The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2008 VOL. 358 NO. 18

Treatment of Hypertension in Patients 80 Years of Age or Older

Nigel S. Beckett, M.B., Ch.B., Ruth Peters, Ph.D., Astrid E. Fletcher, Ph.D., Jan A. Staessen, M.D., Ph.D., Lisheng Liu, M.D., Dan Dumitrascu, M.D., Vassil Stoyanovsky, M.D., Riitta L. Antikainen, M.D., Ph.D., Yuri Nikitin, M.D., Craig Anderson, M.D., Ph.D., Alli Belhani, M.D., Françoise Forette, M.D., Chakravarthi Rajkumar, M.D., Ph.D., Lutgarde Thijs, M.Sc., Winston Banya, M.Sc., and Christopher J. Bulpitt, M.D., for the HYVET Study Group*

ABSTRACT

BACKGROUND

Whether the treatment of patients with hypertension who are 80 years of age or older is beneficial is unclear. It has been suggested that antihypertensive therapy may reduce the risk of stroke, despite possibly increasing the risk of death.

METHODS

We randomly assigned 3845 patients from Europe, China, Australasia, and Tunisia who were 80 years of age or older and had a sustained systolic blood pressure of 160 mm Hg or more to receive either the diuretic indapamide (sustained release, 1.5 mg) or matching placebo. The angiotensin-converting–enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mm Hg. The primary end point was fatal or nonfatal stroke.

RESULTS

The active-treatment group (1933 patients) and the placebo group (1912 patients) were well matched (mean age, 83.6 years; mean blood pressure while sitting, 173.0/90.8 mm Hg); 11.8% had a history of cardiovascular disease. Median follow-up was 1.8 years. At 2 years, the mean blood pressure while sitting was 15.0/6.1 mm Hg lower in the active-treatment group than in the placebo group. In an intention-to-treat analysis, active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% confidence interval [CI], –1 to 51; P=0.06), a 39% reduction in the rate of death from stroke (95% CI, 1 to 62; P=0.05), a 21% reduction in the rate of death from any cause (95% CI, 4 to 35; P=0.02), a 23% reduction in the rate of death from cardiovascular causes (95% CI, –1 to 40; P=0.06), and a 64% reduction in the rate of heart failure (95% CI, 42 to 78; P<0.001). Fewer serious adverse events were reported in the active-treatment group (358, vs. 448 in the placebo group; P=0.001).

CONCLUSIONS

The results provide evidence that antihypertensive treatment with indapamide (sustained release), with or without perindopril, in persons 80 years of age or older is beneficial. (ClinicalTrials.gov number, NCT00122811.)

From Imperial College London (N.S.B., R.P., R.L.A., W.B., C.J.B.) and the London School of Hygiene and Tropical Medicine (A.E.F.) — both in London; the University of Leuven, Leuven, Belgium (J.A.S., L.T.); the Beijing Hypertension League Institute, Beijing (L.L.); Spitalul Judetean Cluj, Clinica Medicală 2, Cluj, Romania (D.D.); the National Transport Multi-Profile Hospital, Sofia, Bulgaria (V.S.); the University of Oulu, Oulu, Finland (R.L.A.); the State Scientific Research Institute of Internal Medicine, Novosibirsk, Russia (Y.N.); the George Institute for International Health, Sydney (C.A.); L'Etablissement Public de Santé Charles Nicolle, Service de Cardiologie, Tunis, Tunisia (A.B.); Hôpital Broca, University Paris V, Paris (F.F.); and the Brighton and Sussex Medical School, Brighton, United Kingdom (C.R.). Address reprint requests to Dr. Beckett at Care of the Elderly, Division of Medicine, Imperial College London, Du Cane Rd., London W12 ONN, United Kingdom.

*The committee members and investigators for the Hypertension in the Very Elderly Trial (HYVET) are listed in the Appendix.

This article (10.1056/NEJMoa0801369) was published at www.nejm.org on March 31, 2008.

N Engl J Med 2008;358:1887-98.

Copyright © 2008 Massachusetts Medical Society.

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

Blood-pressure reduction is effective in preventing stroke and other vascular events, including heart failure.[1] In the past decade, treatment benefits have appeared to be broadly consistent among a range of subpopulations and among antihypertensive agents.[2] However, as highlighted by earlier[3] and more recent[4] guidelines, evidence that treating patients 80 years of age or older is beneficial is inconclusive. Although the risk of stroke increases continuously with increasing blood pressures above approximately 115/75 mm Hg, the association of blood pressure and stroke attenuates with increasing age.[1] Epidemiologic population studies have consistently suggested that blood pressure and the risk of death are inversely related among people 80 years of age or older,[5-9] possibly reflecting increased risks of therapy for blood-pressure reduction or reverse causation due to conditions that may be associated with blood-pressure reduction (such as cancer, dementia, myocardial infarction, and heart failure).

A recent retrospective cohort analysis of patients 80 years of age or older with hypertension, of whom 84.5% were receiving antihypertensive medication, reported a shorter survival for those with systolic blood pressure levels below 140 mm Hg, even after adjustment for known predictors of death.[10] Randomized controlled trials involving older adults either have excluded those 80 years of age or older[11,12] or have recruited too few to show an advantage of treatment.[13-16] A meta-analysis of results regarding the treatment of hypertension specifically in this age group suggested that the benefit — a 36% reduction in the risk of stroke — might be offset by possible adverse effects, given a nearly significant increase, by 14%, in the risk of death from any cause ($P=0.05$).[17] These positive results were not robust, since addition of data from just one hypothetical, properly designed trial that showed no treatment effect would render the results not significant.

The results of the pilot study for the Hypertension in the Very Elderly Trial (HYVET)[18] were consistent with those from the meta-analysis. Both results suggest that treatment for hypertension was associated with a reduction in stroke but also a possible increase in death from any cause, such that for each stroke prevented, there was one death from a cause other than stroke. In the main HYVET study, we aimed to resolve persistent areas of clinical uncertainty about the relative benefits and risks of antihypertensive treatment in patients 80 years of age or older.

METHODS

The detailed protocol for HYVET has been published previously.[19] HYVET was a randomized, double-blind, placebo-controlled trial performed in 195 centers in 13 countries in Western and Eastern Europe, China, Australasia, and North Africa. Approval for the trial was obtained from the appropriate authorities and central or local ethics committees, as required. All patients gave written informed consent, except those who were illiterate, for whom an independent witness signed the consent form.

