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Di Bari, M.; Pahor, M.; Franse, L.V.; Shorr, R.I.; Wan, J.Y.; Ferrucci, L.; Somes, G.W.; Applegate, W.B.

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# Dementia and Disability Outcomes in Large Hypertension Trials: Lessons Learned from the Systolic Hypertension in the Elderly Program (SHEP) Trial

Mauro Di Bari,[1] Marco Pahor,[2] Lonneke V. Franse,[3] Ronald I. Shorr,[3] Jim Y. Wan,[3] Luigi Ferrucci,[4] Grant W. Somes,[3] and William B. Applegate[5]

In the Systolic Hypertension in the Elderly Program (SHEP) trial (1985–1990), active treatment reduced the incidence of cardiovascular events, but not that of dementia and disability, as compared with placebo. This study aims to evaluate if assessment of cognitive and functional outcomes was biased by differential dropout. Characteristics of subjects who did or did not participate in follow-up cognitive and functional evaluations were compared. The relative risks of incident cognitive impairment and disability were assessed in the two treatment groups, with the use of the reported findings and under the assumption that the proportions of cognitive and functional impairment among dropouts increased. Assignment to the placebo group and the occurrence of cardiovascular events independently predicted missed assessments. From the reported findings, the risk of cognitive and functional impairment was similar between the two treatment groups. However, when 20–30% and 40–80% of the subjects who missed the assessment were assumed to be cognitively and, respectively, functionally impaired, assignment to active treatment reduced the risk of these outcomes. In the SHEP, the cognitive and functional evaluations were biased toward the null effect by differential dropout. This might have obscured the appraisal of a protective effect of treatment on the cognitive and functional decline of older hypertensive adults. *Am J Epidemiol* 2001;153:72–8.

bias (epidemiology); clinical trials; dementia; disability evaluation; hypertension

Physical functioning and cognition are important determinants of the ability to live independently in the community and of quality of life in old age (1–3). The need for care and the utilization of resources increase dramatically in the presence of disability and dementia, which are therefore major causes of health-related expenditure in aging populations (4). Thus, preservation of functional and cognitive abilities is a compelling outcome of therapeutic interventions in the elderly, which must be directly measured with the appropriate instruments set up in geriatric medicine (5).

Treatment of hypertension has been clearly shown to prevent severely disabling cardiovascular events in older adults, such as stroke, myocardial infarction, and congestive heart failure (6–9). Hypertension has been associated with cognitive decline (10–12) and, therefore, treatment of hypertension can be expected to reduce the incidence of both physical disability and dementia in the elderly. Yet, the effectiveness of treatment on these outcomes has been rarely reported or seemed negligible in published studies, even when active treatment achieved a substantial benefit on mortality and morbidity (6, 13).

Only recently the vascular dementia project of the Systolic Hypertension in Europe (Syst-Eur) trial reported a significantly lower incidence of dementia in participants assigned to an active treatment based on nitrendipine, as compared with placebo (14). Conversely, the Systolic Hypertension in the Elderly Program (SHEP) (6, 15) and the Medical Research Council (13) trials failed to find any significant difference in the incidence of cognitive decline between participants receiving active treatment (low-dose diuretic and/or β-blocker) and those receiving placebo. It is debated whether these discordant findings are explained by the type of antihypertensive agents being used or by other factors, such as the impact of missing data and loss to follow-up on outcome assessment (16). Because selective loss to follow-up can profoundly affect the findings of a trial, we have reassessed the SHEP trial and performed sensitivity analyses to evaluate whether the effects of the intervention on cognitive and functional status have been biased by a differential dropout during the follow-up in the two treatment groups.

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Abbreviations: SHEP, Systolic Hypertension in the Elderly Program; short-CARE, short-Comprehensive Assessment and Referral Evaluation.

[1] Department of Gerontology and Geriatrics, University of Florence, and Azienda Ospedaliera "Careggi," Florence, Italy.
[2] Sticht Center on Aging, Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, NC.
[3] Department of Preventive Medicine, University of Tennessee, Memphis, TN.
[4] Geriatric Department, Ospedale "I Fraticini," Florence, Italy.
[5] Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, NC.
Correspondence to Dr. Marco Pahor, Department of Internal Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157 (e-mail: mpahor@wfubmc.edu).

