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)

SHEP Cooperative Research Group

Objective.—To assess the ability of antihypertensive drug treatment to reduce the risk of nonfatal and fatal (total) stroke in isolated systolic hypertension.

Design.—Multicenter, randomized, double-blind, placebo-controlled.

Setting.—Community-based ambulatory population in tertiary care centers.

Participants.—4736 persons (1.06%) from 447 921 screenees aged 60 years and above were randomized (2365 to active treatment, 2371 to placebo). Systolic blood pressure ranged from 160 to 219 mm Hg and diastolic blood pressure was less than 90 mm Hg. Of the participants, 3161 were not receiving antihypertensive medication at initial contact, and 1575 were. The average systolic blood pressure was 170 mm Hg; average diastolic blood pressure, 77 mm Hg. The mean age was 72 years, 57% were women, and 14% were black.

Interventions.—Participants were stratified by clinical center and by antihypertensive medication status at initial contact. For step 1 of the trial, dose 1 was chlorthalidone, 12.5 mg/d, or matching placebo; dose 2 was 25 mg/d. For step 2, dose 1 was atenolol, 25 mg/d, or matching placebo; dose 2 was 50 mg/d.

Main Outcome Measures.—*Primary.*—Nonfatal and fatal (total) stroke. *Secondary.*—Cardiovascular and coronary morbidity and mortality, all-cause mortality, and quality of life measures.

Results.—Average follow-up was 4.5 years. The 5-year average systolic blood pressure was 155 mm Hg for the placebo group and 143 mm Hg for the active treatment group, and the 5-year average diastolic blood pressure was 72 and 68 mm Hg, respectively. The 5-year incidence of total stroke was 5.2 per 100 participants for active treatment and 8.2 per 100 for placebo. The relative risk by proportional hazards regression analysis was 0.64 ($P = .0003$). For the secondary end point of clinical nonfatal myocardial infarction plus coronary death, the relative risk was 0.73. Major cardiovascular events were reduced (relative risk, 0.68). For deaths from all causes, the relative risk was 0.87.

Conclusion.—In persons aged 60 years and over with isolated systolic hypertension, antihypertensive stepped-care drug treatment with low-dose chlorthalidone as step 1 medication reduced the incidence of total stroke by 36%, with 5-year absolute benefit of 30 events per 1000 participants. Major cardiovascular events were reduced, with 5-year absolute benefit of 55 events per 1000.

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THIS article presents the final results of the Systolic Hypertension in the Elderly Program (SHEP), a double-blind, randomized, placebo-controlled trial of treatment for isolated systolic hypertension (ISH) in persons 60 years of age and older. The full-scale SHEP study, begun in 1984, set as its primary objective "the determination of whether antihypertensive drug treatment reduces risk of total stroke (nonfatal and fatal) in a multi-ethnic cohort of men and women age 60 years and older with ISH."[1] Previous trials have demonstrated beneficial effects of antihypertensive treatment of diastolic hypertension on major morbidity and mortality, but none has investigated the ability to influence these events for persons with ISH.[2-21]

For editorial comment see p 3301.

Isolated systolic hypertension is increasingly prevalent with age, especially in those aged 60 years and above. Epidemiologic studies have demonstrated an increase in risk of stroke, other cardiovascular diseases, and death for those with ISH, independent of other risk factors.[22-28]

The SHEP pilot study demonstrated the feasibility of undertaking trials in older people with ISH, including ability to recruit participants. It also established ability of drug therapy to reduce blood pressure among persons with ISH.[29] For SHEP, ISH was defined as systolic blood pressure (SBP) greater than 160 mm Hg and diastolic blood pressure (DBP) less than 90 mm Hg, based on the average of four measurements at two baseline visits.[1,30]

Secondary objectives included assessment of the relationship of antihypertensive treatment to (1) multiple cardiovascular morbidity and mortality end points, including cardiac end points; (2) cause-specific and all-cause mortality; (3) multi-infarct dementia, clinical depression, and deterioration of cognitive function; (4) possible adverse effects; (5) hospitalizations and intermediate or skilled nursing facility admissions; (6) falls and fractures; and (7) multiple indexes of quality of life.[1,30]

The SHEP protocol also stipulated two other questions for investigation as subgroup hypotheses[1]: (1) Would treatment of ISH reduce the frequency of total stroke (fatal and nonfatal) similar-

See the end of the article for a list of the principal investigators of the Systolic Hypertension in the Elderly Program.

Reprint requests to Clinical Trials Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Federal Building, Room 5C-10B, 7550 Wisconsin Ave, Bethesda, MD 20892 (Dr Jeffrey L. Probstfield).

ly in those receiving and not receiving antihypertensive medication at initial contact? (2) Would treatment of ISH reduce the incidence of sudden cardiac death or of coronary death plus nonfatal myocardial infarction similarly in those free of baseline electrocardiographic (ECG) abnormalities and in those with such abnormalities?

METHODS

The design and methods of SHEP have been reported in detail elsewhere.[1,30,31] They are summarized here.

Sample Size

The SHEP design specified a sample size of 4800 participants to test the primary hypothesis.[32] This sample size was used to detect a difference of at least 32% in total stroke incidence with 90% power and a two-sided α of .05.

Recruitment and Screening

For recruitment, SHEP used primarily mass mailing and community screening techniques.[33] All identified potential participants underwent an initial contact to exclude individuals ineligible by age, blood pressure, and other criteria.[31] One seated blood pressure reading was taken. All blood pressures during screening and trial follow-up were measured by trained, certified technicians using standardized techniques with a Hawksley random-zero manometer.[34] The SBP was defined as the reading at the first Korotkoff sound and DBP as the reading at the last Korotkoff sound. For persons not receiving antihypertensive drugs who had a first SBP reading greater than 150 mm Hg, two more readings were taken. When the mean of the last two readings was between160 and 219 mm Hg for SBP and less than 100 mm Hg for DBP, the person was eligible for the first baseline visit.