HYVET was funded by grants from the British Heart Foundation and the Institut de Recherches Internationales Servier. The trial was coordinated by staff of the Department of Care of the Elderly, Imperial College London. Imperial College London required all committee members and investigators to sign confidentiality agreements. All data management was performed by the authors who were at Imperial College London. The interim analyses were performed by, and the final analysis verified by, an academic author, independently of Imperial College London. All the authors contributed to the writing of the manuscript and the lead authors vouch for the completeness and accuracy of the results.

Patients had to be 80 years of age or older (confirmed by national documentation) with persistent hypertension (defined as a sustained systolic blood pressure of 160 mm Hg). Exclusion criteria included a contraindication to use of the trial medications, accelerated hypertension, secondary hypertension, hemorrhagic stroke in the previous 6 months, heart failure requiring treatment with antihypertensive medication, a serum creatinine level greater than 150 μmol per liter (1.7 mg per deciliter), a serum potassium level of less than 3.5 mmol per liter or more than 5.5 mmol per liter, gout, a diagnosis of clinical dementia, and a requirement of nursing care.

Patients were instructed to stop all antihypertensive treatment and to take a single placebo tablet daily for at least 2 months and to undergo two blood-pressure measurements during each of two visits, 1 month apart, after having been seated for 5 minutes. On the third visit and thereafter, the standing blood pressure was taken twice,

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

after the patient had been standing for 2 minutes. At the start of the trial, blood pressures were recorded with the use of either a mercury sphygmomanometer or a validated automated device, but by the end of the trial, a validated automated device was used in the majority of centers.

If the mean of the four systolic blood-pressure measurements taken at the second and third visits (two at each visit) was between 160 and 199 mm Hg, patients underwent randomization, provided that all inclusion and exclusion criteria were met. Randomization was stratified according to age (80 to 89 years and 90 years or older) and sex; permuted blocks of 4 and 6 of any 10 patients were used to ensure roughly equal assignment to each of the two groups within large centers. At the start of the trial in 2000, the mean diastolic blood pressure while seated had to be 90 to 109 mm Hg, but in 2003 a protocol amendment relaxed this criterion to be under 110 mm Hg, allowing for the inclusion of patients with isolated systolic hypertension. The criterion of systolic blood pressure while standing remained the same throughout the trial, at 140 mm Hg or more.

After randomization, patients received either indapamide (sustained release, 1.5 mg) or matching placebo alone. At each visit (or at the discretion of the investigator), if needed to reach the target blood pressure, perindopril (2 mg or 4 mg) or matching placebo could be added. The target systolic blood pressure was less than 150 mm Hg, and the target diastolic blood pressure was less than 80 mm Hg. The use of additional antihypertensive agents for more than 3 months resulted in withdrawal of the patient from double-blind follow-up, with an option to enter open follow-up. Patients were also withdrawn from double-blind treatment if they had received the maximum dose of the study drugs yet had a systolic blood pressure while sitting of 220 mm Hg or more or if they had a diastolic blood pressure while sitting of 110 mm Hg or more on at least two consecutive visits that were 2 or more weeks apart.

DATA COLLECTION

Baseline characteristics were recorded during the placebo run-in period. After randomization, patients were seen at least every 3 months during the first year and at least every 6 months thereafter. Investigators were permitted to adjust the dose of the trial medication more frequently than at each visit, if desired. At the annual visits, information was collected on current diseases, medication, blood pressure, biochemical levels (sodium, potassium, urea, creatinine, glucose, uric acid), cholesterol levels (total and high-density lipoprotein), and hematologic measures (hemoglobin, hematocrit), and electrocardiography and an assessment of cognitive function with the use of the Mini–Mental State Examination were performed. If the patient was enrolled in an optional add-on study, a quality-of-life questionnaire was also completed. At the 3-month and 6-month visits, only data on current diseases, medication, and blood pressure were collected.

END POINTS

The primary end point of the trial was any stroke (fatal or nonfatal). This end point did not include transient ischemic attacks. Secondary end points included death from any cause, death from cardiovascular causes, death from cardiac causes, and death from stroke. All events that were possible end points were reviewed by an independent committee, unaware of the group assignment, using predefined definitions from the protocol.[19] Events were classified as cardiovascular or noncardiovascular. Death from cardiac causes included fatal myocardial infarction, fatal heart failure, and sudden death. Heart failure was diagnosed if the patient had at least one of four symptoms (paroxysmal nocturnal dyspnea, dyspnea at rest, orthopnea, or symptoms consistent with New York Heart Association class III heart failure[20]) and at least two of seven signs (rales or crepitations, moderate ankle edema, tachycardia [120 or more beats per minute], a third heart sound, elevated jugular venous pressure, cardiomegaly, or radiologic signs characteristic of heart failure). If the two signs present were rales and ankle edema, a third sign was required.

DATA MONITORING

An independent data monitoring committee met twice a year throughout the trial to monitor the quality of the data and also met at prespecified intervals (after every 70 reported stroke events) to perform interim analyses. The interim analyses of the primary end point were monitored according to an O'Brien–Fleming guideline; death from any cause was monitored to detect a possible increased risk in the active-treatment group. On the basis of the committee's recommendations,

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

four centers were closed after the first year of the trial because of concerns that these centers failed to provide complete and accurate data. Specifically, one center was closed because of a failure to identify all the biochemical data in the source documents, one because of a failure to obtain appropriate regulatory approval, one owing to inappropriate drug delivery, and one owing to a failure to use validated equipment for measuring blood pressure.

STATISTICAL ANALYSIS

HYVET was designed to detect a 35% reduction in the rate of any stroke, with a statistical power of 90% at the 1% level of significance and assuming an event rate of 40 per 1000 patient-years. We calculated that 10,500 patient-years of follow-up would be required, with equal numbers of patients assigned to the active-treatment group and the placebo group. The first patient underwent randomization in February 2001. After the first interim analysis in 2005, the data monitoring committee recommended that the trial continue with no change to the protocol. At the second interim analysis, in July 2007, after 140 strokes had been reported (through April 30, 2007; a total of 7399 patient-years of follow-up), the active-treatment group showed evidence of a reduction in the rate of the primary end point of any stroke (relative risk, 0.59; 95% confidence interval [CI], 0.40 to 0.88; P=0.009) and, unexpectedly, for death from any cause (relative risk, 0.76; 95% CI, 0.62 to 0.93; P=0.007). The trial was terminated at that point, for ethical reasons. All final visits were completed by October 12, 2007. Data and events reported before the final visit were included in the final analysis.

