

Withdrawal from treatment in the Syst-Eur Trial

Christopher J. Bulpitt^a, Nigel S. Beckett^a, Astrid E. Fletcher^b, Lutgarde Thijs^c, Jan A. Staessen^c, Dan L. Dumitrascu^d, Francoise Forette^e, Gastone Leonetti^f, Choudomir Nachev^g, Jaakko Tuomilehto^h and Robert H. Fagard^c, on behalf of the Syst-Eur investigators

Objective To investigate the reasons for withdrawal from double-blind randomized trials, and the reasons for changing treatment within a randomized therapeutic group.

Design The Syst-Eur trial, in which 4695 older patients with systolic hypertension were randomized to active or placebo treatment.

Methods The reasons for withdrawal from the trial were examined, both for patient-initiated and investigator-initiated withdrawals. In addition, the reasons for stopping the first-line treatment (nitrendipine), the second-line treatments (enalapril and hydrochlorothiazide) and the corresponding placebos, were determined.

Results A total of 135 patients (6%) were withdrawn by the investigators from placebo treatment because their blood pressure was too high, and, similarly, 36 (1.6%) through patient initiation. The corresponding results for the actively treated patients were 14 (0.6%) and 7 (0.3%). Very few patients were withdrawn from the trial because of the adverse effects of treatment. However, 39 (4%) stopped taking active nitrendipine because of ankle oedema, compared with 4 (0.5%) on placebo. Similarly, 28 versus three stopped due to flushing. Forty-one (10%) stopped taking enalapril because of cough, against eight (2%) for enalapril placebo. In all, 15.0% stopped active nitrendipine, 20.2% enalapril and 6.3% hydrochlorothiazide, versus placebo 7.1, 9.1 and 5.1%.

Introduction

The cardiovascular benefits of treating isolated systolic hypertension have been clearly demonstrated in the Systolic Hypertension in Europe (Syst-Eur) trial [1] but it is important to evaluate carefully any adverse consequences of treatment, and this article reports reasons for withdrawal for patients in the Syst-Eur trial. To fully evaluate the benefits and risks, the reasons for withdrawal from the trial are reported together with the reasons for stopping and changing the treatments (nitrendipine, enalapril and hydrochlorothiazide) in the trial.

The rate of withdrawal of patients from randomized treatment in large placebo-controlled antihypertension

Conclusions The numbers withdrawn from the trial for adverse treatment consequences were small in comparison to the cardiovascular benefits. Nevertheless the numbers stopping individual treatments were higher than expected. *J Hypertens* 20:339–346 © 2002 Lippincott Williams & Wilkins.

Journal of Hypertension 2002, 20:339–346

Keywords: trials, hypertension, treatment, adverse effects, withdrawal rates

^aImperial College Faculty of Medicine, Hammersmith Hospital, London, UK; ^bLondon School of Hygiene and Tropical Medicine, London, UK; ^cHypertension and Cardiovascular Rehabilitation Unit, Catholic University of Leuven, Leuven, Belgium; ^dUniversity of Medicine and Pharmacy Cluj, Romania; ^eHopital Broca, Centre de Gerontologie, Paris, France; ^fIstituto Auxologico Italiano, Ospedale San Luca, Milano, Italy; ^gAlexandrov University Hospital, Sofia, Bulgaria; ^hNational Public Health Institute and Department of Public Health, University of Helsinki, Helsinki, Finland; a list of all Syst-Eur Trial participants is given in the Appendix.

Sponsorship: The Syst-Eur Trial was a concerted action of the BIOMED Research Program sponsored by the European Union. The trial was sponsored by Bayer AG (Wuppertal, Germany). The National Fund for Scientific Research (Brussels, Belgium) provided additional support. Study medication was donated by Bayer AG, Merck Sharp, and Dohme Inc (West Point, Pennsylvania, USA).

Correspondence and requests for reprints to C.J. Bulpitt, Section of Care of the Elderly, Imperial College Faculty of Medicine, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK.
Tel.: +44 (0) 20 8383 3958; fax: +44 (0) 20 8743 0798;
email: c.bulpitt@ic.ac.uk

Received 26 July 2001 Revised 24 October 2001

Accepted 6 November 2001

trials has not been reviewed recently. This article therefore also compares the results in the Syst-Eur trial with withdrawal from the European Working Party on High Blood Pressure in the Elderly trial (EWPHE) [2]; the Medical Research Council trial in subjects aged 35–64 years (MRC Middle Age) [3]; the MRC trial of treatment of hypertension in older adults aged 65–74 years (MRC Elderly) [4]; the STOP-hypertension trial (STOP) [5]; and the Systolic Hypertension in the Elderly Program (SHEP) trial [6].