Persons receiving antihypertensive medication at initial contact who had SBPs between 130 and 219 mm Hg and DBPs less than 85 mm Hg and who were free of major illness were eligible for a drug withdrawal procedure. They were asked to obtain permission from their personal physicians and to sign an informed consent form for drug withdrawal. They were then monitored at multiple drug evaluation visits during a 2- to 8-week period to determine blood pressure eligibility off medication.

The baseline phase consisted of two visits. Eligibility was determined based on study inclusion and exclusion criteria. When the average of four seated blood pressure measurements, two at each of these visits, was between 160 and 219 mm Hg for SBP and less than 90 mm Hg for DBP, the participant was eligible for the trial. Persons were excluded on the basis of history and/or signs of specified major cardiovascular diseases.[31] Other major diseases, eg, cancer, alcoholic liver disease, established renal dysfunction, with competing risk for the SHEP primary end point or the presence of medical management problems, were also exclusions. Screenees also underwent a physical examination, and a 12-lead ECG was done, with a 2-minute rhythm strip.

Those remaining eligible at the second baseline visit underwent behavioral assessment (including cognition, mood, and activities of daily living),[35] signed an additional informed consent form for participation in the trial, and had blood drawn.

Randomization

At the completion of the second baseline visit, after verification of eligibility, screenees were randomly allocated by the coordinating center to one of two treatment groups. Randomization was stratified by clinical center and by antihypertensive medication status at initial contact.

Treatment Program

Participants were randomized in a double-blind manner to a once-daily dose of either active drug treatment or matching placebo. Baseline SBP (average of four seated blood pressure readings at the first and second baseline visits) was used to establish a goal blood pressure for each participant. For individuals with SBPs greater than 180 mm Hg, the goal was a reduction to less than 160 mm Hg. For those with SBPs between 160 and 179 mm Hg, the goal was a reduction of at least 20 mm Hg.

The objective of the stepped-care treatment program was to use the minimal amount of medication to maintain SBP at or below the goal. All participants were given chlorthalidone, 12.5 mg/d, or matching placebo (step 1 medication). Drug dosage was doubled (including matching placebo) for participants failing to achieve the SBP goal at follow-up visits. If the SBP goal was not reached at the maximal dose of step 1 medication, atenolol, 25 mg/d, or matching placebo was added as the usual step 2 drug. When atenolol was contraindicated, reserpine, 0.05 mg/d, or matching placebo could be substituted. When required to reach the blood pressure goal, the dosage of the step 2 drug could be doubled. Potassium supplements were given to all participants who had serum potassium concentrations below 3.5 mmol/L at two consecutive visits.

Follow-up Procedures

The SHEP participants were followed up monthly until SBP reached the goal or until the maximum level of stepped-care treatment was reached.[31] All participants had quarterly visits from the date of randomization, at which they underwent measurement of blood pressure (average of two readings), heart rate, and body weight, and a general medical history and detailed review of medication use (prescribed and over the counter) were done. At semiannual visits, standardized questionnaires were administered to screen for depression and dementia.[35,36] Annual visits also included (1) a detailed medical history, (2) a complete physical examination, (3) laboratory tests, and (4) behavioral assessment. An ECG was also done at the second and final annual visits. Other visits were scheduled when indicated, eg, SBP above the goal, SBP or DBP above the escape criteria (see below), low serum potassium concentration (<3.2 mmol/L), or as requested by the clinician or participant. Blood pressure above a priori escape criteria, despite maximal stepped-care therapy, was an indication for prescribing known active drug therapy. Escape criteria included SBP greater than 240 mm Hg at a single visit, DBP greater than 115 mm Hg at a single visit, sustained SBP greater than 220 mm Hg, or sustained DBP greater than 90 mm Hg.

When adverse conditions occurred that were considered drug related, the dosage of the study medication could be reduced, or therapy could be discontinued. Whenever the dosage was reduced or therapy was discontinued, consideration was given to resuming drug therapy when it appeared safe, when the participant's blood pressure was above the goal, and when the participant agreed.

Ascertainment of End Points

Total stroke was the primary end point. Stroke was defined as rapid onset of a new neurologic deficit attributed to obstruction or rupture in the arterial system.[37] The defined deficit had to persist for at least 24 hours unless death supervened and had to include specific localizing findings confirmed by neurologic examination or brain scan, with no evidence of an underlying nonvascular cause. Determination of fatal stroke was based on either autopsy or death certificate plus data on preterminal hospitalization with a definite diagnosis of stroke. Definitions of individual secondary end points were (1) sudden cardiac death—death within 1 hour of the onset of severe cardiac symptoms, unrelated

to other known causes; (2) rapid cardiac death—death within 1 to 24 hours of the onset of severe cardiac symptoms, unrelated to other known causes; (3) nonfatal myocardial infarction—typical symptoms consistent with acute myocardial infarction plus either typical ECG changes (including new Q waves) or significant enzyme elevation (1.25 times normal), but not including silent myocardial infarction; (4) fatal myocardial infarction—autopsy diagnosis or death certificate diagnosis plus preterminal hospitalization, with a definite or suspected diagnosis of myocardial infarction within 4 weeks of death; (5) left ventricular failure—a symptom, such as significant dyspnea, plus a chest roentgenogram characteristic of congestive heart failure, or an abnormal physical sign, such as rales or 2+ (moderate) ankle edema; (6) other cardiovascular death—presumed myocardial infarction that did not meet diagnostic criteria, or other cardiovascular causes; (7) transient ischemic attack—rapid onset of a focal neurologic deficit lasting more than 30 seconds and less than 24 hours, presumed to be due to cerebral ischemia, with no evidence of an underlying nonvascular cause; (8) coronary artery therapeutic procedures—coronary artery bypass graft or coronary angioplasty; and (9) renal dysfunction—serum creatinine concentration greater than 265.2 μmol/L. For combined end points, participants with multiple end points were counted only once.