The primary analysis was performed according to the intention-to-treat principle. Data from patients were analyzed for the groups to which the patients were assigned, regardless of which study drugs (or which doses) the patients actually received and regardless of other protocol irregularities. Patients from closed centers were included in the intention-to-treat population and contributed person-years and events up to the date of closure of the center, after which no further information was available.

In the intention-to-treat analysis, patient-years were calculated from the date of randomization through the date of death or the last available visit, irrespective of the type of follow-up (double-blind or open). Patients who were withdrawn from double-blind follow-up for reasons other than withdrawal of consent were followed in an open-label fashion, with the same schedule of visits. Events that occurred during the open follow-up period were included in the intention-to-treat analysis. A per-protocol analysis was also performed; it excluded data from any patients who underwent randomization in error, who were stratified incorrectly for either age or sex, or who did not receive the correct, assigned study drugs. For this analysis, patient-years were calculated from the date on which the study drugs were initiated through the time the patient became ineligible to continue with double-blind follow-up, according to the protocol[19] (i.e., when the patient had an event that required withdrawal from double-blind treatment).

We compared the means of continuous variables by using the z-test, proportions by using the chi-square test, and incidence rates by using the log-rank test. In the log-rank and Cox analyses of fatal or nonfatal strokes and death from specific causes, death from any cause and death from a cause other than the specific cause, respectively, were regarded as events for which data were censored. Cumulative-incidence curves were estimated by means of the Kaplan–Meier method. P values less than 0.05 were considered to indicate statistical significance. For patients with more than one end point during the follow-up period, the time to the first relevant end point was used in each analysis. Results for death from fatal or nonfatal stroke, death from any cause, and death from cardiovascular causes were adjusted for sex, age, baseline systolic blood pressure measured while the patient was seated, and previous cardiovascular disease. The proportional-hazard assumption was verified by plotting the Schoenfeld residuals. All reported P values are two-sided and were not adjusted for multiple testing. Data management and analyses were performed with the use of Stata software (version 8.1) (StatCorp) and SAS software (version 9.1.3) (SAS Institute).

RESULTS

A total of 4761 patients entered the placebo run-in phase. Of these, 3845 were randomly assigned to one of the two study groups. The reasons for nonrandomization are listed in Figure 1. Patients were recruited from Western Europe (86 patients), East-

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

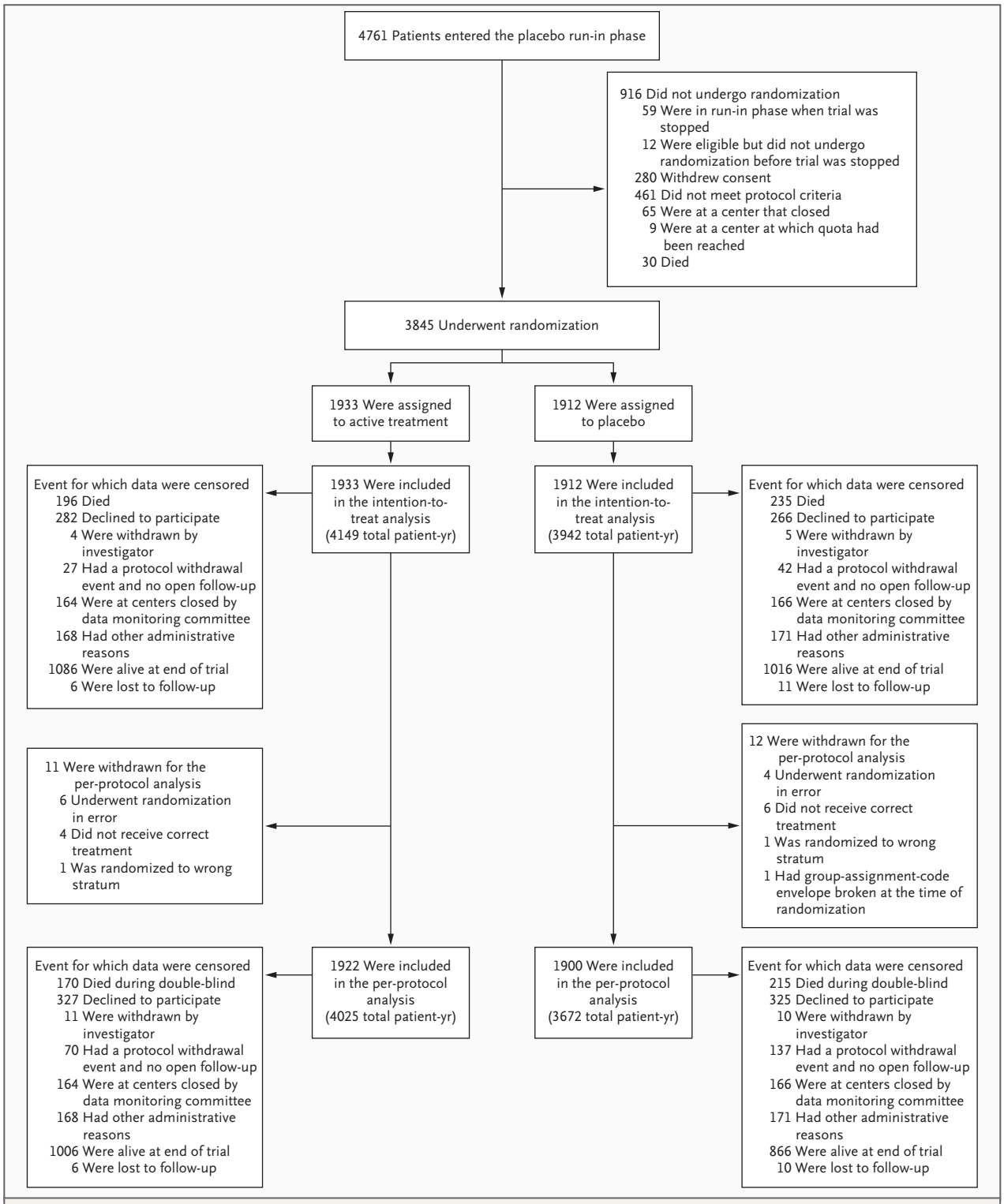


Figure 1. Entry, Randomization, and Follow-up of Patients in the Hypertension in the Very Elderly Trial.

