniques of measurement. In the 42 patients who had repeat measurements, clinic blood pressure levels and the amplitude of the diurnal blood pressure profile (fitted by Fourier analysis) were equally reproducible. However, both were less reproducible than ambulatory blood pressure levels. The repeatability coefficients, expressed as per cent of near maximum variation (four times the standard deviation of a given measurement), were 52% and 45% for the clinic systolic and diastolic pressures, 56% and 42% for the amplitude of the diurnal profile, and 29% and 26% for mean 24-h pressures.

Conclusions: In older patients with ISH, clinic and ambulatory systolic blood pressure measurements may differ largely: the prognostic significance of this difference remains to be elucidated. Furthermore, in these patients the level of pressure is more reproducible by daytime ambulatory blood pressure measurement than by clinic measurement.

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Introduction

The European Working Party on High Blood Pressure in the Elderly (EWPHE) has recently initiated a double-blind placebo controlled trial in elderly patients with isolated systolic hypertension (ISH; Syst-Eur) [1]. The value of 24-h ambulatory blood pressure measurement in the prediction of cardiovascular complications is

From: see Appendix.

Sponsorship: Syst-Eur is a concerted action of the European Community's Medical and Health Research Programme. The 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. Coordination at the European level is financially supported by a European Community grant. The study is also supported by: the National Research Fund, Brussels, Belgium; the Ministry of the Flemish Community, Brussels, Belgium; the Belgian Insurance Federation, Brussels, Belgium; and by Bayer AG, Wuppertal, Germany. The study medication is provided free of cost by Bayer AG, Wuppertal, Germany and by Merck Sharpe and Dohme, Rahway, New Jersey, USA. The side project on ambulatory blood pressure monitoring is sponsored by the European Economic Community. Oxford Medical Ltd, Abingdon, UK, Novacor, Rueil-Malmaison, France and SpaceLabs Gmbh, Kaarst, Germany offer equipment for sale to Syst-Eur investigators at a reduced cost.

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currently being assessed in a side project to this trial [2].

The diagnosis of hypertension is traditionally based upon clinic blood pressure measurement [3]. Casual blood pressure readings taken in the clinic are an expression of the blood pressure at a particular moment of the day and could therefore poorly represent blood pressure prevailing during daily activities [4–6]. The variability of blood pressure has been reported to increase with both age [7,8] and the level of pressure [8,9]. Moreover it has been suggested that ISH may not be a sustained condition, but a temporary response to the clinic measurement of blood pressure [10].

The objectives of this paper are: (1) to evaluate the level of agreement between blood pressure readings obtained with clinic and ambulatory measurement; (2) to assess the reproducibility of both techniques; and (3) to describe the diurnal blood pressure profile in elderly patients with ISH.

Methods

Syst-Eur trial Protocol

Full details of the protocol have been published elsewhere [1]. Entry criteria included: (1) a minimum age of 60 years; (2) sitting systolic blood pressure (SBP) measured in the clinic during a placebo run-in period averaging 160–219 mmHg, with a diastolic blood pressure (DBP) of <95 mmHg; and (3) willingness of the patient to co-operate and submit to regular follow-up.

Clinic blood pressure measurements

The sitting blood pressure readings reported in the present paper were obtained during the placebo run-in period of the Syst-Eur trial. Blood pressure was measured twice on each of three consecutive visits, with an interval of 1 month [11].

Ambulatory blood pressure measurements

The procedures for ambulatory blood pressure monitoring have been published previously [2]. On 15 May 1991, 102 patients from different European centres took part in the side project on ambulatory blood pressure measurement. Ambulatory blood pressure was recorded non-invasively on the second visit during the placebo run-in phase. In 42 patients an additional recording was obtained 1 month later. Measurements were collected during an entire 24-h period, with intervals of not longer than 30 min. The protocol recommends using only recorders that have been validated according to the guidelines provided by the Association for the Advancement of Medical Instrumentation [12] or by the British Hypertension Society [13]. Of the recordings taken, 43% were obtained with the SpaceLabs 90202 device and 39% with the SpaceLabs 90207 device, (Spacelabs Gmbh, Kaarst, Germany). A cuff size suitable to the arm circumference was selected.

Statistical analysis

The mean of the two clinic blood pressure readings obtained at each of the three run-in visits was used for analysis.