Information related to study end points was collected by clinic staff. For suspected stroke and transient ischemic attack, a standardized neurological evaluation was carried out by a SHEP neurologist. For suspected stroke, this evaluation and notes by the attending neurologist and scans or other studies of the brain were forwarded to the coordinating center. For participants with suspected myocardial infarction or left ventricular failure, data requested included ECGs, cardiac enzymes, chest roentgenogram reports, and other clinical information. Death certificates and autopsy reports were obtained for decedents. For hospitalizations and nursing home admissions, discharge or admission sheets were obtained.

Occurrence of study events listed above was confirmed by a coding panel of three physicians blind to randomization allocation. For a neurological event, the coding panel included two neurologists. For myocardial infarction, left ventricular failure, and all causes of death, the panel included at least one cardiologist.

Possible adverse clinical and biochemical effects of the SHEP treatments were evaluated by (1) using a standardized questionnaire that asked participants questions about side effects at annual visits, at visits after the administration of study drugs was started or stepped up, and at visits at which complaints were thought to be due to SHEP medication and by (2) examining serum chemistry data from annual laboratory evaluations.

The behavioral assessment included a questionnaire to detect depression and dementia, administered at baseline and semiannually. Based on specified questionnaire scores,[36] participants were referred for expert diagnostic evaluation[31] in accordance with American Psychiatric Association criteria.[38] A diagnosis of dementia had to be confirmed by the SHEP coding panel, including two neurologists. A diagnosis of depression was not reviewed centrally.

Table 1.—Baseline Characteristics of Randomized SHEP Participants by Treatment Group*

Characteristic	Active Treatment Group	Placebo Group	Total
No. randomized	2365	2371	4736
Age, y			
Average†	71.6 (6.7)	71.5 (6.7)	71.6 (6.7)
%			
60-69	41.1	41.8	41.5
70-79	44.9	44.7	44.8
≥80	14.0	13.4	13.7
Race-sex, %‡			
Black men	4.9	4.3	4.6
Black women	8.9	9.7	9.3
White men	38.8	38.4	38.6
White women	47.4	47.7	47.5
Education, y†	11.7 (3.5)	11.7 (3.4)	11.7 (3.5)
Blood pressure, mm Hg†			
Systolic	170.5 (9.5)	170.1 (9.2)	170.3 (9.4)
Diastolic	76.7 (9.6)	76.4 (9.8)	76.6 (9.7)
Antihypertensive medication at initial contact, %	33.0	33.5	33.3
Smoking, %			
Current smokers	12.6	12.9	12.7
Past smokers	36.6	37.6	37.1
Never smokers	50.8	49.6	50.2
Alcohol use, %			
Never	21.5	21.7	21.6
Formerly	9.6	10.4	10.0
Occasionally	55.2	53.9	54.5
Daily or nearly daily	13.7	14.0	13.8
History of myocardial infarction, %	4.9	4.9	4.9
History of stroke, %	1.5	1.3	1.4
History of diabetes, %	10.0	10.2	10.1
Carotid bruits, %	6.4	7.9	7.1
Pulse rate, beats/min†§	70.3 (10.5)	71.3 (10.5)	70.8 (10.5)
Body-mass index, kg/m²†	27.5 (4.9)	27.5 (5.1)	27.5 (5.0)
Serum cholesterol, mmol/L†			
Total	6.1 (1.2)	6.1 (1.1)	6.1 (1.1)
High-density lipoprotein	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)
Depressive symptoms, %‖	11.1	11.0	11.1
Evidence of cognitive impairment, %¶	0.3	0.5	0.4
No limitation of activities of daily living, %§	95.4	93.8	94.6
Baseline electrocardiographic abnormalities, %#	61.3	60.7	61.0

*SHEP indicates the Systolic Hypertension in the Elderly Program.
†Values are mean (SD).
‡Included among the whites were 204 Orientals (5% of whites), 84 Hispanics (2% of whites), and 41 classified as "other" (1% of whites).
§$P<.05$ for the active treatment group compared with the placebo group.
‖Depressive symptom scale score of 7 or greater.[31]
¶Cognitive impairment scale score of 4 or greater.[31]
#One or more of the following Minnesota codes: 1.1 to 1.3 (Q/QS), 3.1 to 3.4 (high R waves), 4.1 to 4.4 (ST depression), 5.1 to 5.4 (T wave changes), 6.1 to 6.8 (AV conduction defects), 7.1 to 7.8 (ventricular conduction defects), 8.1 to 8.6 (arrhythmias), and 9.1 to 9.3 and 9.5 (miscellaneous items).[30,31]

Statistical Analyses

Comparability of baseline characteristics of the two treatment groups was ascertained by χ^2 tests for categorical variables and standard normal (z) tests for continuous variables. The primary hypothesis was assessed with the log-rank test[39] using time to first stroke as the variable of interest. Cumulative event rates were calculated using life table methods. Relative risks and percentage differences were calculated by proportional hazards regression analy-

Table 2.—Participants Receiving Antihypertensive Medication by Year of Follow-up

Year	No. of Participants at End of Year*		Medication Status, %						
			Treated (Active Treatment Group)	Treated with Known Active Drug Only		Untreated		Unknown	
	Active Treatment Group	Placebo Group		Active Treatment Group	Placebo Group	Active Treatment Group	Placebo Group	Active Treatment Group	Placebo Group
1	2342	2336	90.3	3.4	13.1	5.5	81.4	4.1	5.5
2	2308	2293	89.2	8.7	23.7	6.7	70.9	4.1	5.4
3	2241	2270	89.4	12.8	32.7	7.6	62.8	3.0	4.5
4	1605	1591	90.0	17.1	38.5	8.0	58.8	2.0	2.8
5	773	738	89.7	21.5	44.4	8.9	53.6	1.4	2.0

*The number of participants drops off in years 4 and 5 mainly due to follow-up time.

sis[40] using the entire duration of follow-up. All analyses were by treatment assignment at randomization. Two subgroup hypotheses were specified a priori. Subgroup hypotheses were tested by the proportional hazards model using the appropriate interaction term.[40] Power analyses for the subgroup hypotheses have been previously described.[1]

A Data and Safety Monitoring Board met twice per year to review unblinded data on efficacy and safety. The board used stochastic curtailment[41,42] to evaluate whether the trial should be stopped early. This was used to calculate the probability that a conclusion based on interim study results would remain unchanged at the trial's end, even if there were no benefit from antihypertensive treatment for the rest of the trial.

