The Prevention of Dementia With Antihypertensive Treatment

New Evidence From the Systolic Hypertension in Europe (Syst-Eur) Study

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Background: After the double-blind, placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial ended in February 1997, randomized patients were offered active study medication for a further period of observation.

Objective: To refine the estimates of the long-term effects of antihypertensive therapy on the incidence of dementia.

Methods: Eligible patients had no dementia and were at least 60 years old. Their systolic blood pressure at entry was 160 to 219 mm Hg, with diastolic blood pressure below 95 mm Hg. Antihypertensive therapy was started immediately after randomization in the active treatment group, but only after termination of the double-blind trial in the control patients. Treatment consisted of nitrendipine (10-40 mg/d), with the possible addition of enalapril maleate (5-20 mg/d), hydrochlorothiazide (12.5-25 mg/d), or both add-on drugs.

Results: Median follow-up increased from 2.0 years in the double-blind trial to 3.9 years overall. The incidence of dementia doubled from 32 to 64 cases, 41 of whom had Alzheimer disease. Throughout follow-up, systolic/diastolic blood pressure was 7.0/3.2 mm Hg higher in the 1417 control patients than in the 1485 subjects randomized to active treatment. At the last examination, the blood pressure difference was still 4.2/2.9 mm Hg: 48.1%, 26.4%, and 11.4% of the control patients were taking nitrendipine, enalapril, and/or hydrochlorothiazide, whereas in the active treatment group these proportions were 70.2%, 35.4%, and 18.4%, respectively. Compared with the controls, long-term antihypertensive therapy reduced the risk of dementia by 55%, from 7.4 to 3.3 cases per 1000 patient-years (43 vs 21 cases, \( P < .001 \)). After adjustment for sex, age, education, and entry blood pressure, the relative hazard rate associated with the use of nitrendipine was 0.38 (95% confidence interval, 0.23-0.64; \( P < .001 \)). Treatment of 1000 patients for 5 years can prevent 20 cases of dementia (95% confidence interval, 7-33).

Conclusion: The extended follow-up of Syst-Eur patients reinforces the evidence that blood pressure–lowering therapy initiated with a long-acting dihydropyridine protects against dementia in older patients with systolic hypertension.

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Hypertension is associated with increased risk of both vascular dementia and Alzheimer disease.\(^1,2\) In view of the increasing longevity of populations worldwide, prevention of dementia has turned into a major public health challenge.\(^3\) In the patients randomized in the double-blind Systolic Hypertension in Europe (Syst-Eur) trial, we observed that antihypertensive therapy, compared with placebo, reduced the incidence of dementia by 50%, from 7.7 to 3.8 cases per 1000 patient-years (21 vs 11 cases, \( P = .05 \)).\(^4\) However, Collins and MacMahon\(^5\) suggested that our estimates of benefit were of limited value, largely because the number of incident cases in the two treatment groups combined was only 32.

On February 14, 1997, the Syst-Eur trial was terminated early, because at the second interim analysis significant benefit was reached with respect to stroke, the primary end point.\(^6\) However, for a variety of ethical and scientific reasons,\(^7\) we decided to extend the Syst-Eur trial into an open-label, active-treatment follow-up study in the same population and based on the original active study medication (Syst-Eur 2). To review our initial estimates of benefit,\(^8\) we also continued the Vascular Dementia Project.\(^8\) In the present article, we have updated the incidence rates of dementia in Syst-Eur patients, whose blood pressure was actively...
lowered from randomization compared with those who received active treatment only since the start of Syst-Eur 2.

**SUBJECTS AND METHODS**

Ethics committees of the University of Leuven, Leuven, Belgium, and the participating centers approved the protocol of the Syst-Eur study. Eligible patients had no dementia, were at least 60 years old, and had a sitting systolic blood pressure ranging from 160 to 219 mm Hg, with diastolic blood pressure below 95 mm Hg. The patients were randomized to active treatment or placebo. Active treatment started with the dihydropyridine calcium channel blocker nitrrendipine (10-40 mg/d), which could be combined with or replaced by enalapril maleate (5-20 mg/d), hydrochlorothiazide (12.5-25 mg/d), or both second-line drugs. In the placebo group, matching placebos were used in a similar way. However, after the double-blind trial had stopped, patients originally allocated placebo were offered the same active treatment sequence as the other patients. The study drugs were stepwise titrated and/or combined to reduce the sitting systolic blood pressure by 20 mm Hg or more to a level below 130 mm Hg.

