Risk and benefit of treatment of isolated systolic hypertension in the elderly: evidence from the Systolic Hypertension in Europe Trial

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The Syst-Eur trial investigated whether active treatment starting with the dihydropyridine calcium channel blocker (CCB) nitrendipine, could reduce the cardiovascular complications of isolated systolic hypertension (ISH) in the elderly. The intention-to-treat analysis showed that active treatment improved outcome. The per-protocol analysis largely confirmed these results. The effect of treatment on total and cardiovascular mortality might be attenuated in very old patients. Further analysis also suggested benefit in those patients who remained on nitrendipine monotherapy. Active treatment was more beneficial in patients with diabetes as compared with those without diabetes at entry and reduced the incidence of dementia by 50%. Analyses of data from the Ambulatory Blood Pressure Monitoring (ABPM) Side Project suggested that most of the benefit of treatment was seen in patients with a daytime systolic BP $\geq$ 160 mm Hg. Finally, a meta-analysis partly based on Syst-Eur data showed that in older hypertensive patients pulse pressure and not mean pressure is the major determinant of cardiovascular risk. Curr Opin Cardiol 2001, 16:342–348

This review was written for the Systolic Hypertension in Europe Trial Investigators, Hypertension and Cardiovascular Rehabilitation Unit, Department of Molecular and Cardiovascular Research, Faculty of Medicine, University of Leuven K.U. Leuven, Leuven, Belgium. A complete list of the investigators appears in reference [1].

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Current Opinion in Cardiology 2001, 16:342–348

The presence of isolated systolic hypertension (ISH) rises curvilinearly with age. Among septagenarians it averages 8% and beyond 80 years it rises to more than 25% [2]. Isolated systolic hypertension thus affects a large proportion of the elderly population. Against this background, the European Working Party on High Blood Pressure in the Elderly started the placebo-controlled double-blind Syst-Eur (Systolic Hypertension in Europe) trial [3]. In 1991 the Systolic Hypertension in the Elderly (SHEP) trial showed that diuretic-based treatment prevented stroke, myocardial infarction, and congestive heart failure [4]. However, because of the remaining uncertainties about the treatment of ISH in the elderly [5], the Syst-Eur trial continued after the publication of the SHEP results [4]. Furthermore, the controversy on the role of calcium channel blockers (CCBs) as first-line antihypertensive agents [6–9], highlighted the lack of evidence regarding the reduction of cardiovascular risk by these agents. The Syst-Eur trial stopped on February 14th, 1997, after the second of four planned interim analyses, because the primary endpoint of a significant benefit for stroke was reached [3].

Patients and methods

The protocol of the Syst-Eur trial, described in detail elsewhere [3], was approved by the Ethics Committees of all participating centers. Eligible patients had to be 60 years or older and have a sitting systolic BP of 160 to 219 mm Hg with sitting diastolic BP below 95 mm Hg during a run-in phase on single-blind placebo. After stratification by center, sex, and previous cardiovascular complications, patients were randomly assigned double-blind treatment with active treatment or placebo. Active treatment was initiated with nitrendipine (10–40 mg per day), if necessary combined or replaced by enalapril (5–20 mg per day) or hydrochlorothiazide (12.5–25 mg per day) or both drugs. In the control group matching placebos were used. The study medications were stepwise titrated and combined to reduce the systolic BP by 20 mm Hg or more to below 150 mm Hg. Patients withdrawing from double-blind treatment remained in open follow-up.

Overview of previously published Syst-Eur results

Of 4695 randomized patients, 2398 were randomly assigned to active treatment [1,10•,11,12,13••,14,15••,16•].

In the intention-to-treat analysis [1], the between-group difference in BP was 10.1 mm Hg systolic and 4.5 mm Hg diastolic at the median follow-up of 2.0 years. Cardiovascular mortality was slightly lower on active treatment (–26%, $P = 0.08$), but all-cause mortality was not significantly changed (–13%, $P = 0.28$) [10]. Active treatment reduced the incidence of total stroke by 42% ($P = 0.002$) and of nonfatal stroke by 45% ($P = 0.004$) [10]. All fatal and nonfatal cardiac endpoints decreased by 25% ($P = 0.03$) and all fatal and nonfatal cardiovascular endpoints by 30% ($P < 0.001$) [10]. The incidence of fatal and nonfatal cancer (–12%, $P = 0.42$) and of bleeding (excluding cerebral and retinal hemorrhages; –9%, $P = 0.75$) was not different in the two treatment groups [10]. In terms of absolute benefit, treating 1000 elderly patients with ISH for 5 years could prevent 29 strokes or 53 major cardiovascular events.