RESULTS

Recruitment

Recruitment was done at 16 clinical centers between March 1, 1985, and January 15, 1988. Details of recruitment results have been published elsewhere.[38] Altogether, 447 921 individuals aged 60 years and above were identified and contacted; 11.6% met initial criteria, and 2.7% completed baseline visit 1. Of those individuals, 64% were eligible for baseline visit 2; of those, 70% were eligible for randomization; of those, 88% were randomized.

Screenees meeting blood pressure criteria and not receiving antihypertensive medication proceeded directly through two baseline visits; 3161 such participants were randomized. Those taking medication (198 620 persons [43.2%]) and meeting blood pressure criteria underwent drug withdrawal as previously described; 1575 such participants were randomized. A total of 4736 participants were randomized into the trial, two thirds of whom were not receiving antihypertensive medication at initial contact. The yield from initial contact to randomization for those not taking antihypertensive medication was 1.24% and for those taking medication was 0.82%. Of those ineligible, 90% were excluded because of failure to meet blood pressure criteria.

Table 3.—Mean Systolic and Diastolic Blood Pressures by Treatment Group and Year of Follow-up

Year	Blood Pressure, mm Hg*		
	Active Treatment Group	Placebo Group	Difference (Active-Placebo)
	Systolic Blood Pressure		
Baseline	170.5 (9.5)	170.1 (9.2)	+0.4
1	142.5 (15.7)	156.5 (17.3)	−14.0
2	141.8 (17.1)	154.4 (18.7)	12.6
3	142.4 (17.2)	155.0 (20.0)	−12.6
4	143.1 (18.0)	154.6 (19.8)	−11.5
5	144.0 (19.3)	155.1 (20.9)	−11.1
	Diastolic Blood Pressure		
Baseline	76.7 (9.6)	76.4 (9.8)	+0.3
1	69.5 (9.9)	73.4 (12.1)	−3.9
2	68.2 (10.9)	72.3 (12.0)	−4.1
3	68.0 (10.6)	72.1 (12.3)	−4.1
4	67.2 (11.6)	71.2 (12.6)	−4.0
5	67.7 (10.2)	71.1 (12.8)	−3.4

*Values are mean (SD).

Randomization and Baseline Characteristics of SHEP Participants

Randomization.—Stratified randomization by antihypertensive drug treatment status at initial contact and by center produced two SHEP groups—assigned to active treatment and placebo—comparable at baseline (Table 1).

Baseline Characteristics.—Mean age of participants was 72 years, 57% were women, and 14% were black (Table 1). Included among the whites were 204 Orientals (5% of whites), 84 Hispanics (2% of whites), and 41 classified as "other" (1% of whites). Of all participants, 1.4% reported a history of stroke, and 5% reported a history of myocardial infarction. On physical examination, 7% had carotid bruits. About 61% had an ECG abnormality. As a group, the cohort was overweight, with a body-mass index averaging 27.5 kg/m^2 (almost 30% overweight by actuarial criteria).[43] Fewer than 1% had cognitive impairment, and about 11% manifested symptoms of depression based on standardized questionnaire criteria. Only 5% reported limitation in activities of daily living. Mean SBP was 170.3 mm Hg; mean DBP was 76.6 mm Hg. The distribution of SBP at baseline was 160 to 169 mm Hg, 57%; 170 to 179 mm Hg, 27%; 180 to 189 mm Hg, 10%; and greater than 190 mm Hg, 5%.

Antihypertensive Drug Treatment Status by Year of Follow-up

Active Treatment Group.—Most participants randomized to the active treatment group received active antihypertensive medication (either according to the SHEP protocol or by prescription) throughout the trial—89% of participants at year 3 and 90% of participants at year 5 (Table 2). About 3% of active treatment group participants were assigned to receive known active therapy because their blood pressure met the escape criteria; medication was stopped in 13% due to side effects. At the 5-year visit, of all participants in the active treatment group, 30% were receiving step 1, dose 1 medication only; 16% were receiving step 1, dose 2 medi-

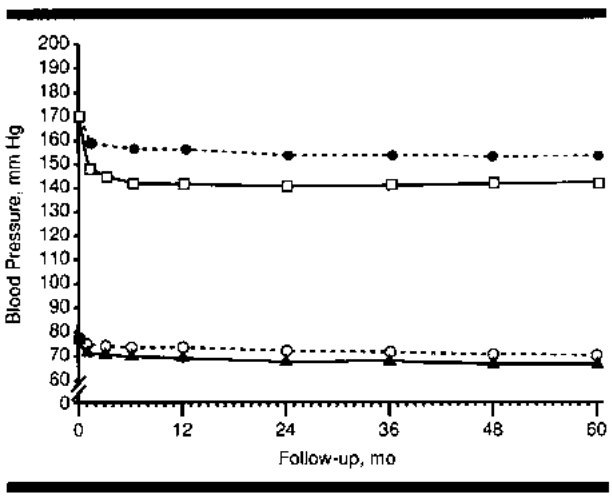

Fig 1. - Average systolic and diastolic blood pressure during the Systolic Hypertension in the Elderly Program follow-up plotted at 1, 3, 6, and 12 months and yearly therafter. Solid line with open squares indicates average systolic blood pressure for the activa treatment group; broken line with closed circles, average systolic blood pressure for the placebo group; solid line with triangles, average diastolic blood pressure for the active treatment group; and broken line with open circles, diastolic blood pressure for the placebo group.