Syst-Eur investigators opting to take part in the dementia project had to screen all their patients for cognitive impairment at baseline and at annual follow-up visits, using the Mini-Mental State Examination (MMSE). Sequential diagnostic procedures to establish the presence and cause of dementia were started if the MMSE score was 23 or less, if symptoms reported by the patients or their relatives or clinical signs suggested cognitive impairment, or if for any reason a planned MMSE questionnaire had not been administered. The diagnosis of dementia relied on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R), which when Syst-Eur began in 1988 was the generally accepted standard. If the DSM-III-R criteria confirmed the diagnosis of dementia, the modified ischemic score, including brain imaging by computed tomography (CT), served to differentiate vascular from degenerative disease. If a CT scan could not be performed, the Hachinski score replaced the modified ischemic score to establish the cause of dementia. A blinded review board validated all cases of dementia, and an independent blinded neuroradiologist reviewed the CT scans. To evaluate the functional status of the patients, the Index of Independence in Activities of Daily Living (ADL score) was recorded at randomization and thereafter at yearly intervals.

Stroke was the primary end point in the Syst-Eur trial. This disorder was defined as a neurologic deficit with symptoms continuing for more than 24 hours or leading to death with no other cause than vascular. The Endpoint Committee, which was unaware of a patient’s treatment status, ascertained all stroke cases by reviewing the patients’ files and other source documents, by requesting detailed written information from the investigators, or by both approaches. Transient ischemic attack was defined as focal cerebral dysfunction lasting for less than 24 hours. Physicians who were unaware of the treatment group status checked the diagnosis of transient ischemic attack at the coordinating office.

Database management and statistical analysis were performed with SAS statistical software, version 8.01 (SAS Institute Inc, Cary, NC). Means and medians were compared by the standard normal z test and Wilcoxon 2-sample test and proportions by the χ² statistic. The incidence of dementia was analyzed by means of Kaplan-Meier survival function estimates and the log-rank test. Covariates associated with the risk of dementia were identified using single and multiple Cox regression.

At 106 centers in 19 European countries, 3228 patients were enrolled. However, 9 patients already had dementia at baseline, whereas in 59 patients cognitive impairment could not be excluded (Figure 1). On December 1, 2000, a follow-up examination was planned but had not yet taken place in 258 patients. Thus, the number of patients included in the present analysis was 2902 (Figure 1). At randomization, the patients of the former placebo (n=1417) and active treatment (n=1485) groups had similar characteristics. Median age at randomization was 68 years (range, 60-92 years). Mean±SD body mass index (calculated as weight in kilograms divided by the square of height in meters) averaged 26.6±3.2 in 984 men and 27.3±4.4 in 1918 women. A total of 764 patients (26.3%) had previous cardiovascular complications. In addition, 17 patients randomized to placebo (1.2%) and 20 of the active treatment group (1.3%) had a history of stroke. Mean±SD age when leaving school was 16.7±4.5 years.

The number of patient-years of follow-up was 5849 in the former placebo group and 6359 in the patients initially allocated active treatment. Overall, median follow-up from randomization was 3.9 years (interquartile range [IQR], 2.8-5.6 years). Table 1 shows treatment status at the last follow-up visit by randomization group. The proportion of patients who remained untreated was larger in the control group than in the patients allocated active treatment (25.2% vs 3.0%, P<.001), because 277 control patients (19.5%) were taking only double-blind placebo medication. At the last visit, blood pressure of the control patients averaged 156.1±12.0 mm Hg systolic and 82.5±6.0 mm Hg diastolic. In the patients randomized to active treatment, these levels were 149.1±9.7

**RESULTS**

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mm Hg and 79.4±6.1 mm Hg, respectively. During the entire follow-up, the net baseline-subtracted between-group differences (P<.001) were 7.0 mm Hg systolic (95% confidence interval [CI], 6.2-7.8 mm Hg) and 3.2 mm Hg diastolic (95% CI, 2.8-3.6 mm Hg). At 8 years, these differences remained significant (P<.01, Figure 2), averaging 4.2 mm Hg systolic (95% CI, 1.5-6.9 mm Hg) and 2.9 mm Hg diastolic (95% CI, 1.5-4.4 mm Hg).

There were 64 incident cases of dementia (Table 2). The diagnosis relied on the DSM-III-R.