## MATERIALS AND METHODS

### Design and participants

The SHEP was a multicenter, randomized, placebo-controlled, clinical trial. The methods have been described in detail elsewhere (6). Briefly, persons aged ≥60 years were screened from the community in 16 clinical centers for the presence of isolated systolic hypertension. After two baseline evaluations, 4,736 participants were recruited and followed for 5 years. The blood pressure inclusion criteria were a seated systolic blood pressure of 160–219 mmHg and a diastolic blood pressure of <90 mmHg, assessed as the average of four measurements in two visits. Exclusion criteria were a systolic blood pressure of ≥220 mmHg, recent myocardial infarction or stroke, or the presence of a major illness such as cancer, alcoholic liver disease, renal failure, insulin-treated diabetes, and depression. The primary endpoint of the trial was combined fatal and nonfatal stroke, whereas secondary endpoints were myocardial infarction, fatal coronary disease, and major cardiovascular morbidity and mortality.

The participants were randomized to active treatment or placebo. A systolic blood pressure of <160 mmHg or at least 20 mmHg lower than baseline was the treatment goal. A stepped care approach was used in the active treatment group. The step 1 drug was chlorthalidone, 12.5–25 mg/day. The step 2 drugs were atenolol, 25 mg/day, or reserpine, 0.05 mg/day, if atenolol was not tolerated. A matching placebo was administered to participants in the control group, in a double-blind fashion.

### Cognitive and functional assessment

The short-Comprehensive Assessment and Referral Evaluation (short-CARE) (17), Center for Epidemiologic Studies-Depression Scale (18), Activity of Daily Living (19), and Social Network Questionnaires (20) were used for behavioral evaluation. The present study focuses on the screening of disability and cognitive impairment, which was carried out with the short-CARE. (15).

As a rule, behavioral evaluations were administered at baseline and semiannually thereafter, and they were anticipated to the next quarterly visit if the participant reached or exceeded a clinical cutpoint on either the dementia or the depression scales, or if the SHEP drugs were modified. Behavioral evaluation during the follow-up was usually joined to the collection of core clinical data (events, blood pressure measurement).

The dementia score enumerated the errors on the cognitive component of the short-CARE questionnaire. A score of ≥4, in a range from 0 to 9, was the cutoff for a positive screening. Participants who screened positive on two consecutive visits were referred for clinical evaluation, which will not be considered in this analysis. Basic Activity of Daily Living disability was present if the participant reported difficulty or need for help in at least one of the following: walking in the house, bathing, grooming, dressing, eating, transferring from bed to chair, and using the toilet (15).

### Analytical procedure

In the present study, we defined eligibility for cognitive and functional assessments during the follow-up on the basis of the vital status at each expected annual visit. An assessment was missing if a participant was alive but had received no annual or quarterly behavioral assessment at the expected annual visit (±6 months).

Sex, age, race, years of formal education, and the occurrence of major nonfatal cardiovascular events (stroke, myocardial infarction, heart failure, coronary artery by-pass surgery) before the expected annual follow-up visits were compared between participants who did and did not miss functional and cognitive assessments. Age and years of education were dichotomized according to the median (71 and 12 years, respectively). Bivariate and multivariate associations with the outcome of a missed assessment were tested with the $\chi^2$ test and logistic regression analysis.

From the reported findings, relative risks and 95 percent confidence intervals for an abnormal (≥4) cognitive score and for disability in the active treatment versus the placebo group at each annual assessment were compared, after exclusion of those with dementia or disability at baseline. Moreover, to evaluate the potential effect of missing data on risk estimates, the relative risks were recalculated, assuming a 20 percent, 25 percent, and 30 percent proportion having an abnormal cognitive score and a 40 percent, 60 percent, and 80 percent proportion having disability among those who missed the assessment (sensitivity analyses). These proportions were selected to obtain estimated overall incidences of cognitive impairment and disability, after 1 year of follow-up, comparable to published data. Depending on the screening instrument used, previous studies on the cognitive impairment of older adults reported incidence values in a very broad range. For the purpose of this study, the 11.4 percent annual incidence reported by Brayne et al. (21) was considered a meaningful comparison. As far as disability is concerned, a 9–10 percent annual incidence of Basic Activity of Daily Living disability has been reported in unselected home dwellers in a similar age range (22). Participants who became disabled or, respectively, cognitively impaired during the follow-up were not excluded from sensitivity analyses in each of the subsequent annual assessments.