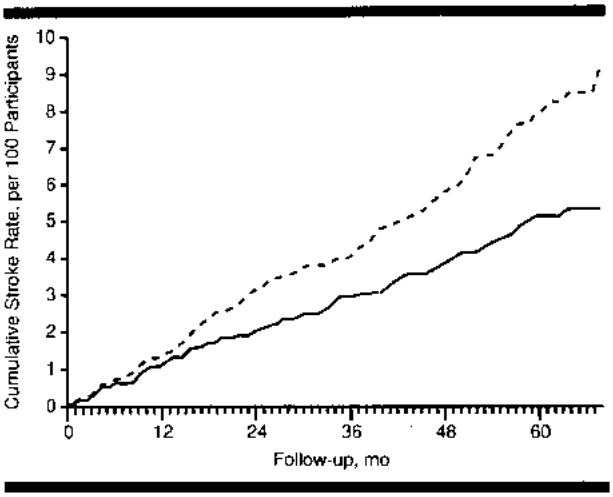

Fig 2.—Cumulative fatal plus nonfatal stroke rate per 100 participants in the active treatment (solid line) and placebo (broken line) groups during the Systolic Hypertension in the Elderly Program.

cation only; 11% were receiving step 2, dose 1 medication; 12% were receiving step 2, dose 2 medication; 21% were receiving other active medication; and 9% were receiving no antihypertensive drug. Thus, almost half of the participants were receiving the step 1 drug only, and more than two thirds of the participants were receiving the step 1 and/or step 2 drug only.

Placebo Group.—The majority of participants randomized to the placebo group continued to receive no active antihypertensive medication throughout the trial (Table 2). However, the percentage for whom active antihypertensive drug therapy was prescribed increased progressively, from 13% at year 1 to 33% at year 3 and 44% at year 5 (Table 2). Throughout the trial, about 15% of placebo group participants were assigned to receive active therapy because their blood pressure met the escape criteria (mostly due to DBP); medication was stopped in 7% due to side effects.

The proportion of participants receiving active antihypertensive medication was consistently higher throughout the trial for persons in the active treatment group than for those in the placebo group—89% vs 33% at 3 years and 90% vs 44% at 5 years (Table 2).

Mean SBP and DBP by Treatment Group and Year of Follow-up

Throughout the trial, the mean SBP of the active treatment group was substantially lower than at baseline, by about 26 mm Hg overall (Table 3 and Fig

Table 4. Total (Nonfatal Plus Fatal) Stroke Rates by Treatment Group and Year of Follow-Up*

Year	Starting No.	No. of Events†	No. Unavailable for Follow-up	Cumulative Stroke Rate (SE), per 100 Participants
		Active Treatment Group		
1	2365	28	0	1.2 (0.2)
2	2316	22	0	2.1 (0.3)
3	2264	21	0	3.0 (0.4)
4	2153	18	0	4.0 (0.4)
5	1438	13	5	5.2 (0.5)
6‡	613	1	0	5.5 (0.6)
		Placebo Group		
1	2371	34	0	1.4 (0.2)
2	2308	42	0	3.2 (0.4)
3	2229	22	2	4.2 (0.4)
4	2131	34	2	6.0 (0.5)
5	1393	24	1	8.2 (0.7)
6	584	3	0	9.2 (0.9)

*For the active treatment group compared with the placebo group, $\chi^2(1\ df) = 12.90$, $P = .0003$; relative risk, 0.64 (95% confidence interval, 0.50 to 0.82).

†There were 103 total events (96 nonfatal and 10 fatal) in the active treatment group and 158 (149 nonfatal and 14 fatal) in the placebo group. Three participants in the active treatment group and four participants in the placebo group had both a nonfatal and a fatal stroke. Only the first event (nonfatal) was counted in the total number of events and in calculations of the cumulative stroke rate.

‡The last stroke occurred during the 67th month of follow-up.

Table 5.—Stroke Events by Treatment Group and Antihypertensive Medication Status at Initial Contact

Treatment Group	No. of Participants	No. of Events: Nonfatal Stroke	No. of Events: Fatal Stroke	No. of Events: Nonfatal Plus Fatal Stroke*
	Not Receiving Antihypertensive Medication at Initial Contact			
Active	1584	64	5	67
Placebo	1577	88	11	95
Relative risk (95% confidence interval)†		0.69 (0.51-0.95)		
	Receiving Antihypertensive Medication at Initial Contact			
Active	781	32	5	36
Placebo	794	61	3	63
Relative risk (95% confidence interval)‡		0.57 (0.38-0.85)		

*Three participants in the active treatment group and four participants in the placebo group had both a nonfatal and a fatal stroke. Only the first event (nonfatal) was counted in the total number of events.

†For the active treatment group compared with the placebo group, $\chi^2(1\ df) = 5.40$, $P = .02$.

‡For the active treatment group compared with the placebo group, $\chi^2(1\ df) = 7.70$, $P = .01$.