Of the 461 patients who did not meet the protocol criteria, 229 did not meet the criteria on the basis of blood pressure, 18 on the basis of age, 61 on the basis of serum potassium level, 20 on the basis of serum creatinine level, 26 because they were receiving other antihypertensive treatment, and 107 for other reasons. The other administrative reasons for the censoring of data were death or retirement of a local investigator and change in national legislation as to where patients in clinical trials could be seen.

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

ern Europe (2144), China (1526), Australasia (19), and Tunisia (70). The two study groups were well balanced at baseline (Table 1). The age range at entry was 80 to 105 years, with 73.0% of patients 80 to 84 years of age, 22.4% of patients 85 to 89 years of age, and 4.6% of patients 90 years of age or older (interquartile range, 81.2 to 85.3). More than 90% of patients were known to be hypertensive, of whom approximately one third had not been previously treated. A history of cardiovascular disease was reported in 11.8%, and diabetes was reported in 6.9%.

The median duration of follow up was 1.8 years (mean, 2.1; range, 0 to 6.5). The number of patient-years of follow-up was 3964 in the placebo group and 4159 in the active-treatment group. At the end of the trial, vital status was unknown in 17 patients, 1882 patients were still undergoing double-blind follow-up, and 220 patients were undergoing open follow-up.

According to the intention-to-treat analysis, at 2 years, as compared with baseline, the systolic and diastolic blood pressure values obtained while the patient was seated had fallen by a mean (±SD) of 14.5±18.5 mm Hg and 6.8±10.5 mm Hg, respectively, in the placebo group and by 29.5±15.4 mm Hg and 12.9±9.5 mm Hg, respectively, in the active-treatment group. At 2 years, the mean systolic and diastolic blood pressure values obtained while the patient was standing had decreased by

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Active Treatment (N=1933)	Placebo (N=1912)
Age — yr	83.6±3.2	83.5±3.1
Female sex — no. (%)	1174 (60.7)	1152 (60.3)
Blood pressure — mm Hg		
While sitting	173.0±8.4/90.8±8.5	173.0±8.6/90.8±8.5
While standing	168.0±11.0/88.7±9.3	167.9±11.1/88.6±9.3
Orthostatic hypotension — no. (%)†	152 (7.9)	169 (8.8)
Isolated systolic hypertension — no. (%)	625 (32.3)	623 (32.6)
Heart rate — beats/min	74.5±9.1	74.5±9.3
Cardiovascular history		
Cardiovascular disease — no. (%)	223 (11.5)	229 (12.0)
Hypertension — no. (%)	1737 (89.9)	1718 (89.9)
Antihypertensive treatment — no. (%)	1241 (64.2)	1245 (65.1)
Stroke — no. (%)	130 (6.7)	131 (6.9)
Myocardial infarction — no. (%)	59 (3.1)	62 (3.2)
Heart failure — no. (%)	56 (2.9)	55 (2.9)
Cardiovascular risk factors		
Current smoker — no. (%)	123 (6.4)	127 (6.6)
Diabetes — no. (%)‡	132 (6.8)	131 (6.9)
Total cholesterol — mmol/liter	5.3±1.1	5.3±1.1
High-density lipoprotein cholesterol — mmol/liter	1.35±0.38	1.35±0.37
Serum creatinine — μmol/liter	88.6±20.5	89.2±20.5
Uric acid — μmol/liter	280.4±79.3	279.0±81.3
Body-mass index§	24.7±3.8	24.7±3.5

* Plus–minus values are means ±SD. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586; to convert values for uric acid to milligrams per deciliter, divide by 59.48; and to convert values for serum creatinine to milligrams per deciliter, divide by 88.4.

† Orthostatic hypotension is defined as a drop in systolic blood pressure of more than 20 mm Hg or a reduction in diastolic blood pressure of more than 10 mm Hg while standing.

‡ Diabetes is defined as reported diabetes, the receipt of antidiabetes treatment, or a random blood glucose measurement of more than 11.1 mmol per liter (200 mg per deciliter).

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

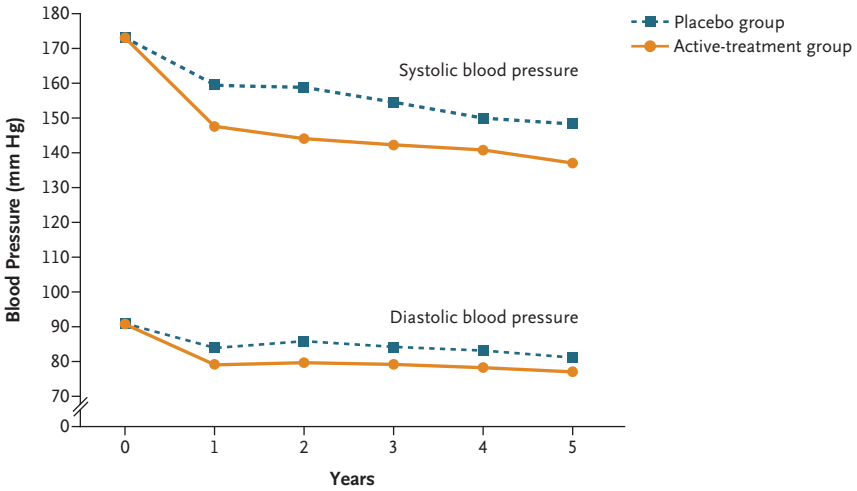
13.6±18.9 mm Hg and 7.0±10.9 mm Hg, respectively, in the placebo group and by 28.3±16.5 mm Hg and 12.4±10.3 mm Hg, respectively, in the active-treatment group. There was a difference of 15.0/6.1 mm Hg in blood pressure, measured while patients were seated, between the two groups at 2 years (Fig. 2). Also at 2 years, the target blood pressure was reached in 19.9% of patients in the placebo group and in 48.0% in the active-treatment group (P<0.001).

At 2 years, 25.8%, 23.9%, and 49.5% of patients in the active-treatment group were receiving indapamide alone, indapamide and perindopril (2 mg), and indapamide and perindopril (4 mg), respectively; 14.2%, 13.4%, and 71.8% of patients in the placebo group, respectively, were receiving the corresponding placebos. The final main intention-to-treat analysis included an extra 724 patient-years of follow-up, with an additional 13 strokes and 54 deaths. This final analysis confirmed the treatment benefit for the risk of death from any cause and yielded a nearly significant benefit for the risk of fatal or nonfatal stroke.

