REPORT ON THE SYST-EUR MULTICENTRE TRIAL

# Twenty-four hour blood pressure monitoring in the Syst-Eur trial

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SUMMARY. This article describes the objectives and protocol of a study on ambulatory blood pressure in elderly patients with isolated systolic hypertension. This study constitutes an optional side-project to the Syst-Eur trial.

The multicentre Syst-Eur trial investigates whether antihypertensive treatment of elderly patients with isolated systolic hypertension will influence the incidence of stroke. Secondary endpoints include cardiovascular events, such as myocardial infarction.

The main objective of the side-project is to investigate whether ambulatory blood pressure monitoring will improve the prediction of cardiovascular complications based on blood pressure measurement in the clinic. The side-project also provides the opportunity to evaluate the diurnal profile of blood pressure in elderly patients with isolated systolic hypertension randomized to placebo or active antihypertensive treatment.

## INTRODUCTION

Casual blood pressure measurement in the clinic is the universal method to assess blood pressure in medical practice (1). However, this technique is associated with some limitations; first, a large random variation exists in blood pressure readings (2), and second, the presence of the observer performing the measurement can induce a temporary but substantial rise in blood pressure, the so-called white coat effect (3, 4). These limitations have stimulated the use of ambulatory blood pressure monitoring in clinical practice (5). In addition, because the variability of blood pressure rises with both age (6, 7) and the blood pressure level (6-8), the clinic blood pressure may not always provide an accurate estimate of the degree of blood pressure elevation nor of the cardiovascular risk especially in the elderly hypertensive patient (9-11).

## OBJECTIVES

The protocol of the Syst-Eur trial was described in detail elsewhere (12). To be eligible for entry into the Syst-Eur study, patients should be at least 60 years old and have a systolic pressure in the clinic ranging from 160 to 219 mmHg with a diastolic below 95 mmHg (12). Eligible patients are randomly allocated to placebo or active antihypertensive treatment, and are followed in a double-blind manner. The incidence of cardiovascular events, in particular stroke, is carefully monitored. The side-project on ambulatory blood pressure monitoring constitutes an optional part of the Syst-Eur trial (12). However, centres deciding to participate in the side-project, should enroll all their patients.

Key words: Cardiovascular complications, elderly, isolated systolic hypertension, stroke.
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The main objective of this side-project is to test the hypothesis that ambulatory blood pressure monitoring will improve the prediction of cardiovascular events based on blood pressure measurement in the clinic; to this end, both clinic and ambulatory blood pressures must be recorded during the placebo run-in phase of the trial.

This side-project also provides the opportunity to evaluate the diurnal profile of the blood pressure in elderly patients with isolated systolic hypertension randomized to placebo or to active antihypertensive treatment. Sudden or unexpected falls in blood pressure may be of particular interest, as these may be best correlated with subsequent cardiovascular events.

## MEASUREMENT OF AMBULATORY BLOOD PRESSURE

### *The recorder*

Only recorders that measure blood pressure non-invasively will be employed. Both Korotkoff sound detecting and oscillometric devices are acceptable. The monitors should enable the registration of blood pressure over a full day and must, therefore, have an autonomy of at least 24 hours or 80 cuff inflations. The use of a cuff with a bladder of 35x12 cm is recommended (13); it must be inflated automatically, and the timing of the inflations must be programmable over the day. A software package for downloading the data from the monitor to a micro-computer must also be available.

Before being used in this project, recorders must have been validated according to the guidelines provided by the Association for the Advancement of Medical Instrumentation (14), or the British Hypertension Society (15) and the validation reports should have been published in refereed medical journals.

### *Interval of the recordings*

Ambulatory blood pressure must be recorded over an entire period of 24 hours at intervals not longer than 30 minutes. As blood pressure measurements prior to randomization are extremely important for the prediction of cardiovascular complications, it is recommended to record ambulatory pressure twice during the placebo run-in period of the study. Further recordings are obtained 6 months and 1 year following randomization, and thereafter at yearly intervals, as long as the patients are available for follow-up (12).