Table 6.—Morbidity and Mortality by Cause and Treatment Group

	No. of Events		
	Active Treatment Group (n = 2365)	Placebo Group (n = 2371)	Relative Risk (95% Confidence Interval)*
Nonfatal Events			
Stroke	96	149	0.63 (0.49-0.82)
Transient ischemic attack	62	82	0.75 (0.54-1.04)
Myocardial infarction†	50	74	0.67 (0.47-0.96)
Coronary artery bypass graft	30	47	0.63 (0.40-1.00)
Angioplasty	19	22	0.86 (0.47-1.59)
Left ventricular failure	48	102	0.46 (0.33-0.65)
Renal dysfunction	7	11	...
Fatal Events			
Total deaths	213	242	0.87 (0.73-1.05)
Total cardiovascular	90	112	0.80 (0.60-1.05)
Stroke	10	14	0.71 (0.31-1.59)
Total coronary heart disease	59	73	0.80 (0.57-1.13)
Sudden death (<1 h)	23	23	1.00 (0.56-1.78)
Rapid death (1-24 h)	21	24	0.87 (0.48-1.56)
Myocardial infarction	15	26	0.57 (0.30-1.08)
Other cardiovascular	21	25	0.87 (0.49-1.55)
Left ventricular failure	8	7	...
Other	13	18	0.71 (0.35-1.46)
Total noncardiovascular	109	103	1.05 (0.80-1.38)
Neoplastic disease	75	78	0.96 (0.70-1.31)
Renal disease	2	2	...
Diabetes mellitus	2	1	...
Gastrointestinal disease	2	2	...
Respiratory disease	6	5	...
Infectious disease	10	7	...
Accident, suicide, homicide	5	5	...
Other noncardiovascular	7	3	...
Indeterminate cause‡	14	27	...
Combined End Points			
Nonfatal myocardial infarction or coronary heart disease death	104	141	0.73 (0.57-0.94)
Fatal or nonfatal stroke, nonfatal myocardial infarction, or coronary heart disease death	199	289	0.67 (0.56-0.80)
Coronary heart disease§	140	184	0.75 (0.60-0.94)
Cardiovascular disease‖	289	414	0.68 (0.58-0.79)

*Relative risk assessments were done for all types of events except those with fewer than 20 events and indeterminate cause of death.

†Nonfatal myocardial infarction does not include silent myocardial infarction.

‡Results of death certificate coding for indeterminate causes according to the ninth revision of the *International Classification of Diseases, Adapted*, were as follows: stroke, two in the active treatment group and three in the placebo group; myocardial infarction, one in the placebo group; left ventricular failure, one in the placebo group; other cardiovascular disease, seven in the active treatment group and 10 in the placebo group; neoplasm, one in the active treatment group; respiratory disease, one in the placebo group; renal disease, one in the active treatment group; infectious disease, three in the placebo group; other noncardiovascular disease, one in the active treatment group and five in the placebo group; and unknown or no death certificate, one in the active treatment group and four in the placebo group.

§Coronary heart disease includes definite nonfatal or fatal myocardial infarction, sudden cardiac death, rapid cardiac death, coronary artery bypass graft, and angioplasty.

‖Cardiovascular disease includes definite nonfatal or fatal myocardial infarction, sudden cardiac death, rapid cardiac death, coronary artery bypass graft, angioplasty, nonfatal or fatal stroke, transient ischemic attack, aneurysm, and endarterectomy.

1). The mean DBP of the active treatment group was lower by about 9 mm Hg throughout the trial compared with baseline. For the placebo group, the mean SBP was consistently lower than at baseline, by about 15 mm Hg. The mean DBP of the placebo group was lower than at baseline by about 4 to 5 mm Hg. During the trial, the SHEP goal blood pressure was reached by 65% to 72% of persons in the active treatment group but only by 32% to 40% of those in the placebo group.

Mean SBP levels were substantially lower throughout the trial for the active treatment group than for the placebo group, by 11 to 14 mm Hg (Table 3 and Fig 1). Mean DBP was reduced more in the active treatment group than in the placebo group, by about 3 to 4 mm Hg.

Total Stroke Incidence

All Participants.—With a mean follow-up of 4.5 years, incident stroke, the primary end point of the trial, was diagnosed in 103 persons in the active treatment group and 159 persons in the placebo group (Table 4). By life table analyses, 5-year cumulative stroke rates were 5.2 per 100 participants for the active treatment group and 8.2 per 100 for the placebo group. The cumulative rates for the total period of follow-up (70 months) were 5.5 per 100 participants for the active treatment group and 9.2 per 100 for the placebo group. Based on proportional hazards regression analysis, relative risk was 0.64 (95% confidence interval [CI], 0.50 to 0.82; $P = .0003$) (Table 4 and Fig 2). The absolute reduction in 5-year risk of stroke was 30 events per 1000 participants. There were few stroke deaths—10 in the active treatment group and 14 in the placebo group. The cumulative difference in total stroke incidence rates, with rates lower in the active treatment group than in the placebo group, increased progressively over the 5 years of the trial (0.2, 1.1, 1.2, 2.0, and 3.0 events per 100 participants) (Table 4). Seventeen of 96 people in the active treatment group and 28 of 149 people in the placebo group who had a nonfatal stroke died during the trial—about 20% in each group.

By Age, Sex, Race, and Baseline SBP.—Stroke incidence was lower in those randomized to active treatment than in those randomized to placebo for all baseline age groups: 60 to 69 years, 34 vs 47 events; 70 to 79 years, 48 vs 74 events; and 80 years or older, 21 vs 38 events. A favorable effect of active treatment was also noted for three of the four major sex-race groups: white men, 39 vs 64 events; white women, 48 vs 66 events; and black women, seven vs 21 events. The apparent lack of any trend for the small number of black men was based on few events (nine vs eight events). With proportional hazards regression using SBP as a continuous variable, the favorable trend in stroke incidence for the active treatment compared with the placebo group prevailed irrespective of baseline SBP.

By Antihypertensive Drug Treatment Status at Initial Contact.—One of the two SHEP subgroup hypotheses was related to the effects of active treatment on participants receiving and not receiving antihypertensive medication at initial contact. Randomization was stratified by whether or not participants were receiving antihypertensive medication at initial contact. For the subgroup not receiving antihypertensive medication at initial contact, relative risk of stroke for active treatment compared with placebo was 0.69 (95% CI, 0.51 to 0.95) (Table 5). For participants receiving antihypertensive medication at initial contact, relative risk for stroke was 0.57 (95% CI, 0.38 to 0.85).

Thus, SHEP primary end point data indicate a high degree of consistency in favorable findings for the active treatment group.