Twenty-four-hour blood pressure recordings were excluded from the present analysis when they were incomplete, i.e. when >20% of the readings were either missing or labelled as technically erroneous by the monitor software, or when blood pressure readings were not available during more than two consecutive hours. Unedited ambulatory recordings comprised all blood pressure readings successfully completed by the monitor software. The following individual ambulatory blood pressure readings were considered for exclusion [14,15]: (1) SBP <DBP; (2) SBP >240 mmHg or <50 mmHg, or DBP >140 or <40 mmHg; (3) pulse rate >150 or <40 beats/min; and (4) pulse pressure <10% SBP.

Daytime was defined as the period from 0010 to 2200 h and night-time from 0000 to 0600 h because previous studies have shown that this definition excludes the periods of rapid blood pressure change that occur in the morning and evening [16]. Intra-individual ambulatory blood pressure means and variances were weighted for the time interval between successive readings. The agreement between daytime ambulatory measurements and blood pressure readings obtained in the clinic was investigated by the method proposed by Gould [17]. Ambulatory blood pressure recordings presenting a significant ($P<0.05$) diurnal rhythm were identified by the one-sample runs-test [17]. The diurnal blood pressure profile was analysed using time-weighted Fourier series with four harmonics [18].

Reproducibility of clinic and ambulatory blood pressure was studied by the Bland and Altman technique [19]. The repeatability coefficient was calculated as twice the standard deviation of the differences between repeated measurements. To allow comparisons between various measurements, the repeatability coefficients were expressed as per cent of near maximal biological variation, i.e. four times the standard deviation of the first measurement. Consistency was estimated by subtracting the first from the repeat measurement and omitting the sign.

Values are expressed as means ± s.d. The SAS-system was used for analysis [20].

Results

Characteristics

Of the 102 participants, 15 were excluded from analysis because their ambulatory recordings were incomplete. The remaining 87 patients (30 men, 57 women) were aged between 60 and 92 years (median age, 7(years). Body mass index was similar for both sexes and averaged 26.0 ± 3.8 kg/m^2.

Clinic blood pressure measurements

Sitting blood pressure values recorded at each of the three run-in visits are given in Table 1. The mean of six readings obtained at the three visits was 178 ± 12 mmHg for SBP and 86 ± 6 mmHg for DBP.

Table 1. Clinic blood pressure measurements.

	Men (n = 30)	Women (n = 57)	All (n = 87)
Visit 1:			
SBP (mmHg)	173 ± 15	181 ± 18	178 ± 17
DBP (mmHg)	86 ± 10	87 ± 7	86 ± 8
Visit 2:			
SBP (mmHg)	177 ± 20	181 ± 16	179 ± 17
DBP (mmHg)	86 ± 9	86 ± 8	86 ± 8
Visit 3:			
SBP (mmHg)	177 ± 14	176 ± 16	177 ± 15
DBP (mmHg)	86 ± 7	85 ± 8	86 ± 7

Values are expressed as means ± s.d. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Ambulatory blood pressure measurements

The unedited ambulatory blood pressure recordings comprised a total of 5674 single blood pressure readings. Only 1.6% of the readings complied with at least one of the four editing criteria. Of the 87 subjects, 46 had no single reading meeting one of the four exclusion criteria. Because editing did not materially alter the shape of the diurnal blood pressure curves, nor the means of the day- and night-time blood pressures, only analyses based on unedited recordings are given.

Blood pressure levels and the parameters of the diurnal profile were similar for men and women and are given for both sexes combined in Table 2. According to the one-sample runs test, 90% of the recordings presented a significant diurnal rhythm for SBP and 85% for DBP.

Table 2. Ambulatory blood pressure measurements.

	SBP	DBP
Mean level:		
Twenty-four hour (mmHg)	151 ± 14	81 ± 9
Daytime (mmHg)	157 ± 15	86 ± 11
Night-time (mmHg)	139 ± 17	71 ± 9
Diurnal profile:		
Day–night difference (mmHg)	18 ± 16	15 ± 10
Amplitude (mmHg)*	24 ± 10	17 ± 7
Acrophase (hh:mm)*	13:45 ± 5:33	13:45 ± 4:22

Values are expressed as means ± s.d. of the unedited recordings, n = 87. The amplitude is half of the difference between the minimum and the maximum blood pressure predicted from the Fourier curve. The acrophase is the time of the blood pressure maximum predicted from the Fourier curve. *Calculations were restricted to the recordings showing a significant diurnal rhythm: systolic blood pressure (SBP), n = 42; diastolic blood pressure (DBP), n = 38.