Methods

The protocol for the Syst-Eur trial [7] and the main results [1] have been published in detail. To be eligible

for the Syst-Eur trial patients had to be aged 60 years or more, and have an average sitting blood pressure (mean of six measurements over three visits, 1 month apart in a run-in phase) of 160–219 mmHg systolic and less than 95 mmHg diastolic. The average standing systolic blood pressure needed to be 140 mmHg or greater. Active treatment was nitrendipine (10–40 mg daily), with the addition of enalapril (5–20 mg daily) and, finally, hydrochlorothiazide (12.5–25mg daily) if required, to achieve a target sitting systolic blood pressure of less than 150 mmHg with a reduction from baseline of at least 20 mmHg. The control group received matching placebos.

Every individual entering the trial started with double-blind treatment. The patient could then continue on double-blind treatment or transfer to open follow-up treatment, for example when a non-fatal terminating event occurred. Terminating events were defined in the protocol. The investigator also had the right to transfer a patient to open follow-up for reasons not specified in the protocol and the patients themselves may have taken actions that resulted in open follow-up. Rarely, a patient was lost to follow-up completely: 4695 patients were randomized into the Syst-Eur trial, 935 (20%) were transferred to open follow-up and 124 (2.6%) were lost to follow-up [8]. In addition, 282 (6.0%) died [1].

A proportion of patients stopped taking active nitrendipine and were followed in the per protocol analysis on either enalapril or hydrochlorothiazide or both [1]. Similarly, a number of patients given placebo nitrendipine stopped taking these preparations and received placebo enalapril, placebo hydrochlorothiazide or both.

This paper reports the number and reasons for withdrawal from double-blind treatment and the number and reasons for withdrawal from active and placebo treatment during double-blind follow-up.

During the trial the End Point Committee evaluated all reasons for withdrawal.

Statistical method

When considering the reasons for withdrawal from randomized treatment, these totalled about 100. In view of the fact that numerous statistical tests could be made to test for active treatment–placebo differences, we decided not to employ formal statistical testing in this paper. In the text the reader's attention is drawn to differences in symptom side-effects that are more than twofold and are all statistically significant at the 0.001% level, unless otherwise stated. Many of our findings are firmly based on the well-known effects of the treatments employed.

Results

Withdrawal from the double-blind part of the trial

Table 1 gives the reasons for withdrawal and shows that 1581 (69%) completed the trial in the placebo group compared with 1822 (76%) in the active group. The lower proportion on placebo was mainly due to patients being withdrawn by clinicians from the trial because of the blood pressure being too high in the placebo group (135 patients (6%) compared to 14 (0.6%)). In addition there tended to be more fatal events (87) in the placebo group than in the active group (73); and more non-fatal cardiovascular end points in the placebo group (101 compared with 76). The other reasons for withdrawal were infrequent and did not differ statistically between the groups. Three patients on placebo were withdrawn through ankle oedema, and six on active treatment; no patient was withdrawn from placebo for a cough but three were withdrawn on active treatment; and, similarly, no patients were withdrawn from the placebo group with flushing, but two were withdrawn from the active group. Overall 15% in both groups were withdrawn for reasons other than predetermined end points or cardiovascular problems identified by the investigator.

Table 1 All reasons for withdrawal from the double-blind part of the trial (intention-to-treat analysis). First reason given

Reason for withdrawal	Placebo group number (%)	Active group number (%)
Fatal events	87 (4)	73 (3)
Non-fatal cardiovascular end points	101 (4)	76 (3)
Investigator-initiated withdrawal		
Cardiovascular		
BP too high	135 (6)	14 (0.6)
IHD/dysrhythmia etc.	24 (1)	19 (0.8)
Angina	15 (0.7)	12 (0.5)
Oedema	3 (0.1)	6 (0.3)
Valvular disease	0 (0)	2 (0.1)
Hypotension	1 (–)	4 (0.2)
Other vascular	3 (0.1)	6 (0.6)
Total	181 (8)	63 (3)
Central nervous system		
Dementia	7 (0.3)	5 (0.2)
TIA	5 (0.2)	6 (0.3)
Headache/dizziness	4 (0.2)	2 (0.1)
Other	2 (0.3)	3 (0.1)
Total	18 (0.8)	16 (0.7)
Cancer	13 (0.6)	13 (0.5)
Respiratory/cough/infection	8 (0.3)	10 (0.4)
Skin problems/flushing	4 (0.02)	8 (0.03)
Gastrointestinal	3 (0.1)	4 (0.2)
Trauma	2 (0.1)	3 (0.1)
Endocrine	3 (0.1)	1 (–)
Miscellaneous	27 (1)	34 (1)
Centre stopped collaboration	9 (0.4)	22 (1)
Unknown reasons	24 (1)	41 (2)
Patient initiated withdrawal	236 (10)	212 (9)
Completed trial (%)	1581 (69)	1822 (76)
TOTAL	2297	2398

BP, blood pressure; IHD, Ischaemic heart disease; TIA, transient ischaemic attack. A total of 22 patients in the placebo group and 27 in the active group left the trial after 5 years but as this was the original trial length, they are recorded as completing the trial.