### *Standardization of the ambulatory recordings*

*Guidelines for patients.* Patients are encouraged to wear the recorders for at least 25 hours in order to obtain recordings over a full 24-hour period. The patients hold their arm still, whenever the cuff is inflated while they are awake. On the days of the recordings, patients or their relatives keep a diary. To accomodate the expertise and local needs of each centre, investigators may design the diary as they believe it appropriate, and be able to retrieve it after a sleeping period has ended. Sleep is defined as the period elapsing from the moment a patient lies down with the intention to sleep, to the time of the first visual sensation after a night's sleep. In addition, the diary must report symptoms, if any, and the time of their occurrence and indicate when the main meal was taken.

*Guidelines for technicians.* Training sessions will be organized for centres that do not have any previous experience with ambulatory blood pressure monitoring. The calibration of the monitors should be checked at intervals that comply with the manufacturer's recommendations but do not exceed one year. Prior to each recording, the patient's arm circumference must be measured, and the appropriate cuff size determined. If necessary, a cuff with a bladder size greater than 35x12 cm will be employed. The cuff may be secured either to the left or right arm, as most convenient for the patient. In the case of a systematic difference in blood pressure of at least 10 mmHg by ordinary sphygmomanometry between both arms, the arm giving the highest readings should be chosen. However, all recordings throughout the study in each individual patient must be made with the same type of recorder, a constant bladder size, and the cuff secured to the same arm.

*Guidelines for doctors.* The times of administration and the doses of the study drugs must be similar on the days of the clinic visits, when the casual blood pressure readings are obtained,

and on the days when the ambulatory blood pressure is recorded. The doctor will therefore schedule the ambulatory blood pressure recordings as close as possible to the days of the clinic visits. The physician will repeat a recording before making any treatment adjustment if the registration quality is insufficient, i.e., when 20% of the readings are either missing or labeled as technically inaccurate by the software of the monitor.

## DATA MANAGEMENT

### *The data flow*

Ambulatory recordings are first downloaded from the blood pressure monitor to a microcomputer. Three to 6 months later, ambulatory measurements are sent to the Coordinating Office either by electronic mail, or alternatively by regular mail after data transfer to a magnetic medium. For each recording, the investigator also completes a special form, in which patient-related information is provided, as well as the technical details that are needed for a correct interpretation of the recordings. At the Coordinating Office, the ambulatory measurements are stored in the main Syst-Eur database. Quality checks are performed and, if necessary, error correction forms are mailed to the local investigators to request additional information.

### *Editing of the ambulatory pressure recordings*

The ambulatory recordings may be edited at the Coordinating Office to exclude faulty readings. To avoid bias, editing will be limited initially to the exclusion of measurements which were marked as a technically inaccurate during the registration, and to readings with a systolic pressure lower than the diastolic. In further steps of the editing process, the analyst at the Coordinating Office may decide not to consider readings in which the systolic pressure is higher than 240 mmHg or lower than 50 mmHg, the diastolic pressure is higher than 140 mmHg or lower than 40 mmHg, the pulse rate is higher than 150 or lower than 40 beats per minute, and the pulse pressure is less than 10% of systolic pressure.

## STATISTICAL CONSIDERATIONS

### *Sample size*

As this project constitutes only an optional part of the Syst-Eur trial (12), it was attempted to estimate the number of Syst-Eur centres that would be required to test its main hypothesis.

In the previous trial by the European Working Party on High Blood Pressure in the Elderly (EWPHE), which included a total of 840 patients, blood pressure was only measured at out-patient clinics (16-18). This number of patients was followed for a period of 3 to 4 years, and sufficed to demonstrate that the entry systolic, but not diastolic blood pressure was positively correlated with the incidence of fatal and non-fatal cardiovascular events (18).

Not many studies have addressed the issue of a relationship between ambulatory blood pressure and the incidence of cardiovascular events (19-21). Perloff reported that the residual ambulatory blood pressure (the part of the ambulatory blood pressure that was unrelated to the clinic pressure) predicted the incidence of cardiovascular complications independently of the clinic pressure. However, the slopes and standard errors of these relationships were not reported, and thus sample size calculations for this project based on Perloff's experience (20, 21) are precluded. Nevertheless, if one assumes that the correlations between blood pressure and the incidence of cardiovascular complications in the Syst-Eur trial will be at least as strong as in Perloff's studies, then approximately 5,000 patient-years or the participation of one third of the Syst-Eur centres will be necessary to test the main hypothesis of this side-project with sufficient statistical power. However, considerably less patient-years may be needed, because the projected rate of cardiovascular complications in elderly hypertensives is higher than in the middle-aged patients described by Perloff.