Agreement between clinic and daytime ambulatory measurements

The correlation coefficients between daytime ambulatory pressure and the mean of the two conventional blood pressure readings, obtained at the outpatient visit when the ambulatory recording was carried out, were 0.56 ($P < 0.001$) for SBP and 0.44 ($P < 0.001$) for DBP (Fig. 1).

Clinic SBP was, on average, 21 mmHg higher ($P < 0.001$) than the daytime ambulatory pressure (mean ± 2 s.d interval ranging from −9 to +51 mmHg). The disparity between both techniques of measure-

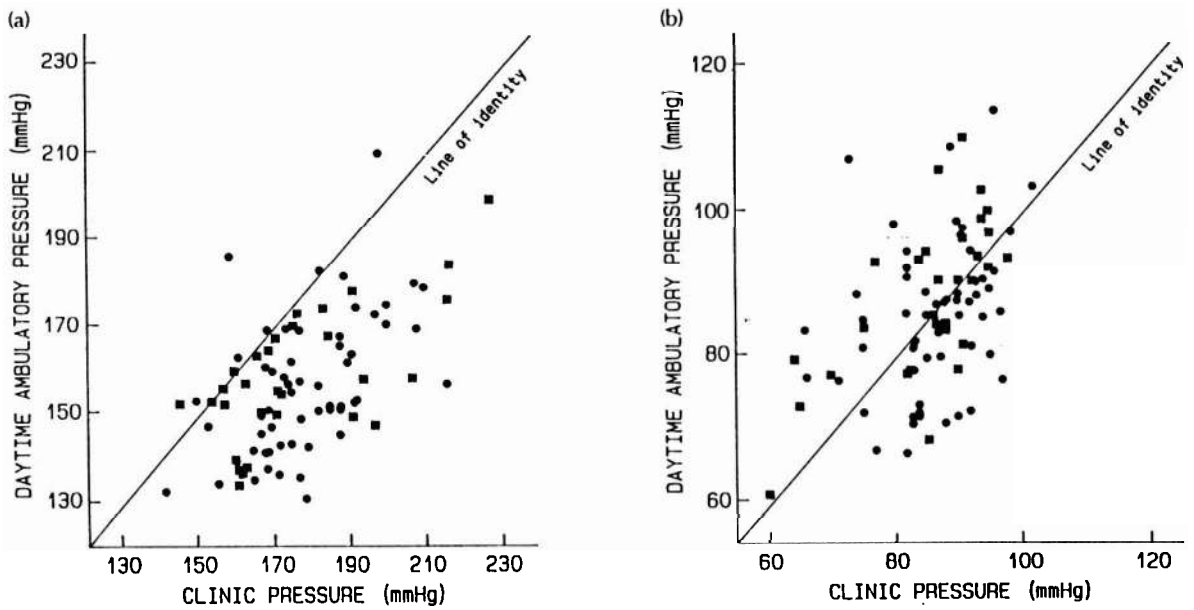

Fig. 1. Scatterplot of (a) systolic and (b) diastolic daytime ambulatory blood pressure against clinic blood pressure in men (■) and women (●). Clinic blood pressure is calculated as the mean of the two measurements obtained at the outpatient visit when ambulatory recording was carried out; n = 87.

ment was not significantly different in men and women (18 ± 15 versus 23 ± 15 mmHg, respectively; $P = 0.19$), and was not related to age ($r = 0.17$; $P = 0.12$). In contrast to SBP, mean clinic and daytime DBP were similar (mean ± 2 s.d. interval ranging from −21 to +21 mmHg).

Table 3. Reproducibility of clinic and ambulatory systolic blood pressure in individual patients.