In addition to these reasons why the investigators withdrew patients, there were also patients who withdrew themselves from the trial; these were termed 'self-withdrawals'. There were 236 (10%) self-withdrawals in the placebo group and 212 (9%) in the active treatment group. Table 2 shows that this small difference was due to more patients reporting a high blood pressure or preferring a different treatment in the placebo group (36 and 23 patients) compared with the actively treated group (seven and 12 patients, respectively). The 'other clinical problems' included five withdrawals from active treatment due to flushing, compared with two in the placebo group. There was only a very small excess of withdrawals due to recognized drug side-effects and these withdrawals were too few to affect the quality of life and symptomatic enquiry estimates in the trial. However, it must be stressed that the Syst-Eur trial allowed the substitution of different treatments should adverse events occur. Examining the results of both Table 1 and Table 2, the major cause of withdrawal was blood pressure being too high; in addition 40 or more patients withdrew due to moving house; dysrhythmia or angina; and over 30 because of headaches or dizziness, preference for a different treatment or poor compliance.

Numbers stopping a particular drug but remaining on double-blind treatment

The numbers stopping the three drugs, nitrendipine, enalapril or hydrochlorothiazide and corresponding placebos at 2 years are given in Table 3. This time point represented the average length of time for a patient in the trial. It must be noted that additional placebo treatment was indicated far more frequently than extra active treatment in an attempt to reach goal blood

pressure, and that a longer period of follow-up was associated with taking three, rather than two or one, drugs. Thus 41% of those in the active group received enalapril compared with 61% receiving the corresponding tablet in the placebo group. Seventeen per cent of the active group also received hydrochlorothiazide, against 36% receiving the placebo equivalent in the placebo group.

Table 3 also shows that a higher proportion stopped active nitrendipine (15%) than placebo nitrendipine (7%), and similarly for active enalapril (20%) compared with placebo enalapril (9%). Neither active hydrochlorothiazide nor the placebo preparation was stopped in many patients, 6 versus 5% respectively.

Table 4 gives the reasons for stopping placebo and active treatments for those patients still on double-blind treatment after 2 years. Thirty-nine patients stopped active nitrendipine due to oedema (given as the first reason in 3.9% of all those given the drug), and 28 stopped because of flushing (2.8%). These two symptoms were chosen for their large differences from the corresponding placebo results (0.5 and 0.3% respectively), and the fact that they explained over 70% of the active-placebo difference in stopping rates. For enalapril a cough was given as the first reason for stopping (10%) compared with 1.5% on placebo. This also explained over 70% of the active-placebo difference. The stopping rates for hydrochlorothiazide did not differ between the active and placebo preparations. However, one patient developed hyperuricaemia and one gout in the actively treated group.

One other interesting observation can be made from Table 4. It appears that when a symptomatic side-effect is expected from active treatment, an excess number had this reason for stopping in the placebo group. Thus no cough was reported for stopping nitrendipine or hydrochlorothiazide placebo but eight subjects on placebo enalapril stopped this treatment. A similar observation may be made for oedema and flushing in the nitrendipine placebo group (four and three patients, respectively).

Table 2 Reasons given for patient initiated withdrawal. First reason given

Reason for withdrawal	Placebo	Active
Cardiac		
BP too high	36	7
Dysrhythmia/angina	5	4
Oedema	2	6
Low/normal BP	3	4
Other vascular	1	1
Central nervous system		
Dementia/confusion	4	2
Headaches/dizziness	12	13
Depression/anxiety/malaise/other	10	5
Other clinical problems	8	12
Moved house	26	26
Transport problems	11	16
Missed visits	10	11
No longer wishes to be in trial	14	14
Poor compliance	18	12
Preferred a different treatment	23	12
Family problems	6	9
Miscellaneous	14	11
Unknown	33	47
Total	236	212

BP, blood pressure.