Table 1. Number of Patients at Last Follow-up Visit*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (n = 1417)</th>
<th>Active Group (n = 1485)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study phase</td>
<td></td>
<td></td>
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<tr>
<td>Double-blind follow-up in Syst-Eur 1</td>
<td>287</td>
<td>292</td>
</tr>
<tr>
<td>Open follow-up in Syst-Eur 1</td>
<td>194</td>
<td>58</td>
</tr>
<tr>
<td>Open follow-up in Syst-Eur 2</td>
<td>1012</td>
<td>1126</td>
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<tr>
<td>Nonsupervised open follow-up</td>
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<td>9</td>
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<td>Antihypertensive treatment</td>
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<td></td>
</tr>
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<td>Active study medication only</td>
<td>751</td>
<td>1201</td>
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<tr>
<td>Other antihypertensive drugs</td>
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</tr>
<tr>
<td>Double-blind placebo treatment</td>
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<tr>
<td>Untreated</td>
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<td>44</td>
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<tr>
<td>Treatment unknown</td>
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<td>48</td>
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<tr>
<td>Antihypertensive drugs†</td>
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<td></td>
</tr>
<tr>
<td>Nitrendipine only</td>
<td>372</td>
<td>627</td>
</tr>
<tr>
<td>Nitrendipine</td>
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<td>1042</td>
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<tr>
<td>Enalapril maleate</td>
<td>374</td>
<td>526</td>
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<tr>
<td>Hydrochlorothiazide</td>
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<td>273</td>
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</table>

*Syst-Eur indicates Systolic Hypertension in Europe.
†Because many patients were undergoing combined drug treatment, numbers do not total.

Table 2. Origin of Dementia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>Active Group</th>
<th>All Participants</th>
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</thead>
<tbody>
<tr>
<td>No. of incident cases</td>
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<td></td>
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<tr>
<td>All causes</td>
<td>43</td>
<td>21</td>
<td>64</td>
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<td>Alzheimer dementia</td>
<td>29</td>
<td>12</td>
<td>41</td>
</tr>
<tr>
<td>Mixed or vascular dementia*</td>
<td>12</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Origin unknown</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Rate, per 1000 patient-years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>7.4</td>
<td>3.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Alzheimer dementia</td>
<td>5.0</td>
<td>1.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Mixed or vascular dementia*</td>
<td>2.1</td>
<td>1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Origin unknown</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*The cause of dementia was likely to be vascular in 4 control patients and 3 patients randomized to active treatment.

The overall incidence of dementia was 5.2 cases per 1000 patient-years (Table 2). Forty-three cases of dementia occurred in the control group, and 21 cases were observed in the patients randomized to active treatment. Thus, the incidence of dementia decreased by 55% (95% CI, 24%-73%) with long-term active treatment compared with the control group (3.3 vs 7.4 cases per 1000 patient-years, P<.001, Figure 3). The incidence of Alzheimer disease and mixed or vascular dementia was reduced (Table 2). At the rate observed in the control group, 1000 patients would have to be treated for 5 years to prevent 20 new cases (95% CI, 7-33 cases). The median MMSE score at baseline was 29 (IQR, 27-30) in both treatment groups (P=.94). Subsequent changes in the MMSE score were also similar in the control and active treatment groups (Table 3).

At the last visit, ADL scores had been recorded for 60 patients with dementia (control, 41; active treatment, 19) and 2815 participants without dementia (control, 1364; active treatment, 1451). The median score was 6 (IQR, 6-6; range, 0-6). Within the groups of patients with and without dementia, there were no differences at
the last visit between the 2 treatment arms in the distributions of the ADL scores ($P > .68$). However, at both entry and the last follow-up visit, the distributions of the ADL scores were shifted toward lower values in patients with dementia compared with those without dementia. At entry, a score of less than 6 (maximum) was observed in 3% of patients with dementia but only in 1% of the participants without dementia ($P < .001$). At the last visit, these proportions were 42% and 4%, respectively ($P < .001$).