	Systolic blood pressure (mmHg)			
Patient	Clinic	Mean 24 h	Daytime	Night-time
1	5.0	−2.6	−3.3	−3.5
2	6.0	30.8	27.0	75.5
3	−5.0	−17.5	−29.1	−6.9
4	−9.5	−0.4	−6.4	2.3
5	−14.0	−5.9	2.0	−16.2
6	−44.0	−9.2	−5.0	6.4
7	34.0	13.1	13.2	3.7
8	−7.5	4.7	7.0	0.9
9	50.0	−3.2	−8.1	−7.9
10	−20.5	−0.1	2.4	−12.4
11	−15.0	5.6	−1.8	8.2
12	−9.0	7.0	10.4	6.7
13	9.5	4.0	8.0	0.4
14	−3.5	0.4	0.1	8.2
15	1.5	−4.2	−3.5	−2.1
16	−15.0	−7.0	−8.3	−3.8
17	−1.0	2.4	6.0	0.3
18	13.0	2.6	1.6	−1.3
19	−2.0	6.8	27.6	−4.2
20	−6.0	−1.5	−1.6	9.7
21	−14.0	−6.8	−11.0	−8.3
22	−5.5	1.2	18.6	−4.0
23	−10.0	−9.1	−9.0	−2.2
24	−16.0	−1.0	−3.5	−5.0
25	−27.5	−4.4	−4.6	0.7
26	−2.5	−1.0	−4.0	6.6
27	−18.0	−3.7	−2.8	−15.3
28	−33.0	−11.7	−16.0	0.8
29	3.0	2.1	6.5	−5.4
30	−12.0	−4.0	−6.9	8.0
31	−7.0	3.2	−15.9	22.0
32	−5.0	4.8	4.5	9.0
33	−19.0	−7.9	−12.3	−3.6
34	−6.0	−7.7	−10.5	−9.0
35	30.0	32.1	24.5	36.5
36	19.0	−0.5	4.2	−3.8
37	25.0	2.8	3.4	1.3
38	−20.0	14.0	12.6	15.7
39	−31.0	−6.1	−9.3	−8.2
40	37.0	−6.0	−2.4	−5.4
41	−4.0	5.9	0.9	5.9
42	−7.0	2.7	0.9	1.5
Mean	−4	1	0	2

Values are calculated as repeated minus first measurement.

Reproducibility of clinic and ambulatory blood pressures

The ambulatory blood pressure recordings were repeated in 42 patients, with a median interval of 1 month. Reproducibility of the clinic blood pressure measurements was studied by comparing the readings obtained at the two outpatient visits when the ambulatory blood pressure recordings were carried out. The differences between repeated clinic and ambulatory blood pressure recordings in each of the 42 patients are listed in Table 3. The repeatability coefficient, expressed as per cent of maximum variation, was lower with 24-h ambulatory measurement than clinic measurement for both SBP (29 versus 52%) and DBP (26 versus 45%; Table 4). There was disagreement between duplicate recordings in the outcome of the runs-test in 24% of the subjects for SBP and in 29% for DBP.

Table 4. Summary statistsics on the reproducibility of clinic and ambulatory blood pressure in 42 patients.

	Change†	Consistency‡	Repeatability§
Blood pressure level (mmHg):			
Clinic			
SBP	−4	12 (1–50)	38 (52)
DBP	−2*	5 (1–19)	14 (45)
Twenty-four hour			
SBP	1	5 (0–32)	19 (29)
DBP	−1	3 (0–17)	11 (26)
Daytime			
SBP	0	6 (0–29)	23 (34)
DBP	−2	5 (0–22)	18 (29)
Night-time			
SBP	2	6 (0–76)	30 (44)
DBP	0	5 (0–14)	13 (32)
Diurnal profile: (mmHg)			
Z-statistic runs-test			
SBP	0.4	1.1 (0.0–3.7)	3.2 (44)
DBP	0.2	1.3 (0.0–3.2)	3.0 (42)
Day–night difference			
SBP	−2	8 (0–49)	28 (51)
DBP	−2	5 (0–18)	15 (36)
Amplitude (mmHg)			
SBP	1	6 (0–44)	24 (56)
DBP	−1	3 (0–24)	13 (42)
Acrophase (hh:mm)			
SBP	0:32	5:02 (0:02–19:11)	13:56 (67)
DBP	−0:27	2:19 (0:00–16:00)	12:22 (80)