Table 7.—Prevalence of Symptoms Ever Characterized as Troublesome or Intolerable by Treatment Group

Symptom	Prevalence, %		
	Active Treatment Group	Placebo Group	z
Cardiopulmonary			
Faintness on standing	12.8	10.6	2.3
Feelings of unsteadiness or imbalance	33.7	32.9	0.6
Loss of consciousness/passing out	2.2	1.3	2.6
Heart beating fast or skipping beats	7.2	8.3	−1.4
Heart beating unusually slowly	3.8	2.1	3.6
Chest pain or heaviness	28.0	21.3	5.3
Unusual shortness of breath	11.9	11.0	1.0
Unusual tiredness	25.8	23.8	1.6
Cold or numb hands	13.6	9.8	4.1
Ankle swelling	19.5	15.6	3.5
Psychosocial			
Unusual worry or anxiety	25.5	24.1	1.1
Trouble with memory/concentration	26.4	20.4	4.9
Depression that interfered with activities	10.7	10.6	0.1
Problems in sleeping	26.4	24.5	1.5
Nightmares	4.2	3.7	0.8
Problems in sexual function	4.8	3.2	2.9
Loss of appetite	6.4	5.5	1.4
Other			
Falls	12.8	10.4	2.5
Fractures	2.4	2.0	0.8
Muscle weakness or cramping	28.4	25.9	1.9
Unusual indigestion	10.3	8.9	1.6
Change in bowel habits	15.4	11.4	4.0
Excessive thirst	7.9	6.4	2.1
Nausea or vomiting	9.7	8.2	1.7
Tarry black stools or red blood in stools	2.2	2.1	0.3
Skin rash or bruising	12.5	10.6	2.0
Unusual joint pain	36.4	31.4	3.6
Severe headaches	7.8	8.7	−1.1
Waking frequently at night to urinate	14.4	12.4	2.0
Any specified problem	91.8	86.4	6.0
Any specified problem characterized as intolerable	28.1	20.8	5.9

Morbidity and Mortality From Cardiovascular and Noncardiovascular Causes

Nonfatal Cardiovascular Events.—The number of nonfatal cardiovascular events was consistently lower for active treatment than for placebo, with relative risks ranging from 0.46 for left ventricular failure to 0.86 for angioplasty (Table 6).

Hospitalizations and Nursing Home Admissions.—Hospitalizations for any reason were recorded for 1027 active treatment group participants (1976 admissions) and 1086 placebo group participants (2204 admissions). Skilled or intermediate care nursing home admissions were recorded for 52 active treatment group participants (58 admissions) and 58 placebo group participants (65 admissions).

Deaths by Cause.—The number of deaths was lower for active treatment than for placebo for mortality from all causes (213 vs 242 deaths), total cardiovascular causes (90 vs 112 deaths), and total coronary causes (59 vs 73 deaths) (range of relative risks, 0.80 to 0.87) (Table 6). The difference observed in total deaths from coronary heart disease was largely due to the difference in the number of fatal myocardial infarctions. The number of deaths from neoplastic diseases, second only to cardiovascular disease as a main cause of mortality for SHEP participants, was similar (75 and 78 deaths) for the active treatment and placebo groups.

Combined Nonfatal and Fatal Cardiovascular Events.—Nonfatal and fatal major cardiovascular events were consistently lower for active treatment than placebo. All coronary heart disease events, nonfatal plus fatal, numbered 140 for the active treatment group and 184 for the placebo group (Table 6). By proportional hazards regression analysis, there were 25% fewer events in the active treatment group, with the 5-year absolute benefit estimated at 16 events per 1000 participants. All nonfatal and fatal cardiovascular events numbered 289 in the active treatment group and 414 in the placebo group. This represented 32% fewer events in the active treatment group, with the 5-year absolute benefit estimated at 55 events per 1000 participants.

Baseline ECG Abnormalities.—The end points for the second SHEP a priori subgroup hypothesis were the incidence of nonfatal myocardial infarction plus coronary death and the incidence of sudden and rapid death. The hypothesis dealt with the relationship of treatment assignment to risk of these events in persons with and without baseline ECG abnormalities. For the subgroup of people free of baseline ECG abnormalities, the relative risk of nonfatal myocardial infarction plus coronary death for active treatment compared with placebo was 0.83 (95% CI, 0.53 to 1.29). There were few events for the end point of sudden and rapid death—15 in the active treatment group and 10 in the placebo group. For participants with baseline ECG abnormalities, the relative risk of nonfatal myocardial infarction plus coronary death was 0.69 (95% CI, 0.50 to 0.94). For the end point of sudden and rapid death, there were 29 events in the active treatment group and 36 events in the placebo group.

The data regarding this subgroup hypothesis suggest benefit from active treatment for both those with and without baseline ECG abnormalities.

Adverse Effects

At baseline, the number of clinical complaints was comparable in the active treatment and placebo groups. During the trial, reported rates of certain problems were greater in the active treatment group than in the placebo group (Table 7).

During follow-up, serum potassium, uric acid, glucose, cholesterol, and sodium levels out of the specified ranges were reported more frequently in the active treatment group than in the placebo group (Table 8). During follow-up, the mean serum potassium concentration was lower in the active treatment group than in the placebo group; the mean serum uric acid, glucose, and cholesterol concentrations were higher in the active treatment group; and the mean serum sodium concentration was similar in the two groups (Table 8).

About 4% of persons in the active treatment and placebo groups met questionnaire referral criteria for expert evaluation of possible dementia (Table 9). For more than 90% of these people a referral was completed; the main reason for failure to achieve referral was participant refusal. Thirty-seven participants (1.6%) receiving active treatment and 44 (1.9%) receiving placebo had a diagnosis of dementia made and confirmed by the coding panel.