Discussion

Withdrawals from double-blind treatment were high and averaged 31% in the placebo group and 24% in the actively treated group. These results agree with the results of many long-term trials, five of which are illustrated in Table 5. Table 5 gives the withdrawal rates from randomized treatment in these trials but excludes deaths and predetermined cardiovascular end points. The Syst-Eur results are added to the table, after removing those who died or had a predetermined non-fatal cardiovascular end point, but including those withdrawn because of poor blood pressure control and

Table 3 Number receiving and stopping the three drugs over a 2-year period

	Placebo treatment	Active treatment
Number ever taking nitrendipine	863	1005
Number stopping nitrendipine (%)	61 (7.1)	151 (15.0)
Number ever taking enalapril	528	415
Number stopping enalapril (%)	48 (9.1)	84 (20.2)
Number ever taking hydrochlorothiazide	315	175
Number stopping hydrochlorothiazide	16 (5.1)	11 (6.3)
Total in analysis	869 ^a	1011 ^a

Analysis is confined to those followed on double-blind treatment after 2 years.

^aSix patients in both groups may not have been given nitrendipine or corresponding placebo; of these, the exact treatments were not known in three on placebo and five on active treatment.

other cardiovascular events determined by the investigator.

Twenty-three per cent were withdrawn for other causes from placebo treatment in the Syst-Eur trial and 18% from active treatment. This compares very closely with the 23 and 16% observed in the STOP trial [5], which had a similar average patient follow-up of 2.1 years. The other trials had a duration of 4.5–5.5 years and withdrawal rates in the placebo groups of between 37 and 53%, and in the active groups between 23 and 63%. The Syst-Eur results appear very acceptable in view of the fact that 198 centres in 23 countries were involved and the communication lines were necessarily long [8].

Many patients withdrew from the double-blind Syst-Eur trial for obvious and unavoidable reasons, such as blood pressure being judged to be too high. In this latter category, 53% were withdrawn according to a

strict protocol, whereas the others were withdrawn without the criteria being met. Moreover, withdrawals were often made without trying triple therapy. The second-largest cause for withdrawal was when the patient decided not to continue in the trial. Most importantly, withdrawal from the trial was rarely due to symptom side-effects. However, this was due to the protocol allowing one treatment to be substituted for another when adverse symptom events were reported. A rigorous trial design of double-blind follow-up, to be replaced when necessary by open supervised follow-up or unsupervised follow-up, ensured that these patients were rarely lost to follow-up. Unfortunately few countries have registration systems that allow the automatic provision of death certification information, and therefore some loss to follow-up was inevitable (2.6% of patients).

The numbers stopping a given active treatment over 2 years were surprisingly high for both nitrendipine and

Table 4 Reasons for stopping both placebo and active treatments for those patients still on double-blind treatment after 2 years. First reason given

	Nitrendipine		Enalapril		Hydrochlorothiazide	
	Placebo	Active	Placebo	Active	Placebo	Active
Cardiac						
BP too high	10	6	5	1	0	0
Dysrhythmia/palpitations	1	7	2	0	1	1
Oedema	4	39	0	0	0	0
Hypotension/normotension	1	4	10	14	4	2
Other	1	0	1	2	0	0
CNS						
Headache	5	13	4	3	1	0
Dizziness	2	8	1	1	0	0
Other	5	6	6	5	0	2
Respiratory						
Cough	0	1	8	41	0	0
Other	2	2	0	1	0	0
Skin problems						
Flushing	3	28	0	0	0	0
Rash/itching/other	10	10	2	4	0	1
Gastrointestinal	5	5	3	3	3	1
Arthropathies/pain in limbs	3	11	0	0	0	0
Hyperuricaemia/gout	0	0	0	0	0	2
Miscellaneous	9	11	6	9	7	2
Total	61	151	48	84	16	11

BP, blood pressure; CNS, central nervous system.

Table 5 Withdrawal rates from randomized treatment (excluding predefined terminating events apart from poor blood pressure control) in five placebo-controlled trials

Trial [reference]	Average duration (years)	Treatment	Number treated	% Withdrawn from randomized treatment
EWPHE [2]	4.7	Hydrochlorothiazide + triamterene ± methyldopa	414	32 ^a
		Placebo	424	39
MRC Middle Age [3]	5.5	Bendroflumazide	4297	38
		Propranolol	4403	41
		Placebo	8654	44
MRC Elderly [4]	5.5	Hydrochlorothiazide	1081	48
		Atenolol	1102	63
		Placebo	2213	53
STOP [5]	2.1	β-blockers or diuretic	812	16
		Placebo	815	23
SHEP [6]	4.5	Chlorthalidone ± atenolol	2365	23 ^b
		Placebo	2371	37
Syst-Eur [1]	2.0	Active treatment	2398	18
		Placebo	2297	23