SBP, systolic blood pressure; DBP, diastolic blood pressure. †Mean difference between duplicate recordings (second minus first recording) taking into account the sign of the difference. ‡Median difference between duplicate recordings, disregarding the sign of the difference (range in parentheses). §Twice the standard deviation of the changes between repeated recordings (per cent of maximal variation in parentheses). The amplitude is half of the difference between the minimum and the maximum blood pressure predicted from the Fourier curve. The acrophase is the time of the blood pressure maximum predicted from the Fourier curve. *$P < 0.05$

Discussion

Discrepancy between clinic and ambulatory measurement

Daytime SBP in the present patients was, on average, 21 mmHg lower than the clinic pressure, whereas

DBP was, on average, similar with both techniques of measurement. Although the present findings are in agreement with a previous study where a discrepancy of 29 mmHg was reported in 10 patients with similar characteristics [10], the interpretation remains unclear and requires further investigation. One interpretation may be that SBP with ambulatory measurement in these patients is near normal. However, such a conclusion requires a generally accepted definition of normality for the 24-h ambulatory pressure. Although some proposals have been published [16,21–23], the discussion on reference values for ambulatory blood pressure measurements has not yet resulted in an agreement among experts [24]. Another interpretation may be that ISH on clinic measurement does not prevail during the day and is therefore not dangerous. However, many studies based upon blood pressure measurements by an observer have proven that ISH on clinic measurement is an outstanding risk factor, especially in the elderly [25,26]. In addition, the recently published Systolic Hypertension in the Elderly Program (SHEP) [27] demonstrated a significant beneficial effect of antihypertensive treatment upon non-fatal stroke, non-fatal myocardial infarction and left ventricular failure.

The difference between clinic and daytime SBP observed in the present study may be accounted for, at least in part, by an alerting reaction to the observer carrying out the blood pressure measurement [4,28]. It has even been suggested that ISH in older patients may not be a sustained condition, but rather an isolated response to office measurement of blood pressure [10]. However, both in the present study and in that by Silagy [10], part of the disparity between clinic and daytime SBP could be related to subject selection [28]. Indeed, entry into these studies was restricted to patients with a minimum clinic SBP of 160 mmHg (mean of six readings), whereas this restriction did not apply to the ambulatory SBP. Therefore, daytime SBP may be somewhat lower than that measured in the clinic.

In contrast to the findings in the present study, studies in healthy subjects have demonstrated much smaller differences in SBP between daytime ambulatory readings and measurements taken by an observer [16,22,29]. Indeed, in a population sample of 328 individuals aged 20–79 years, daytime SBP was, on average, only 5 mmHg higher than blood pressure measured at the subject's home [16]. In a sample of 815 healthy bank employees aged 17–80 years [22], daytime SBP was, on average, 4 mmHg higher than office pressure. The discrepancy between the present and the latter two studies may be due, in part, to the age of the patients, since it has been shown that the difference in pressure between ambulatory and casual readings increase with age [30]. In the study by Silagy [10], daytime systolic blood pressure was, on average, 10 mmHg lower than clinic pressure in 10 normotensive subjects aged ≥70 years. The discrepancy between clinic and daytime ambulatory measurement may also be influenced by the level of blood pressure and by subject activity [28]. Indeed, in a sample of 637 hypertensives (clinic blood pressure, >160/90 mmHg) aged 17–80 years, daytime SBP was, on average, 22 mmHg lower than clinic pressure [31].

Quality and reproducibility

In the present study, 15 of the 102 patients were excluded from analysis because their ambulatory blood pressure recordings were incomplete. There is no indication that the quality of the ambulatory blood pressure recordings is worse in older than in younger subjects: in a Belgian population sample of 328 individuals aged 20–79 years, the percentage of incomplete recordings, i.e. recordings with <80% of the programmed readings and/or with missing readings during more than two consecutive hours, was equal in both those older and younger than 60 years (19.3 versus 19.0%) [16].

Several investigators have shown that both intra-arterial and non-invasive ambulatory blood pressure measurements are more reproducible than clinic measurements [32–34] (Staessen J., Bulpitt C.J., O'Brien E., Cox J., Fagard R., Stanton A., *et al.*, manuscript submitted). In agreement with these findings ambulatory SBP and DBP in the present study were more reproducible than clinic pressures. Indeed, the repeatability coefficients were 52 and 25% lower for 24-h SBP and DBP compared with clinic pressures. One could argue that the poor reproducibility of the clinic blood pressure readings is due to the well-known placebo effect which is not present for ambulatory blood pressure measurements [35–41]. However, in the present study no placebo effect could be demonstrated for clinic SBP.