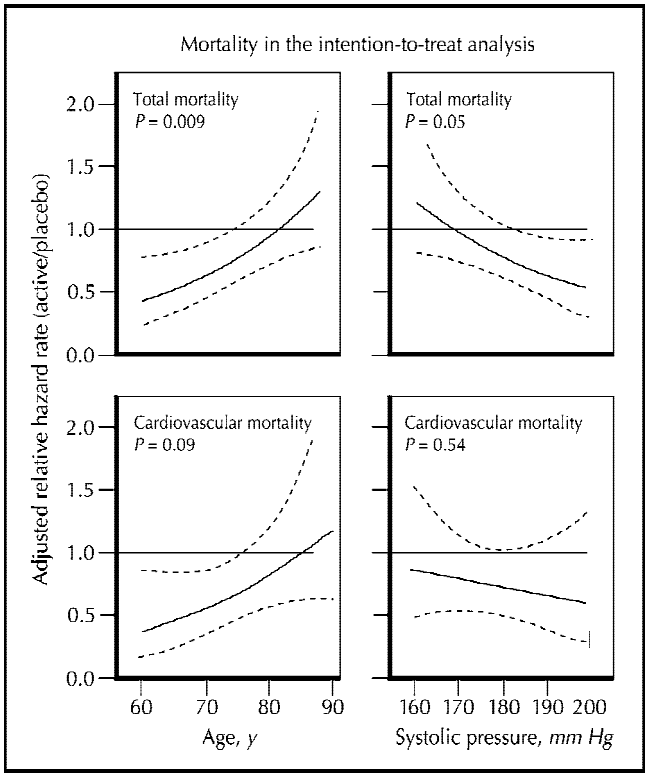
Subgroup analysis [11] showed that male sex, previous cardiovascular complications, older age, higher systolic BP, and smoking at randomization were positively and independently correlated with cardiovascular risk. The relative benefit of active treatment was different according to sex or to the presence of cardiovascular complications at entry. Furthermore, for total ($P = 0.009$) and cardiovascular ($P = 0.09$) mortality, the benefit of antihypertensive treatment weakened with advancing age (Fig. 1). For total mortality ($P = 0.05$), it increased with higher systolic BP at entry (Fig. 1) and for fatal and nonfatal stroke ($P = 0.01$), it was most evident in nonsmokers (92.5% of all patients).

The results of the intention-to-treat [1,10] and per-protocol [11] (including only the endpoints occurring during the double-blind phase) analysis were largely similar. Active treatment reduced total mortality by 26% ($P = 0.05$); similar but nonsignificant trends were observed for cardiac and cerebrovascular mortality. Cardiovascular, cardiac, and cerebrovascular events declined by respectively, 32% ($P < 0.001$), 26% ($P = 0.05$), and 44% ($P = 0.004$). In terms of absolute benefit, the per-protocol analysis suggested that treating 1000 patients for 5 years would prevent 24 deaths, 29 strokes, 25 cardiac endpoints, or 54 major cardiovascular events.

The relative benefits of antihypertensive treatment in the Syst-Eur trial were largely similar to those of other trials in older patients with combined systolic and diastolic hypertension [17–22] or with isolated systolic hypertension [4,23,24].

In view of the persistent controversy about the possible adverse effects of CCBs [8,9,25–28], the question was raised whether treatment with nitrendipine alone would also influence outcome. Further analyses [12] also suggested similar benefit in the patients who remained on nitrendipine monotherapy. In these analyses, 1327 patients who remained on single nitrendipine treatment

Figure 1. Risk according to age and initial systolic blood pressure



Adjusted relative hazard rates of total and cardiovascular mortality according to age and initial systolic blood pressure. The hazard rates (placebo/active treatment), calculated by intention-to-treat, are presented as continuous risk functions with 95% confidence intervals. *P* values refer to the interaction terms between treatment and independent predictor variable. Published with permission [11].

throughout the whole trial, were matched by sex, age, previous cardiovascular complications, and systolic BP at entry, with an equal number of placebo patients from the control group. Compared with this matched control group, treatment with nitrendipine reduced cardiovascular mortality by 41% ($P = 0.05$), all cardiovascular endpoints by 33% ($P = 0.01$), fatal and nonfatal cardiac endpoints by 33% ($P = 0.05$) and fatal and nonfatal heart failure by 48% ($P = 0.05$).