^aExcludes those withdrawn at 5 years, as this was the intended original trial length. ^bAt 3 years, includes subjects where treatment status was not known (3% active group, 4.5% placebo group).

enalapril. If up to a fifth cannot continue on treatment in a randomized, controlled trial, the situation may be worse in the general 'non-trial' setting, where commitment to treatment is not assured by the procedures of informed consent and investigation. The ability to switch treatments, however, must have reduced the withdrawals from the double-blind part of the trial. The reasons for withdrawal from the trial were not due to the adverse effects of treatment and, apart from predetermined end points of the trial and blood pressure levels, were similar in the placebo and actively treated groups. Investigator-initiated withdrawals predominated for the blood pressure being too high, dysrhythmia, angina, cancer and dementia. Patient-initiated withdrawals also included too high a blood pressure, but also moving house, transport problems, preference for a different treatment and family problems. Twenty-eight patients stated they no longer wished to be in the trial, 21 missed appointments and 30 were non-compliant. The patients also gave headaches, dizziness, malaise and oedema as reasons for withdrawal, but the symptomatic reasons did not clearly reflect the side-effects of the drugs. Combining both investigator- and patient-initiated reasons for withdrawal showed clearly the multitude of different reasons for withdrawal. Top of the list were: blood pressure too high on placebo, social problems, patients changing their minds about participation and clinical reasons such as dysrhythmia, angina and cancer.

Some reasons were avoidable, and we must ask what we have learnt for the future. Allowing treatment changes, and close follow-up with good care are probably the most important factors. Helping with transport, reassurance about symptoms, and encouraging good compliance should keep withdrawals to a

minimum. In addition, the selection of centres that will continue to collaborate is important, as 31 patients had to be withdrawn as the centre withdrew from the trial.

A review of withdrawal rates in 11 short-term quality-of-life studies showed that even over 2–6 months, 14% will discontinue the dihydropyridine calcium antagonist nifedipine, 12% will discontinue propranolol but only 6% atenolol or an angiotensin converting enzyme inhibitor. The differential rates of withdrawal were attributed to adverse drug effects affecting quality of life [9]. Obviously a strategy to reduce withdrawals is to employ a drug that is free of adverse effects. Over a 2-year duration in the Syst-Eur trial, 15% discontinued nitrendipine, 20% enalapril and 6% hydrochlorothiazide. Thus, few patients stopped treatment with hydrochlorothiazide but a larger proportion stopped active nitrendipine and enalapril. The reasons for stopping active nitrendipine rather than placebo were oedema and flushing, and for active enalapril, cough. These findings support the use of diuretics in the elderly.

Evidence for the prevention of withdrawal from a trial by allowing a change of treatment comes also from the Nordil Trial [10]. In this trial patients were randomized to diltiazem-based treatment (one group) or to a diuretic or β-blocker-based treatment (the second group). In the second group patients could change treatments, and therefore 93% remained in their randomized treatment group against 77% in the diltiazem group. The switching of treatment between β-blocker and diuretic treatment may have contributed to the low excess rate of dyspnoea in the β-blocker/diuretic group (1%; $P = 0.006$), and the failure to report cold hands and vivid dreams in this group.

In conclusion the withdrawal rates in those actively treated in the Syst-Eur trial were not excessive, and although the proportions developing various symptom side-effects were high, this burden would appear to be acceptable in view of the cardiovascular benefits. It is important to recognize that this burden should be described after taking into account both withdrawals and treatment changes. Trial reports that do not take these important factors into account will overestimate the true benefit : risk ratio.

Acknowledgements

The trial was carried out in consultation with the World Health Organization, the International Society of Hypertension, the European Society of Hypertension, and the World Hypertension League.

References

- 1 Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al. for the SYST-EUR trial investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350**:757–64.
- 2 Amery A, Birkenhäger W, Brixko P, Bulpitt CJ, Clement D, Deruyttere M, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly. *Lancet* 1985; **i**:1349–1354.
- 3 The MRC working party. MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985; **291**:97–104.
- 4 The MRC working party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992; **304**:405–412.
- 5 Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekblom T, Wester P-O. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991; **338**:1281–1285.
- 6 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265**:3255–3264.
- 7 Amery A, Birkenhäger WH, Bulpitt CJ, Clement D, De Leeuw P, Dollery CT, et al. Syst-Eur. A multicentre trial on the treatment of isolated systolic hypertension in the elderly: Objectives, protocol, and organisation. *Aging Clin Exp Res* 1991; **3**:287–302.
- 8 Staessen JA, Thijs L, Birkenhäger WH, Bulpitt CJ, Fagard R on behalf of the Syst-Eur Investigators. Update on the Systolic Hypertension in Europe (Syst-Eur) Trial. *Hypertension* 1999; **33**:1476–1477.
- 9 Bulpitt CJ, Fletcher AE. Quality of life evaluation of antihypertensive drugs. *Pharmacoeconomics* 1992; **1**:95–102.
- 10 Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, et al. for the NORDIL Study Group. Randomised trial of effects of calcium antagonists compared with diuretics and β -blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000; **356**:359–365.