An SPSS for Windows 8.0 package (SPSS, Inc., Chicago, Illinois) was used for analysis. Mean values are expressed as the mean and standard error. A two-tailed $p$ value of less than 0.05 was considered statistically significant.

## RESULTS

Participants in the active treatment and the placebo groups had comparable characteristics at baseline (6). Those who missed either cognitive or functional assessments during the follow-up tended to be older, less educated, and non-Whites as compared with those who were assessed (tables 1 and 2). These differences were more evident at the first annual visit and blunted in following years. Furthermore, participants who missed the assessments were more likely to be in the placebo group and had a higher occurrence of non-

**TABLE 1. Proportion of participants who missed annual dementia assessments, according to age, sex, race, education, treatment assignment, and occurrence of nonfatal cardiovascular events before each annual visit, Systolic Hypertension in the Elderly Program, 1985–1990**

| | Year 1 | | | Year 2 | | | Year 3 | | | Year 4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | *p* value | No. | % | *p* value | No. | % | *p* value | No. | % | *p* value |
| Age | | | | | | | | | | | | |
| ≤71 years | 135 | 5.5 | 0.000 | 199 | 8.2 | 0.026 | 216 | 9.0 | 0.002 | 232 | 14.0 | 0.035 |
| >71 years | 178 | 8.1 | | 218 | 10.2 | | 246 | 11.8 | | 253 | 16.7 | |
| Sex | | | | | | | | | | | | |
| Male | 116 | 5.8 | 0.026 | 160 | 8.1 | 0.047 | 182 | 9.5 | 0.119 | 197 | 15.2 | 0.812 |
| Female | 197 | 7.4 | | 257 | 9.8 | | 280 | 10.9 | | 288 | 15.3 | |
| Race | | | | | | | | | | | | |
| White | 226 | 6.1 | 0.002 | 305 | 8.4 | 0.001 | 353 | 10.0 | 0.124 | 386 | 15.3 | 0.998 |
| Non-White | 87 | 9.0 | | 112 | 11.8 | | 109 | 11.7 | | 99 | 15.3 | |
| Education* | | | | | | | | | | | | |
| >12 years | 68 | 4.7 | 0.000 | 98 | 6.9 | 0.001 | 120 | 8.7 | 0.018 | 128 | 13.5 | 0.066 |
| ≤12 years | 243 | 7.6 | | 317 | 10.0 | | 339 | 11.0 | | 356 | 16.1 | |
| Treatment group | | | | | | | | | | | | |
| Active | 118 | 5.1 | 0.000 | 161 | 7.0 | 0.000 | 193 | 8.6 | 0.000 | 219 | 13.8 | 0.017 |
| Placebo | 195 | 8.4 | | 256 | 11.2 | | 269 | 12.0 | | 266 | 16.8 | |
| Nonfatal event | | | | | | | | | | | | |
| No | 274 | 6.2 | 0.000 | 361 | 8.4 | 0.000 | 388 | 9.4 | 0.000 | 400 | 14.0 | 0.000 |
| Yes | 39 | 18.9 | | 56 | 19.8 | | 74 | 20.6 | | 85 | 26.8 | |
| Total | | | | | | | | | | | | |
| Not assessed | 313 | | | 417 | | | 462 | | | 485 | | |
| Assessed | 4,348 | | | 4,171 | | | 4,015 | | | 2,689 | | |

* Information on education was missing in 13, 12, 11, and 7 participants in annual visits 1, 2, 3, and 4, respectively.

fatal cardiovascular events before each follow-up visit, in both bivariate (tables 1 and 2) and multivariate (table 3) analyses. Assignment to treatment group, entered into logistic regression models together with age, gender, race, and education, proved to be a significant predictor of a missed dementia or disability assessment. Occurrence of a nonfatal cardiovascular event during the follow-up, added in a further step of the logistic analysis, significantly contributed to the prediction of the outcome. Thus, both of these variables were retained in the final logistic models (table 3). When the occurrence of nonfatal events was entered into the logistic models, the percent change in the value of the β coefficients for treatment assignment was 7.0, 7.7, 11.0, and 19.3 percent from year 1 to year 4, respectively, for dementia assessment and 6.6, 5.8, 8.3, and 15.5 percent from year 1 to year 4, respectively, for disability assessment.