With regard to the primary end point (fatal or nonfatal stroke), 51 events occurred in the active-treatment group as compared with 69 events in the placebo group, a reduction in the rate of stroke of 30% (95% CI, –1 to 51; P=0.06) (Table 2 and Fig. 3). This is equivalent to 11 strokes (95% CI, 0 to 21) being prevented because 1000 patients were treated for 2 years or 1 stroke being prevented because 94 patients were treated for 2 years. There were a total of 431 deaths during the trial, with an overall rate of death of 53.1 per 1000 patient-years. There was a 21% reduction (95% CI, 4 to 35; P=0.02) in the rate of death from any cause in the active group. The rate of fatal stroke was reduced by 39% (95% CI, 1 to 62; P=0.05). The rate of death from cardiac causes was not significantly reduced in the active-treatment group. The rate of death from cardiovascular causes was reduced by 23% (95% CI, –1 to 40; P=0.06). The rate of fatal or nonfatal heart failure was reduced by 64% (95% CI, 42 to 78; P<0.001), and the rate of any cardiovascular event (death from cardiovascular causes or stroke, myocardial infarction, or heart failure) was reduced by 34% (95% CI, 18 to 47; P<0.001).

The benefits of treatment began to be apparent within the first year (Fig. 3). When adjusted according to sex, age, baseline systolic blood pressure while seated, and previous cardiovascular disease, the results did not materially change for the end points of fatal or nonfatal stroke, death from any cause, or death from cardiovascular causes.

According to per-protocol analyses, in the active-treatment group as compared with the pla-



No. at Risk						
Placebo group	1912	1468	701	330	191	116
Active-treatment group	1933	1540	754	373	207	118

Figure 2. Mean Blood Pressure, Measured while Patients Were Seated, in the Intention-to-Treat Population, According to Study Group.

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

Table 2. Main Fatal and Nonfatal End Points in the Intention-to-Treat Population.

End Point	Rate per 1000 Patient-Yr (No. of Events)		Unadjusted Hazard Ratio (95% CI)	P Value
	Active	Placebo		
	no. (%)			
Stroke				
Fatal or nonfatal	12.4 (51)	17.7 (69)	0.70 (0.49–1.01)	0.06
Death from stroke	6.5 (27)	10.7 (42)	0.61 (0.38–0.99)	0.046
Death				
From any cause	47.2 (196)	59.6 (235)	0.79 (0.65–0.95)	0.02
From noncardiovascular or unknown causes	23.4 (97)	28.9 (114)	0.81 (0.62–1.06)	0.12
From cardiovascular cause	23.9 (99)	30.7 (121)	0.77 (0.60–1.01)	0.06
From cardiac cause*	6.0 (25)	8.4 (33)	0.71 (0.42–1.19)	0.19
From heart failure	1.5 (6)	3.0 (12)	0.48 (0.18–1.28)	0.14
Fatal or nonfatal				
Any myocardial infarction	2.2 (9)	3.1 (12)	0.72 (0.30–1.70)	0.45
Any heart failure	5.3 (22)	14.8 (57)	0.36 (0.22–0.58)	<0.001
Any cardiovascular event†	33.7 (138)	50.6 (193)	0.66 (0.53–0.82)	<0.001

* Death from cardiac causes was defined as fatal myocardial infarction, fatal heart failure, and sudden death.
† Any cardiovascular event was defined as death from cardiovascular causes or stroke, myocardial infarction, or heart failure.

cebo group, the rate of stroke was reduced by 34% (95% CI, 5 to 54; P=0.03), the rate of any heart failure by 72% (95% CI, 52 to 83; P<0.001), and the rate of death from cardiovascular causes by 27% (95% CI, 3 to 45; P=0.03). In addition, the rate of death from any cause was decreased by 28% (95% CI, 12 to 41; P=0.001) and the rate of death from stroke by 45% (95% CI, 7 to 67; P=0.02).

Among the patients followed for at least 2 years, there were no significant differences between the two groups with regard to changes from baseline in the serum potassium level (–0.02 mmol and 0.03 mmol per liter in the active-treatment group and in the placebo group, respectively; P=0.09), uric acid (11.6 μmol and 3.5 μmol per liter [0.2 and 0.1 mg per deciliter], P=0.07), glucose (0.16 mmol and 0.11 mmol per liter [2.9 and 2.0 mg per deciliter], P=0.56), or creatinine (3.4 μmol and 2.3 μmol per liter [0.04 and 0.03 mg per deciliter], P=0.30). The number of serious adverse events reported was 448 in the placebo group and 358 in the active-treatment group (P=0.001). Only five of these events (three in the placebo group and two in the active-treatment group) were classified by the local investigator as possibly having been due to the trial medication.

DISCUSSION

The results of HYVET indicate that antihypertensive treatment based on indapamide (sustained release, 1.5 mg), with or without 2 to 4 mg of perindopril, significantly reduces the risks of death from stroke and death from any cause in very elderly patients. This finding for stroke is consistent with that seen in the HYVET pilot study[18] and the Individual Data Analysis of Antihypertensive Drug Intervention Trials (INDANA) group meta-analysis.[17] The reduction in death from any cause is a new and unexpected result.

As compared with clinical trials involving other age groups,[11,14-16] the ratio of fatal to nonfatal events was higher in HYVET. Although the number of strokes reported in HYVET (120) was similar to that reported in the Systolic Hypertension in Europe (Syst-Eur)[16] trial (128 strokes) and higher than the number reported in the Swedish Trial in Older Patients with Hypertension (STOP–Hypertension, 82 strokes),[14] in HYVET the proportion of fatal strokes (57.5%) was higher than that in Syst-Eur (28.9%) or STOP (18.3%). This difference probably reflects the older age of the patients in HYVET and the higher rates of stroke