In stepwise Cox regression, the risk of dementia increased with age and diastolic blood pressure at baseline. It was lower in more educated patients and men. The mutually adjusted relative hazard rates were 2.10 (95% CI, 1.76-2.50; $P < .001$) for a 5-year increase in age, 1.39 (95% CI, 1.08-1.81; $P = .01$) for a 5-mm Hg increase in diastolic pressure, 0.88 (95% CI, 0.82-0.95; $P < .001$) for each additional year of education, and 0.53 (95% CI, 0.27-1.03; $P = .06$) for men compared with women. After adjustment for these covariables, the relative hazard rate associated with initial randomization to active treatment was 0.43 (95% CI, 0.25-0.74), which was statistically significant ($P = .003$), whereas the hazard rate for systolic blood pressure at baseline was nonsignificant (1.07 for a 10-mm Hg increase; 95% CI, 0.84-1.36; $P = .58$). Pulse pressure did not significantly predict the risk of dementia. The unadjusted and adjusted relative hazard rates associated with an increase in the daily dose by one tablet (20 mg) were 0.37 (95% CI, 0.23-0.61; $P < .001$) and 0.48 (95% CI, 0.29-0.78; $P = .003$), respectively.

In comparison with our earlier report, the present analysis provides a more precise estimate of the potential of antihypertensive treatment to prevent dementia, because the number of incident cases and the years of follow-up doubled. Antihypertensive therapy starting with the dihydropyridine calcium channel blocker nitrendipine reduced the incidence of dementia by 55%. By inference, treating 1000 patients for 5 years can prevent 20 cases of dementia. Thus, the present analysis demonstrates a high degree of consistency with our previous estimate of 19 prevented cases per 5000 patient-years of antihypertensive treatment.

We observed that long-term antihypertensive treatment decreased the incidence of Alzheimer disease and vascular or mixed dementia. Our initial working hypothesis was that treatment of hypertension would protect mainly against vascular dementia. However, recent prospective studies suggest that hypertension and, more generally, all risk factors involved in arteriosclerosis may contribute to the incidence of degenerative dementias as well. There is a growing awareness that the distinction between Alzheimer disease and vascular dementia is less clear than initially envisaged, both conditions sharing similar mechanisms and lesions albeit to different degrees. In practical terms, it is therefore expedient in prospective clinical trials, such as Syst-Eur, to consider dementia as one clinical entity. In keeping with some but not all studies, men had a lower risk of dementia than women. The Rotterdam Study showed no sex differences in the incidence of dementia up to a very old age. After 90 years of age, the incidence of Alzheimer disease was higher in women than men, whereas at all ages vascular dementia occurred more frequently in men than women.

Three longitudinal observational studies showed significant reductions in the incidence of dementia in routinely treated vs nontreated hypertensive patients. In contrast, the Systolic Hypertension in the Elderly Program and the Medical Research Council trial in older people.
adults failed to demonstrate any effect on cognition, despite differences in systolic/diastolic blood pressures between patients allocated placebo or active treatment, which averaged 11.5/4.1 mm Hg and 10.6/5.6 mm Hg, respectively. In both trials, diuretics or β-blockers were the first-line antihypertensive agents. Recently, the double-blind, placebo-controlled Perindopril Protection Against Recurrent Stroke Study trial demonstrated that among patients with a history of stroke or transient ischemic attack, blood pressure–lowering treatment reduced the risk of recurrent stroke by 28%. Of 6105 patients, 58% were randomized to dual treatment with perindopril erbumine and indapamide vs matching placebo, whereas the remainder were allocated monotherapy with perindopril or matching placebo. Unexpectedly, a prespecified subgroup analysis revealed marked heterogeneity of treatment effect sizes for stroke risk between participants who received combination therapy with perindopril plus indapamide and those who received single-drug therapy with perindopril alone. Combination therapy reduced blood pressure by 12/5 mm Hg and the risk of stroke by 43%, with similar benefits in hypertensive and nonhypertensive patients. Treatment with perindopril alone lowered blood pressure by 5/3 mm Hg but did not affect stroke recurrence. The 95% CI of the relative risk reduction ranged from −19% to 23%. With regard to cognitive function, only stroke-related dementia was reduced by approximately 50% in the group undergoing combined treatment with perindopril and indapamide. In the present study, benefit was predominantly attributable to the prevention of degenerative dementia rather than dementia occurring in association with cerebrovascular events, such as stroke or transient ischemic attack.

Some proponents of the use of the older drug classes speculated that in the Systolic Hypertension in the Elderly Program study differential dropout from the placebo and active treatment groups biased the cognitive and functional evaluations toward a null effect. Nevertheless, the observation that in randomized clinical trials blood pressure reduction induced by thiazides or β-blockers or the angiotensin II–converting enzyme inhibitor perindopril given in monotherapy failed to protect against cognitive impairment or dementia again raises the issue of the mechanism by which antihypertensive treatment may prevent dementia. In the present analysis, the between-group difference in blood pressure during the whole period of follow-up averaged 7/3 mm Hg and persisted until 8 years after randomization, when it was still 4/3 mm Hg. Thus, blood pressure lowering might explain the prevention of stroke. On the other hand, in the present study, the dihydropyridine calcium channel blocker nitrindipine was the mainstay of active treatment, and its use was associated with a dose-dependent reduction in the probability of dementia. Indeed, the risk declined by approximately 50% for every tablet of 20 mg taken per day.