### Dementia assessment

From the reported findings, the cumulative incidence of a clinically relevant cognitive decline, in follow-up years 1–4, was 0.3, 0.4, 0.8, and 0.9 percent in the active treatment group and 0.3, 0.4, 1.0, and 1.3 percent in the placebo group, respectively. In sensitivity analyses in which 20 percent, 25 percent, or 30 percent of the participants who missed the behavioral assessment had an abnormal cognitive score, the active treatment significantly decreased the risk of a score of ≥4, at least in years 1–3 of follow-up (figure 1). In these scenarios, the overall incidence of a cognitive score of ≥4 ranged from 1.7 percent to 2.4 percent in year 1, up to a 4.3–5.8 percent range in year 4.

### Disability assessment

From the available data and considering only the participants who were not disabled at baseline (active treatment, $n = 2{,}246$; placebo, $n = 2{,}210$), the cumulative incidence of Basic Activity of Daily Living disability in follow-up years 1–4 was 3.5, 5.0, 6.8, and 7.4 percent in the active treatment and 3.8, 5.1, 6.8, and 8.6 percent in the placebo group, respectively (figure 2). In sensitivity analyses, data were imputed to adjust for the selective dropout in the placebo group according to different scenarios. With a proportion of disability ranging from 40 percent to 80 percent among participants who missed the assessment, the active treatment significantly decreased the overall incidence of disability in the follow-up (figure 2). In these scenarios, the overall incidence of disability ranged from 6.6 percent to 9.8 percent in year 1, up to a 12.2–17.3 percent range in year 4.

## DISCUSSION

Previous analyses from the SHEP reported that antihypertensive treatment did not affect the incidence of dementia and disability in elderly participants with isolated systolic hypertension (6, 15). Both active treatment and placebo

**TABLE 2. Proportion of participants free from disability at baseline who missed annual disability assessments, according to age, sex, race, education, treatment assignment, and occurrence of nonfatal cardiovascular events before each annual visit, Systolic Hypertension in the Elderly Program, 1985–1990**

| | Year 1 | | | Year 2 | | | Year 3 | | | Year 4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | *p* value | No. | % | *p* value | No. | % | *p* value | No. | % | *p* value |
| Age | | | | | | | | | | | | |
| ≤71 years | 166 | 6.9 | 0.008 | 228 | 9.7 | 0.082 | 248 | 10.7 | 0.033 | 191 | 11.8 | 0.060 |
| >71 years | 184 | 9.1 | | 224 | 11.3 | | 245 | 12.8 | | 198 | 14.1 | |
| Sex | | | | | | | | | | | | |
| Male | 139 | 7.1 | 0.067 | 190 | 9.9 | 0.318 | 211 | 11.3 | 0.550 | 154 | 12.1 | 0.299 |
| Female | 211 | 8.6 | | 262 | 10.8 | | 282 | 11.9 | | 235 | 13.4 | |
| Race | | | | | | | | | | | | |
| White | 253 | 7.2 | 0.000 | 333 | 9.6 | 0.001 | 374 | 11.1 | 0.030 | 308 | 12.7 | 0.593 |
| Non-White | 97 | 10.8 | | 119 | 13.5 | | 119 | 13.7 | | 81 | 13.5 | |
| Education* | | | | | | | | | | | | |
| >12 years | 77 | 5.6 | 0.000 | 108 | 8.0 | 0.001 | 121 | 9.2 | 0.001 | 108 | 11.8 | 0.241 |
| ≤12 years | 271 | 8.9 | | 342 | 11.5 | | 370 | 12.7 | | 280 | 13.4 | |
| Treatment group | | | | | | | | | | | | |
| Active | 141 | 6.3 | 0.000 | 177 | 8.1 | 0.000 | 212 | 9.9 | 0.001 | 177 | 11.6 | 0.036 |
| Placebo | 209 | 9.6 | | 275 | 12.8 | | 281 | 13.3 | | 212 | 14.2 | |
| Nonfatal event | | | | | | | | | | | | |
| No | 313 | 7.4 | 0.000 | 400 | 9.8 | 0.000 | 426 | 10.9 | 0.000 | 328 | 12.1 | 0.000 |
| Yes | 37 | 19.4 | | 52 | 19.8 | | 67 | 19.9 | | 61 | 20.1 | |
| Total | | | | | | | | | | | | |
| Not assessed | 350 | | | 452 | | | 493 | | | 389 | | |
| Assessed | 4,059 | | | 3,892 | | | 3,747 | | | 2,629 | | |