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

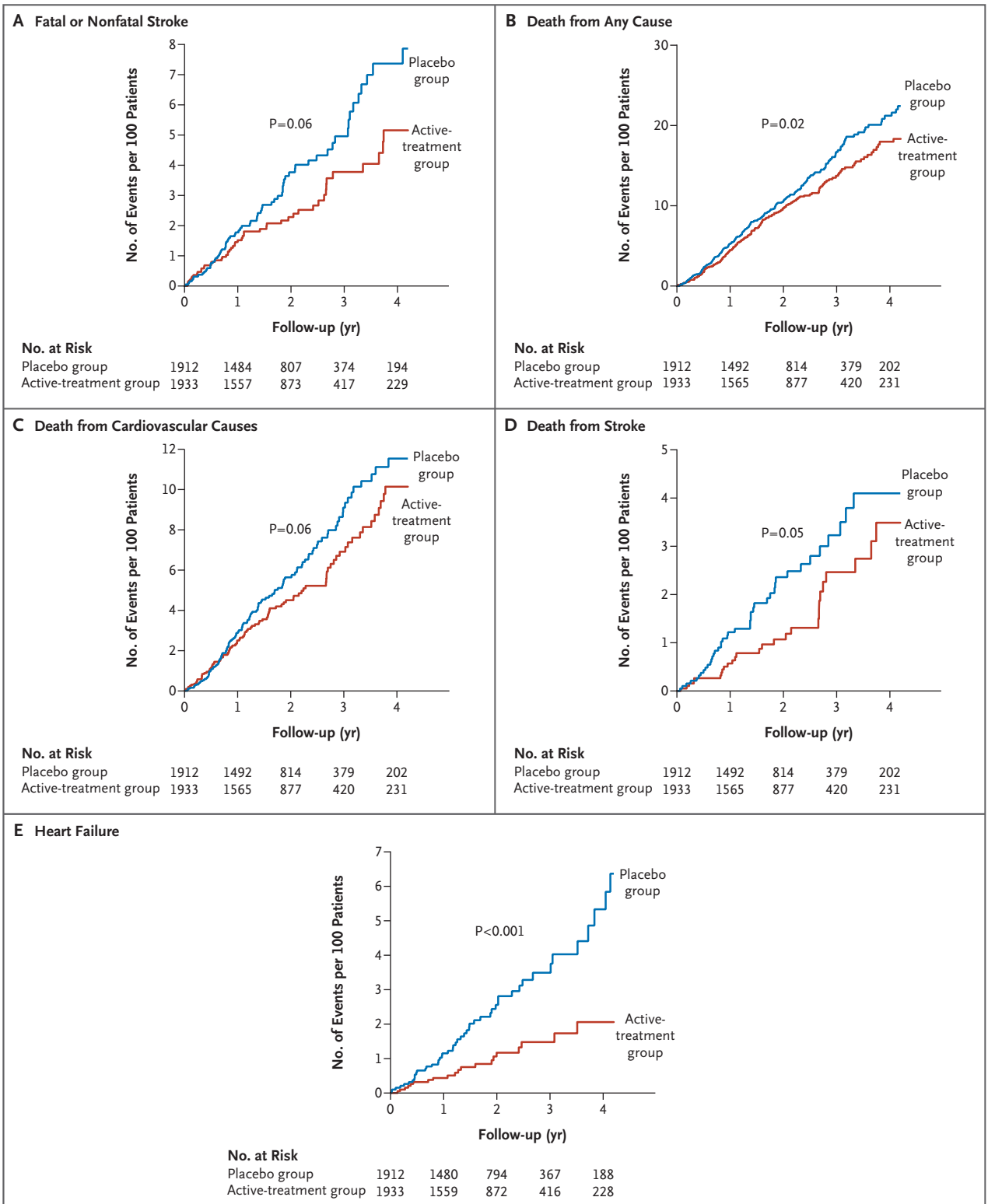


Figure 3. Kaplan–Meier Estimates of the Rate of End Points, According to Study Group.

For the active-treatment group as compared with the placebo group, the unadjusted hazard ratios (95% CIs) were as follows: for fatal or nonfatal stroke, 0.70 (0.49 to 1.01) (Panel A); for death from any cause, 0.79 (0.65 to 0.95) (Panel B); for death from cardiovascular causes, 0.77 (0.60 to 1.01) (Panel C); for death from stroke, 0.61 (0.38 to 0.99) (Panel D); and for heart failure, 0.36 (0.22 to 0.58) (Panel E).

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

that occur with increasing age.[1] Increasing age is a major predictor of death from stroke,[21-25] with rates as high as 52%[21] in persons 80 years of age or older, consistent with our results. A linear association between blood pressure and stroke reduction has been clearly demonstrated, although it is attenuated by increasing age.[25] The reduction in the risk of death from stroke with active treatment was significant in both the intention-to-treat and the per-protocol analyses, as was the reduction in the risk of any stroke in the per-protocol analysis. This reduction is consistent with previous results in younger hypertensive patients and in reviews of data from the very elderly.

An unexpected finding of our trial is the reduction in the risk of death from any cause with active treatment, making HYVET one of the few individual studies of hypertension showing benefits of blood-pressure reduction on mortality.[14,26] The results for death from any cause show a significant benefit of treatment, at odds with the results of the INDANA meta-analysis, the largest analysis to date to focus on very elderly patients with hypertension, which included 1670 patients 80 years of age or older recruited for intervention trials.[17] The INDANA meta-analysis included trials with treatment regimens based on high doses of diuretics other than indapamide or on beta-blockers. Diuretics have not been shown to increase mortality among younger patients, but the very elderly may be more prone to metabolic disturbances from medications, particularly hypokalemia, which can predispose patients to arrhythmias and possibly sudden death. Beta-blockers appear to be less effective than newer agents in the treatment of hypertension.[27] Given the known changes in serum potassium level that can occur with a thiazide-like antihypertensive agent or angiotensin-converting–enzyme (ACE) inhibitor on its own, in combination, they are likely to have a neutral effect. This was evidenced by the similar serum potassium levels in the two groups, with 73.4% of patients in the active-treatment group receiving both indapamide and perindopril at 2 years. Indapamide (sustained release) has also been shown to have a neutral effect on blood glucose and lipids,[28] and the combination of indapamide and perindopril has also been shown to confer a benefit with regard to stroke.[29]

As in most trials, the patients in HYVET were generally healthier than those in the general population, as evidenced by the low overall rates of stroke and death from any cause and the low prevalence of previous cardiovascular disease at baseline. It is possible that the numbers of patients needed to be treated is an overestimate, given the low rate of stroke, though a number needed to treat of 94 is acceptable in the context of prevention. A number needed to treat of 40 to prevent one death during a 2-year period is more impressive, supporting the effectiveness of the intervention used. However, it would be premature to extrapolate the results from HYVET to patients in this age group who are more frail.

