Update on the Systolic Hypertension in Europe (Syst-Eur) Trial

Jan A. Staessen, Lutgarde Thijs, Willem H. Birkenhäger, Christopher J. Bulpitt, Robert Fagard, on behalf of the Syst-Eur Investigators

The Syst-Eur trial was stopped after the second of 4 planned interim analyses, when predefined stopping rules[1] revealed that active treatment diminished the incidence of stroke, the primary endpoint. The ethics committee unanimously resolved that all endpoints that had occurred before February 14, 1997, at 5 PM should be included in the final analysis. The long communication lines between the coordinating office and 198 centers in 23 countries made the practical implementation of this recommendation very difficult. The coordinating office had to strike a delicate balance between reporting long-awaited outcome results or postponing publication until a greater number of terminating report forms had been returned. In the initial Syst-Eur report,[2] 116 (5.1%) of 2297 placebo patients and 121 (5.0%) of 2398 patients randomized to active treatment were classified as lost to follow-up because in the preceding year no report had reached the coordinating office. However, after publication of the outcome results on September 13, 1997,[2] efforts to locate all patients continued. This short letter provides an update based on the final Syst-Eur database.

The number of patients lost to follow-up decreased to 61 (2.7%) in the placebo group and to 63 (2.6%) in the active-treatment group; 1559 and 1795 patients, respectively, were in double-blind follow-up, 147 and 135 had died, 283 and 150 were in supervised open follow-up, and 247 and 255 were in non-supervised follow-up. The number of patient-years accumulated in the placebo and active-treatment groups increased from 5709 to 5844 and from 5995 to 6140, respectively. The greater number of endpoints available for analysis did not affect the conclusions of the initial Syst-Eur report[2] (Table). Fatal and non-fatal cancer (change with active treatment: −12%; 95% CI: −36% to 20%; $P=0.42$) and bleeding episodes not including cerebral and retinal hemorrhage (−9%; 95% CI: −50% to 65%; $P=0.75$) occurred with similar frequency in both treatment groups. Of the 4695 patients, 1994 (42.5%) had been recruited in eastern Europe.

Updated Endpoints in the Systolic Hypertension in Europe Trial

	Rate per 1000 Patient-Years (number of endpoints)		Relative Difference With Rate in Placebo Group	
Nature of Endpoint	Placebo (n=2297)	Active (n=2398)	% Rate (95% CI)	P
Mortality				
Total	25.2 (147)	22.0 (135)	−13 (−31 to 10)	0.28
Cardiovascular	14.0 (82)	10.4 (64)	−26 (−46 to 3)	0.08
Non-cardiovascular	11.0 (64)	10.8 (66)	−2 (−30 to 38)	0.94
Non-fatal endpoints				
Stroke	10.4 (60)	5.7 (35)	−45 (−64, −17)	0.004
Cardiac endpoints	12.8 (73)	8.8 (53)	−32 (−52, −2)	0.04
Fatal and non-fatal endpoints combined				
Stroke	13.9 (80)	8.0 (49)	−42 (−60 to −18)	0.002
Cardiac endpoints*	20.9 (119)	15.6 (94)	−25 (−43 to −2)	0.03
Heart failure	8.9 (51)	6.6 (40)	−26 (−51 to 12)	0.16
Myocardial infarction	8.1 (47)	5.9 (36)	−27 (−53 to 12)	0.16
All fatal and non-fatal cardiovascular endpoints	34.6 (194)	24.2 (145)	−30 (−44 to −13)	<0.001

*Non-fatal and fatal cardiac endpoints included fatal and non-fatal heart failure, fatal and non-fatal myocardial infarction, and sudden death.

Received March 23, 1999; first decision March 23, 1999; revision accepted April 2, 1999.

From the Studiecoördinatiecentrum, Hypertensie en Cardiovasculaire Revalidatie Eenheid, Campus Gasthuisberg, Leuven, Belgium.

Correspondence to Jan A. Staessen, MD, PhD, Studiecoördinatiecentrum, Hypertensie en Cardiovasculaire Revalidatie Eenheid, Campus Gasthuisberg, Herestraat 29, B-3000 Leuven, Belgium.

(Hypertension. 1999;33:1476-1477.)

However, because of the longer follow-up of the western European patients (median: 3.4 versus 1.1 years), more deaths (230 versus 52) and non-fatal cardiovascular endpoints (176 versus 39) were noticed in western European patients.

The number of Syst-Eur patients initially reported as lost to follow-up[2] was substantially lower than, for instance, in the 176 general practices taking part in the Medical Research Council trial of mild hypertension (19%).[3] In the final Syst-Eur database, the proportion of patients lost to follow-up is similar to that in the Hypertension Optimal Treatment trial (2.6%), which stopped according to plan after 1100 events and after all patients had been followed for at least 3 years.[4] In conclusion, the Syst-Eur experience confirms that in large multicenter trials terminating early not all endpoints will be available when the main outcome results are published. Trial researchers should be encouraged to continue searching for unreported endpoints and to publish a final complete analysis. However, the update will not lead to different conclusions unless there was selective under-reporting of events in one treatment group.

References

1. Amery A, Birkenhäger W, Bulpitt CJ, Clement D, De Leeuw P, Dollery CT, Fagard R, Fletcher A, Forette F, Leonetti G, O'Brien ET, O'Malley K, Rodicio JL, Rosenfeld J, Staessen J, Strasser T, Terzoli L, Thijs L, Tuomilehto J, Webster J. Syst-Eur. A multicentre trial on the treatment of isolated systolic hypertension in the elderly: objectives, protocol, and organization. *Aging (Milano).* 1991;3:287–302.
2. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet.* 1997; 350:757–764.
3. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J.* 1985;291:97–104.
4. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. The HOT Study Group. *Lancet.* 1998;351: 1755–1762.