* Information on education was missing in 10 participants at annual follow-up visits 1 through 3 and in seven participants in annual visit 4.

groups, indeed, showed only a modest trend toward deterioration of some measures of physical functioning and cognitive status during the follow-up. Changes in these measures from baseline were comparable between the two groups and, overall, active treatment did not reduce the incidence of disability (15) or the proportion of participants who qualified for dementia evaluation (6). The present study indicates that, in the SHEP, a differential loss of data for participants in the active treatment and the placebo groups could have biased the analysis of the functional and cognitive effects of treatment. In fact, the assignment to placebo and the occurrence of a nonfatal cardiovascular event, added sequentially in logistic models, were both associated with attrition to cognitive and physical functioning assessments, independently of possible confounders such as age, race, gender, and education (table 3). Yet, the treatment group assignment and the occurrence of nonfatal cardiovascular events should probably not be considered as true independent variables, since nonfatal events likely lie in the pathogenetic pathway between uncontrolled high blood pressure and either demen-

**TABLE 3. Odds ratio (OR) and 95% confidence interval (CI) of missed dementia and disability assessments for those who experienced nonfatal cardiovascular events and for treatment assignment for missed dementia and disability assessments, adjusted for age, sex, race, and education, Systolic Hypertension in the Elderly Program, 1985–1990**

| | Year 1 | | Year 2 | | Year 3 | | Year 4 | |
|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Outcome of missed dementia assessment | | | | | | | | |
| Treatment (active vs. placebo) | 0.6 | 0.5, 0.8 | 0.6 | 0.5, 0.8 | 0.7 | 0.6, 0.9 | 0.8 | 0.7, 1.0 |
| Cardiovascular events (yes vs. no) | 3.4 | 2.3, 5.0 | 2.6 | 1.9, 3.5 | 2.4 | 1.8, 3.2 | 2.2 | 1.7, 2.9 |
| Outcome of missed disability assessment | | | | | | | | |
| Treatment (active vs. placebo) | 0.7 | 0.5, 0.8 | 0.6 | 0.5, 0.7 | 0.7 | 0.6, 0.9 | 0.8 | 0.7, 1.0 |
| Cardiovascular events (yes vs. no) | 2.9 | 2.0, 4.3 | 2.1 | 1.5, 3.0 | 1.9 | 1.5, 2.6 | 1.8 | 1.3, 2.4 |