These data from the Syst-Eur trial invalidate circumstantial evidence based on case-controlled and observational studies [6–9,29–33], which according to the investigators' interpretation left a margin of uncertainty regarding the occurrence of potentially dangerous side effects. Several studies investigated the effects of dihydropyridine CCBs in Chinese hypertensive patients [23,24,34–36]. Although some of these trials used unorthodox designs [34,35], they also demonstrated a positive influence on outcome.

At randomization, 492 patients (10.5%) had diabetes mellitus [13]. After adjustment for possible confounders, active treatment reduced all-cause mortality by 55%, car-

diovascular mortality by 76%, all cardiovascular endpoints by 69%, fatal and nonfatal stroke by 73% and all cardiac endpoints by 63% in the group of diabetic patients. In the nondiabetic patients, all cardiovascular endpoints were reduced by 26% and all fatal and nonfatal strokes by 38%. On active treatment, the reductions in total mortality ($P = 0.04$), cardiovascular mortality ($P = 0.02$) and all cardiovascular endpoints ($P = 0.01$) were significantly larger in diabetic patients than in nondiabetic patients.

These data from the Syst-Eur trial [13,37] were the first to prove that antihypertensive drug treatment starting with a dihydripyridine CCB was particularly beneficial in diabetic patients. These results contradicted the suggestion that some (second-generation) dihydropyrine CCBs might be harmful, particularly in hypertensive patients with diabetes mellitus [29–33,38,39].

Systolic hypertension is associated with an increased risk of dementia in elderly people. The primary hypothesis of the Syst-Eur Vascular Dementia Substudy, was that a reduction in BP would protect against vascular dementia [14]. Two thousand four hundred and eighteen patients were enrolled [15]. At the median follow-up of 2.0 years, active treatment reduced the incidence of dementia by 50% ($P = 0.05$) from 7.7 to 3.8 cases per 1000 patient-years. Active treatment prevented mainly Alzheimer's dementia (8 versus 15 cases), but also vascular (0 versus 2) and mixed (3 versus 4) dementia. According to the intention-to-treat analysis, treating 1000 elderly patients with ISH for 5 years might prevent 19 cases of dementia.

The prevention of degenerative dementia was somewhat unexpected, although recent studies indicate that vascular factors, in particular hypertension, might also play a role in the development of degenerative dementia [40]. An alternative explanation, although still unproven, could be that lipophilic CCBs, which cross the blood-brain barrier and bind to brain receptors located in areas affected by Alzheimer's disease, might confer a specific neuroprotective effect [41,42].

Overview of recent Syst-Eur results

Response to antihypertensive therapy in patients with sustained and nonsustained isolated systolic hypertension (ISH)

Patients with nonsustained hypertension (also called white coat or isolated clinic hypertension) have normal ambulatory blood pressure (ABP), but elevated clinic blood pressure (CBP) [43–45]. Target organ damage [46–50] and cardiovascular risk [49,51,52] is reported to be lower in patients with nonsustained as compared with patients with sustained (ABP and CBP both elevated) hypertension, but data on nonsustained hypertension in elderly patients with ISH are generally lacking.

Therefore, the data from the Ambulatory Blood Pressure Monitoring (ABPM) Substudy [53,54] of the Syst-Eur trial were analyzed. The objectives of this analysis were to evaluate the consequences of nonsustained systolic hypertension as well as the impact of antihypertensive treatment. Patients enrolled in the ABPM Substudy were classified according to baseline daytime systolic ABP in 1 of 3 subgroups: nonsustained ISH (< 140 mm Hg), mild sustained ISH (140 to 159 mm Hg), and moderate sustained ISH (≥ 160 mm Hg).