Appendix

Trial coordinators

Robert Fagard, MD and Jan A. Staessen, MD.

Regional coordinators

Guramy G. Arabidze, MD (Bellarussia and the Russian Federation); Willem H. Birkenhäger, MD (The Netherlands); Christopher J. Bulpitt, MD (United Kingdom); Manuel Carrageta, MD (Portugal); Hilde Celis, MD (Belgium); Françoise Forette, MD (France); Jozef Kocemba, MD (Poland); Gastone Leonetti, MD (Italy); Choudomir Nachev, MD (Bulgaria); Eoin T. O'Brien, MD (Ireland); Eberhard Ritz, MD (Germany); José L. Rodicio, MD (Spain); Joseph Rosenfeld, MD (Israel);

Jaakko Tuomilehto, MD (Finland, Estonia and Lithuania).

Steering committee

Guramy G. Arabidze, MD; Paul De Cort, MD; Françoise Forette, MD; Kalina Kawecka-Jaszcz, MD; Gastone Leonetti, MD; Choudomir Nachev, MD; Eoin T. O'Brien, MD; José L. Rodicio, MD; Joseph Rosenfeld, MD; Jaakko Tuomilehto, MD; John Webster, MD; and Yair Yodfat, MD.

Data monitoring committee

Christopher J. Bulpitt, MD; Astrid E. Fletcher, PhD; Jan A. Staessen, MD; and Lutgarde Thijs, BSc.

End point committee

Peter W. de Leeuw, MD; Robert Fagard, MD; Gastone Leonetti, MD; and James C. Petrie, MD.

Ethics committee

Willem H. Birkenhäger, MD; Colin T. Dollery, MD; and Robert Fagard, MD.

Publication committee

Willem H. Birkenhäger, MD; Christopher J. Bulpitt, MD; Jan A. Staessen, MD; and Alberto Zanchetti, MD.

Coordinating office

Nicole Ausseloos; Veerle Boon; Hilde Celis, MD; Elly Den Hond, DSc; Lut De Pauw, RN; Paul Drent, RN; Dimitri Emelianov, MD; Robert Fagard, MD; Jerzy Gasowski, MD; Heng Fan; Tatiana Kuznetsova, MD; Yvette Piccart; Jan A. Staessen, MD; Yvette Toremans; Lutgarde Thijs, BSc; Sylvia Van Hulle, RN; Ji G. Wang, MD; and Renilde Wolfs.

Investigators

Belgium

G. Adhaens, B. Aertgeerts, C. Agten, R. André, J.M. Berthot, G. Beuken, F. Bolly, W. Bos, E. Bourdon, J. Buffels, E. Buts, H. Celis, W. Ceysens, J. Claus, D. Clement, K. Cornelli, P. De Cort, E. De Graef, J.F. De Plaen, G. Decadt, E. Dejaeger, L. Devriendt, F. Dewaele, E. Dierckx, H. Dieu, M. Dobbeleir, M. Druart, H. Duprez, R. Duyck, R.H. Fagard, F. Francis, M. Geeraert, P. Gilbert, M. Glibert-Walgraffe, J. Gremling, W. Holsters, J.B. Lafontaine, B. Langhoo, V. Leyssens, F. Libaut, P.A. Lourtie, B. Maes, W. Onsea, W. Pelemans, H. Proost, J.P. Rijckaert, D.A. Staessen, J.A. Staessen, C. Van Cauwenberge, J. Van Lint, H. Vandenabeele, A. Vandebroek, S. Vandervliet, D. Vantroyen, W. Vanverrewegen, P. Verhaert, A. Vlaeminck.