### *Statistical analysis*

Each 24-hour period will be subdivided into 4 periods: daytime (from 8 a.m. to 10 p.m.); nighttime (from midnight to 6 a.m.); and 2 transition periods. Averages of the ambulatory measurements over any time period will be computed with weighting for the time interval between

successive readings. The fall in blood pressure at night will be calculated from the difference between the average day- and night-time pressures, and the diurnal profile of blood pressure will be studied using cumulative sums (22) and Fourrier analysis (23).

The main hypothesis of this side-project will be tested using Cox's proportional hazards model (24). Office and ambulatory blood pressures, obtained during the placebo run-in phase of the Syst-Eur trial, will be correlated with the incidence of major cardiovascular-renal events (12). Both a per-protocol and intention-to-treat analysis will be performed.

## DISCUSSION

The main objective of this project is to establish whether ambulatory blood pressure measurements contribute to the prediction of cardiovascular events based on the measurement of blood pressure in the clinic. A similar project in middle-aged patients with combined systolic and diastolic blood pressure elevation is now being planned (25). Not many studies to date have addressed the relationship between ambulatory blood pressure and the incidence of cardiovascular mortality and morbidity (19-21). One report (19) contained only preliminary results from a larger database, which is now being compiled (Raftery E.B., personal communication); others (20, 21) did not include blood pressure measurements during sleep and do not allow a direct comparison between the predictive power of the clinic and ambulatory blood pressure.

Exercise blood pressure is not related to the incidence of cardiovascular events, when the blood pressure at rest is accounted for (26, 27). An often raised question is whether ambulatory blood pressure is a significantly better predictor of future cardiovascular events than the office pressure. However, measurement of blood pressure in the doctor's office is the current standard for clinical practice, and will not be readily replaced by ambulatory recordings, as the latter are more expensive and time consuming. On the other hand, if ambulatory blood pressure measurement should be proven to add to the prediction of cardiovascular events based on office blood pressure measurement, the former technique may be recommended for the evaluation of hypertension in selected subjects.

Sample size calculations for this side-project were difficult to perform, due to the scarcity of published data in this area. However, it was assumed that the risks associated with systolic pressure are similar in elderly patients with isolated systolic hypertension and with combined systolic and diastolic hypertension. If this assumption holds, a previous report by EWPHE (18) suggests that approximately 800 patients followed for 3 years would be sufficient to demonstrate a significant relationship between systolic pressure measured in the clinic and the incidence of cardiovascular events. Because ambulatory monitoring provides a more precise estimate of a subject's usual blood pressure (28) than blood pressure measurements in the clinic, it is possible that fewer subjects will be needed in the present study to demonstrate a significant relationship between the incidence of cardiovascular events and ambulatory blood pressure (29). Perloff's studies (20, 21) suggest that approximately 5,000 patient-years may be required to test the hypothesis that ambulatory blood pressure measurement improves the estimation of cardiovascular risk based on the office blood pressure. However, one may speculate that less patients may be needed in the present study, owing to the higher event rate in elderly compared to middle-aged patients. In addition, night-time pressure readings are also being obtained in this project; not only the level of the ambulatory blood pressure, but also the diurnal blood pressure profile as well as the variability of the ambulatory blood pressure will be considered as factors possibly explaining part of the cardiovascular risk.

The use of a single type of blood pressure recorder by all centres was considered at the design stage of this project. However, it is unlikely that manufacturers will continue to produce and support one single type of monitor for the total duration of the study. Moreover, the main objective of this project does not necessitate the use of a single type of blood pressure monitor. Therefore, all monitors that measure the ambulatory pressure accurately in a non-invasive way can be used. However, before use

in this study, monitors should have been validated by at least one of 2 standard protocols (14, 15) and the results of the validation studies should have been accepted for publication in refereed journals.