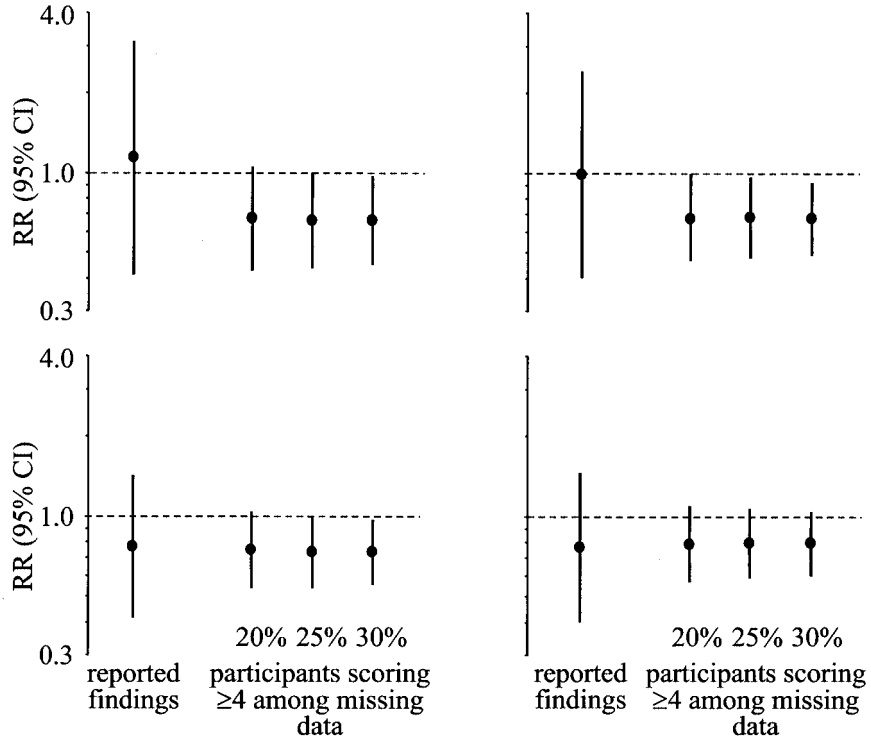


**FIGURE 1.** Relative risk (RR) and 95% confidence interval (CI) of cognitive impairment in the active treatment versus placebo groups in the first 4 years of follow-up, calculated with actual data and sensitivity analyses, Systolic Hypertension in the Elderly Program, 1985–1990. In separate scenarios, 20%, 25%, and 30% of participants who missed a dementia assessment are assumed to have a cognitive score of ≥4, indicative of substantial cognitive impairment.

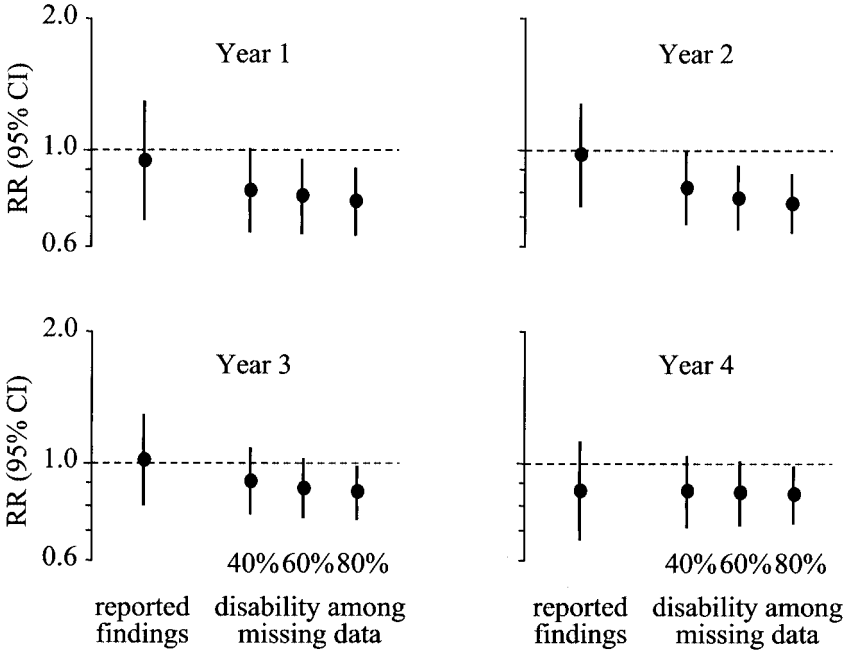


**FIGURE 2.** Relative risk (RR) and 95% confidence interval (CI) of disability in the active treatment versus placebo groups in the first 4 years of follow-up, calculated with actual data and sensitivity analyses, Systolic Hypertension in the Elderly Program, 1985–1990. In separate scenarios, 40%, 60%, and 80% of participants who missed a disability assessment experienced incident disability.

tia or disability. Indeed, the risk of cognitive impairment and disability is disproportionately high in association with conditions such as stroke (23, 24) or heart failure (25, 26).

As a consequence of this apparently selective attrition, the original analyses on the cognitive and functional outcomes of treatment in the SHEP trial were likely biased toward the null effect. A possible explanation for this differential dropout is that, in the SHEP, whereas retention to the basic clinical examination was very high, the behavioral assessment was frequently limited to those who were healthier and able to reach the study clinic. Therefore, many of those who had the outcomes of interest might have been missed.

Several consequences could be derived from this analysis, related both to the methodology of randomized clinical trials in geriatric medicine and to the specific issue of antihypertensive treatment in the elderly. First, before the results of a clinical trial are analyzed, the internal validity of the study population should be accurately checked at each step of the follow-up. Missing-at-random may only reduce the power of statistical comparison and therefore the strength of the association. Selective dropout associated with either the intervention or the outcome may lead to misleading conclusions, if the results of the trial rely only on data collected in those who were eventually assessed. Older, sicker, and physically or mentally impaired participants are more likely to be lost to follow-up, and this makes the conduction of clinical trials in the elderly a challenging task. On the other hand, the proportion of aged persons, who use most of the drugs currently marketed, is progressively increasing. Researchers are hence compelled to face the challenge of assessing the efficacy and safety of drugs in the elderly with the same rational approach as in younger individuals, by means of randomized clinical trials of adequate scope and methodology. The common, paradoxical practice of excluding elderly subjects from clinical trials of drugs largely used in patients at an advanced age has already been criticized (27, 28). The present study further indicates that the collection of data on cognitive impairment and disability cannot be reliably carried out with office visits, but rather requires accurate tracking of the participants and their evaluation at home or in long-term facilities.