The large reduction in the risk of heart failure in HYVET appears to be important. Heart failure is common in people older than 70 years of age, and hypertension is a major risk factor for heart failure.[30] The combination of a diuretic and an ACE inhibitor is likely to confer a benefit. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT; ClinicalTrials.gov number, NCT00000542), the lowest rates of hospitalization and fatal heart failure were found for the groups receiving a diuretic or ACE inhibitor, with a greater (albeit not significantly greater) reduction in the diuretic group.[31]

A challenge and possible limitation in performing our study of the very elderly was the collection of adequate information to validate the end-point data, especially for patients who died at home without receiving any direct medical intervention. The end-point committee required evidence to support a diagnosis of a stroke, and this evidence was not always available. Rapid and unexpected deaths were designated as deaths from cardiovascular causes by the committee. In the very elderly, it is difficult to establish the exact cause of death, since patients are often not monitored during the last hours of life and autopsies are rarely performed. Given these difficulties, the reduction of the risk of death from any cause in the active-treatment group clearly indicates the overall advantage of active treatment in HYVET.

In HYVET, we evaluated the benefit of treating patients who had a sustained systolic blood pressure of 160 mm Hg or higher. The fall in blood pressure in the active-treatment group was consistent with results for indapamide-based strategies in other studies.[32,33] The results support a target blood pressure of 150/80 mm Hg in patients receiving treatment, since that target was reached in nearly 50% of such patients in

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

HYVET after 2 years. Whether further reduction is beneficial still needs to be established.

Elevated blood pressure is common in persons 80 years of age or older,[34] a group constituting the fastest-growing segment of the general population.[35] HYVET provides unique evidence that hypertension treatment based on indapamide (sustained release), with or without perindopril, in the very elderly, aimed to achieve a target blood pressure of 150/80 mm Hg, is beneficial and is associated with reduced risks of death from stroke, death from any cause, and heart failure.

Supported by grants from the British Heart Foundation and the Institut de Recherches Internationales Servier.

Drs. Beckett and Peters and Mr. Banya report receiving grant support from the Institut de Recherches Internationales Servier; Dr. Staessen, consulting fees from Pfizer, Tanabe, Daiichi-Sankyo, and Sigma-Tau and speakers' fees from Pfizer, Tanabe, and Bayer; Dr. Anderson, consulting fees from Boehringer Ingelheim and Servier and speakers' fees from Boehringer Ingelheim, Servier, AstraZeneca, and Sanofi-Aventis; Dr. Forette, consulting fees from Wyeth Elan, Sanofi-Aventis and Bristol-Myers Squibb and speakers' fees from Servier, AstraZeneca, and Sanofi-Aventis; Dr. Rajkumar, speakers' fees from Schering-Plough, Merck Sharp & Dohme, and Menarini; and Dr. Bulpitt, consulting fees from Imperial College Consulting, a consultancy funded by a grant from the Institut de Recherches Internationales Servier. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The committee members and investigators for HYVET were as follows: **Coordinating Center:** C.J. Bulpitt (lead investigator), A.E. Fletcher (coinvestigator), N.S. Beckett (trial coordinator), R. Peters (deputy trial coordinator), HYVET coordinating team at Imperial College London (1999 to 2008); **Steering Committee:** T. McCormack, J. Potter, B.G. Extremera, P. Sever, F. Forette, D. Dumitrascu, C. Swift, J. Tuomilehto, J. Coope (retired in 2001), C. Nachev (deceased); **Data Monitoring Committee:** J. Staessen, L. Thijs, R. Clarke, K. Narkiewicz; **End Points Committee:** C. Davidson (retired in 2003), J. Duggan, G. Leonetti, N. Gainsborough, M.C. De Vernejoul, J. Wang, V. Stoyanovsky; **Dementia Validation Committee:** J. Tuomilehto, R. Clarke, A. Waldman, I. Walton, C. Ritchie; **Ethics Committee:** R. Fagard, J. Grimley Evans, B. Williams; **Investigators:** *Australia* — R. Warne and I. Puddey (national coordinators), M. Woodward, R. Penhall, C. Inderjeeth, S. Roger, R. Scholes, C. Johnson; *Belgium* — H. Celis (national coordinator), G. Adriaens, W. Onsea, K. Cornelli, D. Vantroyen, P. Cleen, P. de Voogt; *Bulgaria* — C. Nachev (deceased) (national coordinator from 1998 to 2005), V. Stoyanovsky (national coordinator after 2005), P. Solakov, R. Prokopova, E. Mantova, D. Smilkova, S. Mantov, K. Yankulova, R. Kermova, D. Popov, V. Sirakova, V. Gergova, D. Kamenova, F. Grigorov, T. Vassileva, R. Alahverdian, M. Tzekova; *China* — L. Liu (national coordinator), H. Ge, S. Wang, J. Wang, W. Zhang, S. Jin, L. Ge, Y.F. Lu, S. Ma, L. Shen, J. Guo, Z. Lv (deceased), R. Huang, X. Li, B. Guo, T. Zhang, L. Zhang, J. Feng, Z. He, J. Wang, L. Deng, L. Liu, Q. Yuan, F. Zhang, H. Li, D. Wang, K. Yang, M. Sun, H. Liu, X. Yan, F. Ren, J. Tang; *Finland* — R. Antikainen (national coordinator), T. Strandberg, T. Konttila, A. Hynninen, M. Jääskivi, J. Airas, T. Jääskeläinen, J. Tuomilehto, H. Litmanen; *France* — F. Forette (national coordinator), J. Doucet, J. Belmin, A. Benetos, G. Berrut, T. Boge, M. Bonnefoy, A. Carre, N. Charasz, J. Covillard, T. Dantoine, M. Escande, Y. Frances, R. Joire, C. Jeandel, S. Legrain, A. Lion, M. Maillet-Vioud, J.P. Escaillas, S. Meaume, P. Pfitzenmeyer, F. Puisieux, E. Quercy, O. Rodat, J. Soubeyrand, B. de Wazieres, H. Hindennach, L. Lugassy, J. Rossi, M. Martel, J.-M. Paladel, C. Ravier, A. Visconti, J.P. Gallet, D. Zygouritsas, D. Charles, F. Flamand, G. Grandmottet, M. Grandmottetegermann, C. Gevrey, P.L. Mesnier, G. Robert, C. Besset-Prat, A. Brousse, P. Lafont, J. Morelli, P. Vernede, A. Volkmann, X. Bodin, B. Destrube, R. Eoche, A. Boye, F. Seropian, P. Gernigon, D. Meker, J. Thomere, Y. Thual, F. Volny, E. Grassart, M. Herent, D. Lejay, J.-P. Lopez, B. Mannessier, G. Pruvost, J.-C. Urbina; *Ireland* — J. Duggan (national coordinator); *New Zealand* — C. Anderson (national coordinator), S. Lillis, J. Gommans; *Poland* — T. Grodzicki (national coordinator), Z. Chodorowski, Z. Gaciong; *Romania* — D. Dumitrascu (national coordinator), M. Comsa, V. Sandru, G. Prada, M. Dunca-Moisin, D. Jianu, D. Jinga-Lazar, V. Enachescu, C. Zaharia; *Russia* — Y. Nikitin (national coordinator), A. Kirichenko, L. Olbinskaya, A. Martynov, V. Zadionchenko, V. Moiseev, G. Storohzakov, S. Nedogoda, R.S. Karpov, O. Barbarash, G. Efremushkin, V. Kostenko, M. Boyarkin, S. Churina, T. Tyurina, M. Ballyuzek, L. Ermoshkina, A. Timofeev, S. Yakusheva, N. Shilkina, V. Barbarich; *Tunisia* — A. Belhani (national coordinator), E. Boughzela, S. Soraya, B. Youssef-Zouari, A.B. Khalfallah, M.H. Houman, A.K. Abida; *United Kingdom* — C. Rajkumar (national coordinator), M. Wilkins, N.D. Pandita-Gunawardena, J. Potter, E. Ekpo, M. Price, N. de Kare-Silver, A. Starczewski, S. Chandran, N. Nasar, M. Datta-Chaudhuri, T. McCormack, N. Majmudar, A. Gordon, L. Brawn, T. Solanki.