Few studies have investigated the repeatability of the diurnal profile [42]. In the present study the reproducibility of the overall amplitude of the diurnal curve was similar to the repeatability of the clinic blood pressure measurements, but both tended to be less reproducible than the level of the ambulatory pressure. The acrophase was not reproducible, probably because this parameter depends upon the subject's daily activities and these were not standardized in the present study.

Conclusion

In this study in elderly patients with ISH, clinic SBP was, on average, 21 mmHg higher than daytime ambulatory pressure. The relation between ambulatory blood pressure and the incidence of cardiovascular mortality and morbidity remains to be investigated. In the Syst-Eur trial [1,2], 24-h ambulatory blood pressure is being measured before randomization and at

yearly intervals thereafter in an attempt to determine the prognostic significance of these measurements.

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Appendix

Centres

On 15 May 1991 the following centres with randomized patients participated in the side project on 24-h ambulatory blood pressure monitoring: H. Celis, R. Fagard, P. Lijnen, R. van Hoof, Inwendige Geneeskunde-Cardiologie, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium; P. de Cort, Kumtich, Belgium; D. Staessen, Mechelen, Belgium; G. Donnarel, Y. Ollivier, Centre Gériatrie de Montolivet, Marseille, France; J.B. Leblond, I. Périlliat, Hôpital Georges Clémenceau, Champcueil, France; D. Ganten, C. Heuel, E. Ritz, Medizinische Universitätsklinik Heidelberg, Heidelberg, Germany; A.D. Efstratopoulos, District General Hospital of Athens, Athens, Greece; G. Leonetti, G. Mancia, G. Parati, A. Ravogli, L. Terzoli, A. Zanchetti, Centro di Fisiologia Clinica e Ipertensione, Milano, Italy; M. del Torre, P. Palatini, Policlinico, Padova, Italy; J. Cox, E.T. O'Brien, K. O'Malley, The Blood Pressure Unit, Beaumont Hospital, Dublin, Republic of Ireland; J. Rosenfeld, J. Zabludowski, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; W. Birkenhäger, P. de Leeuw, Zuiderziekenhuis, Rotterdam, The Netherlands; H. Stom, A.J.J. Woittiez, Twenteborg Ziekenhuis, Almelo, The Netherlands; W.H.L. Hoefnagels, J. Lenders, Sint Radboudziekenhuis, Nijmegen, The Netherlands; V. Cuesta, R. Marin, R. Navarro, F. Vega, Hospital Covadonga, Oviedo, Spain; G. Fowler, J.C. Petrie, J. Webster, Royal Infirmary, Aberdeen, UK.

Committees and Coordination

Ethical Committee: A. Amery; W. Birkenhäger; C.T. Dollery.

Data Monitoring Committee: C.J. Bulpitt; A.E. Fletcher; J. Staessen; L. Thijs.

Steering Committee: P. de Cort; R. Fagard; F. Forette; G. Leonetti; E.T. O'Brien; J. Rodicio; J. Rosenfeld; D. Slovick; J. Tuomilehto; J. Webster; Y. Yodfat.

Endpoint Committee: P. de Leeuw; R. Fagard; G. Leonetti; J.C. Petrie.

Drug Committee: A. Amery; J. Staessen; L. Verhaest; R. Ziegler.

European Community Liaison Committee: A. Amery; W. Birkenhäger; F. Bühler; F. de Padua; C.T. Dollery; A.D. Efstratopoulos; F. Forette; D. Ganten; K. O'Malley; J. Rodicio; T. Strasser; J. Tuomilehto; C. van Ypersele; A. Zanchetti.

Trial Coordinator: A. Amery.

Coordinating Office: L. de Pauw; H. Fan; V. Marien; I. Tassens; Y. Toremans.

Co-ordinators of the side project on ambulatory blood pressure: D. Clement; J. Cox; G. Mancia; E.T. O'Brien; G. Parati; J. Staessen.