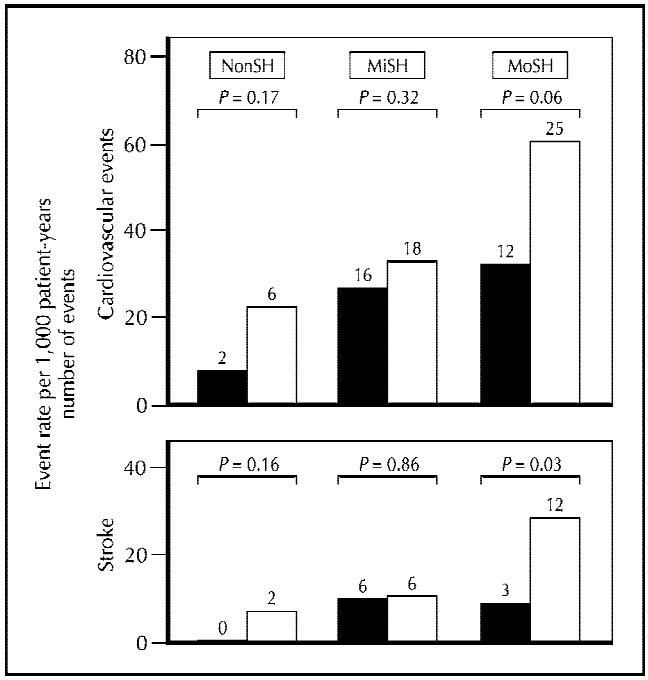
At baseline, diastolic daytime and systolic and diastolic nighttime and clinic BPs were higher in sustained than in nonsustained hypertensives. Patients with nonsustained ISH had smaller ECG voltages than patients with mild and moderate sustained ISH. The differences in ECG voltages between these three groups remained significant after controlling for systolic CBP, but significance was lost after adjusting for daytime systolic ABP.

During follow-up, active treatment reduced daytime and nighttime ABP significantly in the patients with sustained ISH but not in patients with nonsustained ISH. CBP, however, decreased significantly in the three subgroups. Active treatment reduced ABP and CBP more than placebo in patients with mild and moderate sustained ISH. By contrast in patients with nonsustained ISH, the changes in ABP between the treatment groups were not significantly different (except for daytime SBP), whereas the changes in CBP were also more pronounced on active treatment as compared with placebo.

Patients with nonsustained ISH had a lower incidence of stroke ($P < 0.05$) and of cardiovascular events ($P = 0.01$) during follow-up than patients with sustained ISH. Active treatment significantly reduced ($P < 0.05$) the ECG voltages in patients with sustained ISH, but not in these with nonsustained ISH. The influence of active treatment on the incidence of stroke ($P < 0.05$) and cardiovascular events ($P = 0.06$) (Fig. 2) and on ECG voltages was significantly more beneficial than that of placebo only in patients with moderate sustained ISH.

These results confirm previous studies in other hypertensive populations [49,51,52,55,56], which suggested that white coat hypertension is associated with a better outcome [49,51,52] or that the predictive value of ABP persists after controlling for CBP [55,56]. A previous analysis of data from the ABPM Substudy, in which BP was treated as a continuous variable, showed that the systolic ABP was a significant predictor of cardiovascular complications over and beyond CBP [57]. The night/day ratio had a predictive value independent of the 24 hour ABP [57]. In this analysis diastolic ABP and CBP were not related to outcome [57]. The previously reported findings on surrogate (ECG voltages) and hard (outcome) endpoints [43] allow us to conclude that sustained

Figure 2. Risk according to hypertension status and treatment group



Number of strokes and cardiovascular events per 1000-patient-years and absolute number of events during follow-up in patients with Non-SH (nonsustained hypertension), MiSH (mild sustained hypertension), and MoSH (moderate sustained hypertension), divided according to treatment group (open columns, placebo treatment; filled columns, active treatment). Results are from intention-to-treat analysis. *P* value refers to comparison of rates between 2 treatment groups within each subgroup according to daytime systolic BP. Published with permission [43].

ISH is more harmful than nonsustained ISH, in particular when the daytime systolic ABP ≥ 160 mm Hg. Moreover, the benefit of antihypertensive therapy is also mainly seen in the latter patients, and becomes less evident when daytime systolic ABP is less than 160 mmHg.

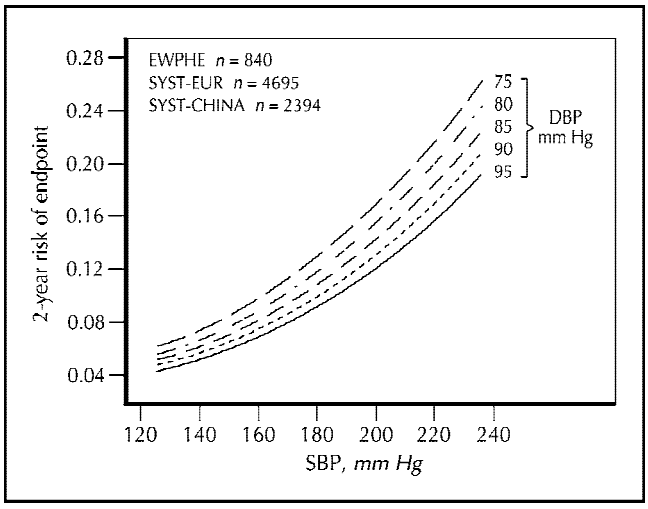
Pulse pressure as cardiovascular risk factor in elderly hypertensives