REFERENCES

1. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke 2004;35:1024.

2. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Lancet 2000;356:1955-64.

3. World Health Organization–International Society of Hypertension guidelines for the management of hypertension. J Hypertens 1999;17:151-83.

4. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105-87. [Erratum, J Hypertens 2007;25:1749.]

5. Mattila K, Haavisto M, Rajala S, Heikinheimo R. Blood pressure and five year survival in the very old. Br Med J (Clin Res Ed) 1988;296:887-9.

6. Langer RD, Criqui MH, Barrett-Connor EL, Klauber MR, Ganiats TG. Blood pressure change and survival after age 75. Hypertension 1993;22:551-9.

7. Rastas S, Pirttilä T, Viramo P, et al. Association between blood pressure and survival over 9 years in a general population aged 85 and older. J Am Geriatr Soc 2006;54:912-8.

8. van Bemmel T, Woittiez K, Blauw GJ, et al. Prospective study of the effect of blood pressure on renal function in old age: the Leiden 85-Plus Study. J Am Soc Nephrol 2006;17:2561-6.

9. Satish S, Freeman DH Jr, Ray L, Goodwin JS. The relationship between blood pressure and mortality in the oldest old. J Am Geriatr Soc 2001;49:367-74.

10. Oates DJ, Berlowitz DR, Glickman ME, Silliman RA, Borzecki AM. Blood pressure and survival in the oldest old. J Am Geriatr Soc 2007;55:383-8.

11. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. Br Med J (Clin Res Ed) 1986;293:1145-51.

12. Medical Research Council trial of

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

treatment of hypertension in older adults: principal results. BMJ 1992;304:405-12.
13. Amery A, Birkenhäger W, Brixko P, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985;1:1349-54.
14. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet 1991;338:1281-5.
15. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-64.
16. Staessen JA, Fagard R, Thijs L, et al. 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;350:757-64.
17. Gueyffier F, Bulpitt C, Boissel JP, et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. Lancet 1999;353:793-6.
18. Bulpitt CJ, Beckett NS, Cooke J, et al. Results of the pilot study for the Hypertension in the Very Elderly Trial. J Hypertens 2003;21:2409-17.
19. Bulpitt C, Fletcher A, Beckett N, et al. Hypertension in the Very Elderly Trial (HYVET): protocol for the main trial. Drugs Aging 2001;18:151-64.
20. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little, Brown, 1994.
21. Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM. Incidence, risk, and case fatality of first ever stroke in the elderly population: the Rotterdam Study. J Neurol Neurosurg Psychiatry 2003;74:317-21.
22. de Jong G, van RL, Kessels F, Lodder J. Stroke subtype and mortality: a follow-up study in 998 patients with a first cerebral infarct. J Clin Epidemiol 2003;56:262-8.
23. Kammersgaard LP, Jørgensen HS, Reith J, Nakayama H, Pedersen PM, Olsen TS. Short- and long-term prognosis for very old stroke patients: the Copenhagen Stroke Study. Age Ageing 2004;33:149-54.
24. Zuliani G, Cherubini A, Ranzini M, Ruggiero C, Atti AR, Fellin R. Risk factors for short-term mortality in older subjects with acute ischemic stroke. Gerontology 2006;52:231-6.
25. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13.
26. Five-year findings of the Hypertension Detection and Follow-up Program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 1997;277:157-66.
27. Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895-906.
28. Ambrosioni E, Safar M, Degaute JP, et al. Low-dose antihypertensive therapy with 1.5 mg sustained-release indapamide: results of randomised double-blind controlled studies. J Hypertens 1998;16:1677-84.
29. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033-41. [Errata, Lancet 2001;358:1556, 2002;359:2120.]
30. Stewart S, MacIntyre K, Capewell S, McMurray JJ. Heart failure and the aging population: an increasing burden in the 21st century? Heart 2003;89:49-53.
31. Davis BR, Piller LB, Cutler JA, et al. Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Circulation 2006;113:2201-10.
32. Puig JG, Marre M, Kokot F, et al. Efficacy of indapamide SR compared with enalapril in elderly hypertensive patients with type 2 diabetes. Am J Hypertens 2007;20:90-7.
33. Emeriau JP, Knauf H, Pujadas JO, et al. A comparison of indapamide SR 1.5 mg with both amlodipine 5 mg and hydrochlorothiazide 25 mg in elderly hypertensive patients: a randomized double-blind controlled study. J Hypertens 2001;19:343-50.
34. Callow AD. Cardiovascular disease 2005 — the global picture. Vascul Pharmacol 2006;45:302-7.
35. U.S. Census Bureau. International Data Base (IDB). (Accessed April 7, 2008, at http://www.census.gov/ipc/www/idb/.)
Copyright © 2008 Massachusetts Medical Society.

RECEIVE IMMEDIATE NOTIFICATION WHEN A *JOURNAL* ARTICLE IS RELEASED EARLY

To be notified when an article is released early on the Web and to receive the table of contents of the *Journal* by e-mail every Wednesday evening, sign up through our Web site at **www.nejm.org**

The New England Journal of Medicine as published by New England Journal of Medicine.
Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on August 17, 2010. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.