Bulgaria

R. Alahverdian, S.G. Andreev, E.D. Anev, M. Antova, V.G. Arabadjiev, B.I. Asenov, V. Baleva, A. Batalov,

S.B. Beleva, R.M. Beltcheva, K.M. Bianov, T. Bojanova, D. Bozhinov, S.T. Brayanova, M.P. Dabcheva, L. Dimitrova, E. Dimotrov, T.I. Draganov, A. Elenkova, R. Eremieva, N.B. Ganov, S.Z. Georgiev, V.I. Gergova, A.I. Gogov, E.G. Goshev, M. Grigorov, V.S. Guidarsky, I.G. Ianev, K. Jankulova, V. Jordanova, D.K. Kamenova, R. Kermova, L. Koeva, Z. Kuneva, G.G. Lazarova, E. Lilov, E. Lubenova, S.I. Mantov, T. Marinova, R. Mateva, A.K. Mihov, L. Mitkova, C. Nachev, L. Naidenova, N. Nikolova, V.N. Nikolova, S.V. Obretenova, J.S. Panteva, V. Pasheva, A. Petkov, P.A. Petrov, A.L. Popov, D.G. Popov, N.S. Popova, T.R. Poryasova, R. Prokopova, L.S. Radeva, R.V. Radoeva, K.N. Ramshiev, K.J. Raykova, P.B. Rusafov, B.E. Shahov, Z. Simeonova, V. Sirakova, A.T. Slavtcheva, D.S. Smilcova, P. Solakov, A. Spasova, M. Staneva, Z.M. Stereva, V. Stoyanovsky, T. Tchernev, S. Tisheva, K.T. Todorova, M. Todorova, M. Tzekova, M.I. Tzenov, V.H. Vasilev, T.N. Vasileva, V. Veselinov, A. Volcov, K. Yablanski, Y.T. Yotov, M.A. Zaprianova, R. Zdravcova, Z. Zozanov.

Croatia

N. Pivac, Z. Rumboldt.

Czechia

J. Filipovsky.

Estonia

T. Laks, T. Podar.

Finland

J. Airas, M. Alaluoto, R. Antikainen, M. Haapio, T. Hakamäki, K. Halonen, M. Jääskivi, S. Junnila, E. Karonen, P. Kivinen, P. Kohonen-Jalonen, P. Kuusisto, K. Lappalainen, E. Lehmus, E. Lëhtomaki, A. Lehtonen, R. Ristolainen, E. Ruotsalainen, C. Sarti, R. Tilvis, J. Tuomilehto, H. Vanhanen, O. Vänskä, M. Viitaniemi, S. Vinni, H. Wallinhiemo.

France

P. Archaud, J.M. Aupy, G. Baudassé, P. Berger, A. Berthelot, F. Bezot, B. Bombecke, L. Boucher, J. Bousac, A. Boye, A. Campagne, J. Castellani, F. Coisne, C. Copere, J.A. Cozic, E. De Sainte Lorette, A. Delelis-Fanien, B. Diadema, G. Donnarel, M. Escande, G. Etchegaray, H. Feuillette, Y.M. Flores, F. Forette, F. Fouquet, G. Francois, I. Gabilly, C. Gaillard, A. Gentric, X. Girerd, R. Gorlier, A. Gracovetsky, M. Grégoire, G. Henry, G. Herry, S. Houdry-Pavie, J.R. Israel, J.P. Jacquemart, P.L. Jacquier, B. La Salle, J.B. Leblond, J.L. Lebrun, M. Masieri, G. Merceay, C.H. Mercier, G. Meridjen, P. Mours, A. Neveur, I. Périlliat, D. Pineau-Valancienne, A. Pistre, L.M. Pommier, A. Ponsot, J. Pontonnier, H. Pujade, E. Quignard, D. Rabaud, F. Regnaut, J.P. Ribat, J. Richard, C. Robin, P. Romejko, M. Safard, R.P. Sarfati, A. Sarradon, N.

Savary, M.L. Seux, M.A. Terrienne, J.M. Vigne, M. Zecconi, G. Zerbé.

Germany

J. Enderlein, H.D. Faulhaber, C. Heuel, S. Matthias, E. Ritz, G. Schundau, U. Zwettler.

Greece

A.D. Efstratopoulos, K. Nikolaidis.

Ireland

L. Bradley, J. Duggan, L. Mee, R. Moran, E.T. O'Brien.

Israel

B. Boner, C. Bott-Kanner, J. Fidel, A. Goldhaber, E. Kisch, I. Kruchin, A. Margalit, I. Moran, J. Rosenfeld, J.B. Rosenfeld, N. Stern, C. Tabenkin, J.R. Viskoper, Y. Yodfat, J. Zabłudowski, S. Zerapha.