For the moment, guidelines for the management of hypertension are mainly based on the measurement of systolic and diastolic BP and these are usually considered as being two isolated variables [44,45,58,59]. However, BP is more correctly described as consisting of a pulsatile (pulse pressure [PP]) and a steady (mean pressure [MP]) component [50]. Ventricular ejection, arterial stiffness and the timing of the wave reflections are the major determinants of PP, while MP mainly depends on peripheral vascular resistance and cardiac output. Several observational studies suggested that in elderly people PP might be a better predictor of cardiovascular risk than MP [60–69]. Since PP widens with advancing age [2], the results of outcome trials in older hypertensives might provide an ideal database to test this hypothesis. Therefore the data of three placebo-controlled trials in older patients with hypertension (EWPHE [17], Syst-Eur [1], Syst-China [23]) were pooled to assess the independent roles of PP and MP as determinants of cardiovascular risk with sufficient statistical power. The meta-analysis was based on individual patient data. Relative hazard rates associated with PP and MP were calculated using Cox regression analysis and adjustments were made for sex, age, previous cardiovascular complications, smoking, and active treatment. Furthermore the relative hazard rates for PP were also adjusted for MP and *vice versa*.

In the overall Cox regression analysis with stratification for the three trials and with adjustment for the previously mentioned covariates, a wider PP at baseline increased the risk of major cardiovascular complications. The increase in risk associated with a 10 mm Hg wider PP, ranged from about 13% for all coronary end points (P = 0.02) to nearly 20% for cardiovascular mortality (P = 0.001). In a similar analysis, MP could only be identified as a significant predictor of risk, after removal of PP as an explanatory variable from the model. The 2-year probability of a major cardiovascular endpoint increased with higher systolic BP ($P < 0.001$) (Fig. 3). Furthermore, at any given level of systolic BP, the risk also increased with lower diastolic BP (P = 0.001). This observation suggests that the wider PP was driving the risk of major complications.

The role of PP as a significant predictor of cardiovascular risk had already been identified by several investigators and in different groups of patients [60,61,63–67,69–71]. Moreover, a recent meta-analysis [45] including data of more than 15 000 patients with ISH from 8 different outcome trials also confirmed the role of PP as a risk

Figure 3. Risk estimates for all cardiovascular endpoints based on three trials



Risk associated with increasing systolic blood pressure at fixed levels of diastolic blood pressure. The 2-year probability of a cardiovascular end point was adjusted for active treatment, sex, age, previous cardiovascular complications, and smoking by Cox multiple regression with stratification for trial (EWPHE [17], Syst-Eur [1], Syst-China [23]). Published with permission [44].

factor. Furthermore, the authors also reported that active antihypertensive treatment was particularly beneficial in men, in patients aged 70 years or more, and in those with previous cardiovascular complications or wider PP at baseline. If PP at baseline was 90 mm Hg or greater, 63 patients had to be treated to prevent one cardiovascular death, whereas 119 patients had to be treated if pulse pressure was less than 90 mm Hg.

From the present data it can be concluded that in older hypertensives, PP, but not MP is the major determinant of cardiovascular risk. These findings must however be interpreted with caution. The positive and independent association between PP and the incidence of cardiovascular complications does not automatically imply a causal or reversible relationship. Whether these data in the elderly can be extrapolated to younger or middle-aged patients also remains to be proven. Furthermore, the present findings may also have important clinical implications [72]. They suggest that the prediction of cardiovascular complications might be improved by accounting for both the pulsatile (PP) and the steady (MP) component of BP. This should however be further investigated in randomized clinical trials in which the pulsatile component of BP is differently affected by antihypertensive drug treatment.

Conclusion

From the previous data some important conclusions emerge. First, that stepwise antihypertensive treatment starting with the CCB nitrendipine improves prognosis in elderly patients with ISH and may particularly be indicated in diabetic patients with ISH or in those at risk of dementia. Second, that most of the benefit of treatment is seen in patients with a daytime systolic ABP $\geq$ 160 mm Hg. And finally, that in elderly hypertensive patients pulse pressure and not mean pressure is the major determinant of cardiovascular risk.

Acknowledgment

The Syst-Eur trial, initiated by Antoon Amery, MD (died on November 2, 1994), was a concerted action of the BIOMED Research Program sponsored by the European Union. 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. 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 and Merck Sharp and Dohme Inc (West Point, PA, USA).

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- •• Of outstanding interest

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