Second, it is possible that the overall benefits of antihypertensive treatment in the elderly had been underestimated in most of the studies carried out so far. In fact, no previous study has carefully evaluated the impact of selective dropout on relevant clinical outcomes, such as disability and dementia. A significant difference in baseline demographic and clinical characteristics, as a function of the number of evaluations available, was acknowledged in the Medical Research Council trial ancillary study on dementia prevention, but a possible differential dropout, secondary to nonfatal events during the follow-up, was not taken into account (13). When these limitations are considered, the apparent lack of any beneficial effect of diuretics and β-blockers on the prevention of disability and dementia in the SHEP (6, 15) and in the Medical Research Council (13) trials should be seriously questioned.

We performed sensitivity analysis to speculate on the possible consequences of selective attrition on behavioral evaluation in the SHEP. More sophisticated techniques have been proposed to deal with "informative dropout" (29, 30), but unfortunately they could not be easily applied to the SHEP data. Our analytical approach has some limitations that must be carefully considered. Indeed, to depict appropriate scenarios of sensitivity analysis, we chose to obtain overall 1-year incidences of cognitive impairment and disability comparable with those reported in previous observational studies, or lower. Individuals enrolled in the SHEP were highly selected and healthier than the general population (31), but the increased risk for disabling cardiovascular events, due to their high blood pressure status, counterbalanced and probably offset a potentially decreased risk, typical of the "healthy volunteer" effect (32). Therefore, we believe that our estimates of incident disability do not overestimate the 9–10 percent annual incidence from observational studies (22). As far as the cognitive assessment is concerned, it should be recalled that a score of ≥4 on the short-CARE dementia questionnaire does not imply a formal diagnosis of dementia, but it is only indicative of a cognitive impairment of clinical significance, requiring further evaluation. Therefore, we compared the results of our sensitivity analyses with those of previous studies on screening for cognitive impairment in the elderly, rather than with data on incident dementia. Brayne et al. (21) reported that 26.5 percent of the subjects in the 75- to 79-year age range had a Mini-Mental State Examination score lower than 24 after a 28-month follow-up, with an average annual incidence of 11.4 percent (calculated from figure 3 of reference 24). In the Cardiovascular Health Study, a clinically significant decrease of 5 points in the Teng Mini-Mental State Examination was observed in 20.5 percent of 3,837 participants older than 65 years, followed up for 3 years (mean duration of follow-up not reported) (33). We must acknowledge that relevant differences do exist between the short-CARE questionnaire and the instruments used in these studies. For this reason, as well as for the different design and population, data from the SHEP and from observational studies on cognitive decline are difficult to compare. Nevertheless, these are probably the best possible comparisons, since we are not aware of published longitudinal studies of cognitive decline based on the short-CARE questionnaire. Furthermore, the incidence of cognitive impairment in our sensitivity analyses is generally lower than those previously reported and therefore still represents a conservative estimate.

Other possible sources of errors in this study should be mentioned, largely derived from limitations in the original SHEP protocol. First, it should be pointed out that the assessment of disability based on self-report is less reliable than the objective evaluation of physical performance, especially in patients with possible cognitive impairment. Finally, it should be emphasized that older adults with hypertension and cognitive impairment frequently show posterior cortical features, which are more extensively captured by specifically designed instruments rather than by common cognitive screening instruments, such as the short-CARE questionnaire (34).

Even with these limitations in mind, the present study shows adequate evidence of a selective dropout in the SHEP, which might have impaired the recognition of a benefit of

active treatment on both dementia and disability outcomes. If antihypertensive drugs can prevent these relevant clinical endpoints, this will strongly add to the overall benefits of treatment. Moreover, pharmacologic reduction of blood pressure might be able per se to reduce the incidence of dementia, independently of the specific agent used, as previous studies apparently suggested (14). With the progressively increasing age of the population, these hypotheses are clearly of crucial importance in clinical medicine and public health. Hence, they must be carefully evaluated with specifically designed investigations and appropriate methodology, well beyond the scope and possibilities of this limited reappraisal of an existing database.

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