Italy

B. Abotel-Hag, E. Agostinacchio, M. Antivalle, M. Baroni, G. Barracchia, A. Bossini, V. Cagli, A. Capra, F. Cavallini, M. Condorelli, M. Del Torre, C. Diveroli, E. Dolce, M. Fastidio, R. Fogari, G. Germano, S. Lattuada, F. Leali, G. Leonetti, A. Libretti, F. Lissoni, A. Longo, G. Maiorano, G. Malamani, P.S. Matteo, M. Merio, P. Nazzaro, P. Palatini, M. Paracicini, C. Pasotti, R. Pieri, N. Pietro, A. Pirrelli, A. Rappelli, M. Rindi, E. Roman, A. Salvetti, M. Simi, L. Terzoli, F. Tettamanti, B. Trimarco, A. Vaccarella, V. Vulpis.

Lithuania

M.R. Babarskiene, A. Bickauskaite, J. Jasilionyte, J. Paukstys, D. Rastenyte, A. Sereniene.

Netherlands

W.H. Birkenhäger, P.W. De Leeuw, W.H. Hoefnagels, A.T.J. Lavrijssen, A.H. Van den Meiracker, N.F. Vogel, P.H. Wassenberg, A.B. Wermenbol, A. Wester, A.J. Woittiez.

Poland

J. Baszak, L. Bieniaszewski, B. Broniarczyk, T. Grodzicki, B. Gryglewska, U. Iwicka, A. Jach, K. Kawecka-Jaszcz, M. Kazmirowicz, J. Kocemba, B. Krupa-Wojciechowska, M. Markiewicz, E. Nartowicz, W. Piwowarska, K. Rachon, M. Rajzer, M. Tendera.

Portugal

R. Afonso, T.B. Afonso, A. Bitoque, A. Caetano, A. Cardoso, M. Carrageta, H. Concalves, A. Costa, D. Deolinda, J. Domingues, A. Franco, G. Leiria, A. Martinez, A. Medeiros, A. Moeda, A. Nunes, P. Nunes, R. Nunes, J. Pascoal, S. Pereira, M.N. Rodrigues, G. Segal.

Romania

S. Babeanu, V. Bogdaneanu, D.L. Dumitrascu, L. Serban.

Russian Federation

G.G. Arabidze, Y.B. Belousov, R.S. Bogachov, L.V. Budrina, T.A. Chiyabi, A. Ershova, G.E. Gendlin, A.Y. Ivleva, T.B. Kasatova, Z.D. Kobalava, I.A. Komisarenko, I.V. Kondratova, I.L. Konstantinova, A. Kopelev, I.U. Korobko, O.A. Kozyrev, A.A. Kubnitskiy, I.V. Lazareva, L.B. Lazebnik, M.V. Leonova, M.M. Liventseva, V.V. Lopykhova, N.V. Malysheva, O.M. Milyukova, S.V. Moissejev, V.S. Moissejev, T.A. Nechesova, S.V. Nedogoda, E.V. Oshchepkova, A.V. Potapova, T.N. Sanina, N.M. Sidakova, B.A. Sidorenko, G.I. Sidorenko, A.K. Starodoubtsev, G.I. Storozhakov, Z.M. Syina, M.V. Taranova, E.A. Toporova, A.L. Tsepov, G.A. Vereshchagina, C.K. Zybkov.

Slovakia

Z. Gérová, K. Jureckova, K. Sedlakova.

Slovenia

R. Accetto, B. Bucic, J. Dobovisek, P. Dolenc, B. Kolsek, Z. Lapanja, M. Mihelic-Breic, J. Petrin, O. Pirc-Cercek, A. Zemva.

Spain

J. Abellan, F.J. Aranda, J. Ariibas, G.C. Barrionuevo, J.M. Bermudez Garcia, V. Cuesta, B.G. Extremera, J. Fernandez, J.M. Gomez, L.G. Gomez, A.H. Herrera, P.A.Lara, A. Madonado, R.I. Marin, J.O. Martinez, F.H. Meneguez, A. Molina, J. Mora-Macia, R. Navarro, E. Lopez de Novales, J. Ortega, A.H. Pardell, F. Plaza, J.O. Pujadas, J. Redon, J.L. Rodicio, L.M. Ruilope, J.A. Ruiperez, F. Vega.

United Kingdom

P. Andrews, S.G. Armstrong, D.G. Beevers, M. Beevers, C.J. Bulpitt, P. Bruce-Jones, D. Choat, P. Crome, C. Davidson, C.T. Dollery, A.E. Fletcher, G. Fowler, N. Gainsborough, L. Gates, N.D.P. Gunawardena, S. Jackson, T.A. Jeffers, C. Kingswood, D. Kluth, D. Lee, P.J. Luce, D. Lyons, G. Mankikar, A. O'Brien, H. O'Neal, J.C. Petrie, J. Richardson, A.K. Scott, P. Sharpstone, D.I. Slovick, I.D. Starke, C.G. Swift, K. Tsang, J. Webster, P.R. Wilkinson.