The present protocol was piloted for one year. Ambulatory blood pressure recordings were obtained in 87 elderly hypertensive patients during the run-in phase of the trial. A preliminary analysis of this data showed that systolic blood pressure was on average 21 mmHg lower on ambulatory than on clinic measurement (157 *vs* 178 mmHg; $p < 0.001$), whereas diastolic blood pressure was similar with both measurement techniques (86 mmHg). In 42 patients who had repeat ambulatory measurements during the placebo run-in phase of the trial, the level of the clinic blood pressure and the amplitude of the diurnal blood pressure profile were equally reproducible, but both were less reproducible than the ambulatory blood pressure level. Repeatability coefficients, expressed as a percentage of near maximum variation (4 times the standard deviation of a given measurement), were 52% and 45% for the clinic systolic and diastolic blood pressure, 56% and 42% for the amplitude of the diurnal profile of systolic and diastolic pressure, and 29% and 26% for the mean ambulatory blood pressure over 24 hours. The pilot study also showed that the logistics of this international multicentre study operated as planned, and that ambulatory blood pressure measurement was well accepted by elderly patients.

Appendix 1

Coordination and committees

Ethics Commitee

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

Endpoint Committee

P. De Leeuw, R. Fagard, G. Leonetti, J. Petrie

Drug Committee

A. Amery, J. Staessen, L. Verhaest, R. Ziegler

EC Syst-Eur 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 de Strihou, A. Zanchetti

Coordinators of the Side-Project on Ambulatory Blood Pressure Monitoring

D. Clement, J. Cox, G. Mancia, E.T. O'Brien, G. Parati, J. Staessen

Coordinators of the Side-Project on Multi-infarct Dementia

F. Forette, T. Strasser

Coordinators of the Side-Project on Quality of Life

C.J. Bulpitt, A.E. Fletcher

Coordinating Office

C. Guo, L. De Pauw, V. Mariën, L. Pira, I. Tassens, Y. Toremans, S. Van Hulle

Appendix 2

On May 15, 1991, the following centres were taking part in the Side-Project on 24-hour Ambulatory Blood Pressure monitoring:

Belgium

- L. Dekempeneer, R. Fagard, C. Guo, P. Lijnen, R. Van Hoof: Inwendige Geneeskunde-Cardiologie, Universitair Ziekenhuis Gasthuisberg, Leuven
- P. De Cort: Kumtich
- D. Staessen: Mechelen

France

- G. Donnarel, Y. Ollivier: Centre Gériatrie de Montolivet, Marseille
- J.B. Leblond, I. Perilliat: Hôpital Georges Clémenceau, Champcueil

Germany

- D. Ganten, C. Heuel, E. Ritz: Medizinische Universitätsklinik Heidelberg, Heidelberg

Greece

- A.D. Efstratopoulos: District General Hospital of Athens, Athens

Italy

- G. Leonetti, G. Mancia, G. Parati, A. Ravogli, L. Terzoli, A. Zanchetti: Centro di Fisiologia Clinica e Ipertensione, Milano

Ireland

- J. Cox, E.T. O'Brien, K. O'Malley: Royal College of Surgeons, Dublin

Israel

- J. Rosenfeld, J. Zabludowski: Sackler School of Medicine, Tel Aviv University, Tel Aviv

Netherlands

- W. Birkenhäger, P. de Leeuw: Zuiderziekenhuis, Rotterdam
- H. Stom, A.J.J. Woittiez: Twenteborg Ziekenhuis, Almelo
- W.H.L. Hoefnagels, J. Lenders: Sint Radboutziekenhuis, Nijmegen

Spain

- J.L. Rodicio, L.M. Ruilope: Fundation Puigvert, Madrid.
- V. Cuesta, R. Marin, R. Navarro, F. Vega: Hospital Covadonga, Oviedo

United Kingdom

- G. Fowler, J.C. Petrie, J. Webster: Royal Infirmary, Aberdeen
- N.D.P. Gunawardena, P.J. Luce, I.D. Starke: Hither Green Hospital, London

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