Several reports suggest that calcium channel blockers may confer specific neuroprotection. In spontaneously hypertensive rats, nicardipine counteracted the neurodegenerative effects of high blood pressure over and above the antihypertensive action of this dihydropyridine compared with hydralazine. In vascular and degenerative dementias, the MMSE scores decreased less with the calcium channel blocker nimodipine compared with placebo. The aging brain loses its ability to regulate intracellular calcium, leading to a cascade of cellular impairments and ultimately to cell death. Alterations in calcium homeostasis are involved in the aging process of the brain and in the neuropathology of Alzheimer disease. In patients with degenerative dementia, β-amyloid may raise the concentration of intraneuronal free calcium and through this mechanism may sensitize the brain to neurotoxins, such as proinflammatory substances or pro-oxidants. The hypothesis of a possible central nervous action of dihydropyridines is also supported by the observation that these drugs cross the blood-brain barrier and reduce the turnover of monoamine neurotransmitters, of which many are deficient in degenerative dementias. Nitrindipine binding in the rat brain also occurs mainly at those sites that are primarily affected by Alzheimer disease, such as the superficial cortex, thalamus, and hippocampus, and not in areas with low synaptic density.

Selective recruitment of relatively healthy patients who accepted long-term follow-up in a double-blind trial is likely to explain the high MMSE scores at entry into the Syst-Eur trial. During follow-up, the changes in the MMSE scores were similar in the control and active treatment groups and the incidence of dementia was low (7.4 cases per 1000 patient-years in the control group) in comparison with population-based studies. Indeed, among elderly patients (≥65 years) enrolled in the EURODEM Study, 528 cases of dementia occurred during 28768 person-years of follow-up (rate, 18.4 cases per 1000 person-years). In the present study, patients in the control group were also given blood pressure–lowering therapy after termination of the double-blind trial. Early cognitive disorder may lead to less compliance to therapy. The direction of all these biases would be to reduce the protective effect of the intervention. Thus, our current findings, however favorable, probably underestimate the potential of preventing dementia by blood pressure–lowering therapy.

In conclusion, the reduction by 55% of the incidence of dementia by antihypertensive drug treatment based on the dihydropyridine calcium channel blocker nitrindipine as the first-line drug may have important public health implications. In view of the increasing longevity of populations worldwide, dementia is a leading cause of disability among all races and continents. At the rate observed in the Syst-Eur control group, treating 1000 hypertensive patients for 5 years can prevent 20 cases of dementia, a benefit that is likely to be even larger in unselected hypertensive patients who experience a higher risk of dementia. Our present findings are in line with those of recent overviews of the actively controlled outcome trials in hypertension, which suggested that calcium channel blockers might provide better protection against stroke than treatment based on diuretics and β-blockers. In view of the growing body of evidence that vascular factors increase the risk of degenerative dementia, we already called for a prospective face-to-face comparison of a long-acting calcium chan-
Current uncertainty, which weighed against the initiation of antihypertensive treatment, in the prevention of cognitive impairment. This would resolve the suffering and societal and economical losses caused by dementia is simply unacceptable.

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REFERENCES


Although this is by no means a rigorously controlled study, it should help alleviate the concerns of physicians who may be reluctant to use an ARB in such patients, despite anticipated benefits.

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Haralambos Gavras, MD, FRCP
Boston, Mass

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Correction

Error in Figure. In the Original Investigation by Forette et al titled “The Prevention of Dementia With Antihypertensive Treatment: New Evidence From the Systolic Hypertension in Europe (Syst-Eur) Study,” published in the October 14, 2002, issue of the ARCHIVES (2002;162:2046-2052), an error occurred in Figure 2 on page 2048. In the key to that figure, patients randomized to placebo should have been indicated with open circles and those allocated to active treatment, with closed circles. The corrected figure is reprinted here. The journal regrets the error.

Figure 2. Average sitting systolic and diastolic blood pressure at randomization and during follow-up. For each mean value, the number of patients is given.