During the trial, 14% of persons in the active treatment group and 15% in the

Table 8.—Serum Biochemical Values by Treatment Group*

	Baseline		1 y			Ever		
	Active Treatment Group (n = 2218)	Placebo Group (n = 2202)	Active Treatment Group (n = 1682)	Placebo Group (n = 1821)	z	Active Treatment Group (n = 2255)	Placebo Group (n = 2189)	z
Serum potassium, mmol/L								
Mean ± SD	4.5 ± 0.5	4.5 ± 0.4	4.1 ± 0.5	4.4 ± 0.4	−25.2	...	...	...
% with values <3.2	0.1	0.0	1.0	0.1	3.8	3.9	0.8	6.7
Serum uric acid, μmol/L								
Mean ± SD	321.2 ± 83.3	315.2 ± 83.3	374.7 ± 101.1	327.1 ± 83.3	16.7	...	...	...
% with values ≥594.8	0.2	0.3	2.8	0.6	5.6	5.3	1.3	7.5
Serum glucose, mmol/L								
Mean ± SD	6.0 ± 1.9	6.0 ± 1.9	6.4 ± 2.4	6.1 ± 2.0	4.2	...	...	...
% with values >11.1	2.8%	3.0%	5.0	3.6	2.1	9.3	7.6	2.0
Serum cholesterol, mmol/L								
Mean ± SD	6.1 ± 1.2	6.1 ± 1.1	6.3 ± 1.2	6.1 ± 1.1	3.3	...	...	...
% with values ≥7.76	8.6	7.0	10.4	7.7	2.8	13.2	11.0	2.2
Serum sodium, mmol/L								
Mean ± SD	139.8 ± 2.5	139.6 ± 2.5	138.9 ± 3.0	139.6 ± 2.6	−7.6	...	...	...
% with values <130	0.3	0.2	1.8	0.4	4.4	4.1	1.3	5.6

*The number of participants in each treatment group and time period varied because of invalid values. We used the minimum number of participants.

Table 9.—Dementia and Depression by Treatment Group

	No. (%)	
	Active Treatment Group	Placebo Group
No. randomized	2365	2371
Dementia		
Qualified for referral	98 (4.1)	94 (4.0)
Referred	83 (3.5)	82 (3.5)
Positive diagnosis	37 (1.6)	44 (1.9)
Depression		
Qualified for referral	329 (13.9)	357 (15.1)
Referred	254 (10.7)	272 (11.5)
Positive diagnosis	104 (4.4)	112 (4.7)

placebo group met the questionnaire referral criteria for expert evaluation of possible depression (Table 9). For more than 75% of these people a referral was completed; the main reason for failure to achieve referral was participant refusal. Of participants in the two groups, 104 (4.4%) randomized to active treatment and 112 (4.7%) randomized to placebo had a diagnosis of depression.

COMMENT

The SHEP antihypertensive drug treatment regimen significantly reduced the risk of total stroke, the primary end point, in people aged 60 years and older with ISH. During the entire 70 months of study follow-up, the total stroke incidence was reduced by 36% in the active treatment group ($P = .0003$), and the absolute benefit estimated at 5 years was 30 events per 1000 participants. This result was observed even though about 35% of those assigned to placebo took known antihypertensive medications during the trial.

The incidence of nonfatal myocardial infarction (not including silent myocardial infarction) plus coronary death was 27% lower in the active treatment group than in the placebo group. This difference was maintained when the combined coronary heart disease end point also included coronary angioplasty and coronary artery bypass grafting. For all cardiovascular events (289 in the active treatment and 414 in the placebo group), the reduction in incidence was 32% for the active treatment group. This is an absolute benefit at 5 years of 55 events per 1000 participants.

In addition to positive findings for the incidence of stroke, coronary heart disease, and cardiovascular disease, there was a favorable trend for total mortality. The death rate from all causes was 13% lower in the active treatment group than in the placebo group. (As anticipated by the SHEP design, given the sample size of the trial, this difference was not statistically significant.)

Favorable outcome for the active treatment group occurred for participants receiving and not receiving antihypertensive medication at initial contact. We recognize that persons not receiving antihypertensive drugs at initial contact might be more accurately characterized as individuals with ISH than those receiving such treatment.[1] However, we conclude that the SHEP drug regimen for reduction of blood pressure significantly reduced the incidence of stroke in persons aged 60 years and above with ISH, regardless of medication status at initial contact. Favorable findings are consistent for the active treatment group compared with the placebo group irrespective of age, sex-race, and baseline SBP.

The SHEP is the first trial to test the efficacy of antihypertensive drug treatment on clinical end points for persons with ISH. The significant positive outcome on its primary end point of stroke is consistent with the trend found in the SHEP pilot study.[44] The 36% reduction in stroke incidence is similar to that found in trials of drug therapy for diastolic hypertension, including the Hypertension Detection and Follow-up Program trial, the Medical Research Council trial, and 12 smaller trials combined.[46] Overall, these previous trials recorded a 42% reduction in stroke incidence (95% CI, 30% to 54%). Findings from SHEP and other trials suggest that antihypertensive drug treatment is broadly effective, with similar reductions in the stroke rate for people with either diastolic hypertension or ISH.

Moreover, the SHEP decrease of 27% in incidence of nonfatal myocardial infarction plus coronary heart disease death for the active treatment group is similar to results of the Hypertension Detection and Follow-up Program and greater than those in other trials. Combined results of all diastolic hypertension trials indicate that sustained net decrease in blood pressure recorded for active intervention produced an overall reduction in incidence of major coronary events of 14% (95% CI, 4% to 24%).[45]

For the coronary heart disease end point, SHEP recorded a favorable trend for participants with and without baseline ECG abnormalities. The SHEP medication regimen showed no evidence of adverse effect on coronary risk for people with baseline ECG abnormalities.[8,46,47] In fact, for SHEP participants with baseline ECG abnormalities (61% of those randomized), the incidence rate of nonfatal myocardial infarction plus coronary heart disease death was 31% lower for active treatment.

The positive SHEP outcome was achieved with minimum effective doses of antihypertensive drugs in a stepped-care regimen structured to achieve and maintain a goal blood pressure at least 20 mm Hg below baseline and below 160 mm Hg. It used low-dose chlorthalidone, 12.5 mg/d, as the step 1 medica-

tion. This was increased to a maximum of 25.0 mg/d if needed. The step 2 medication—usually low-dose atenolol, 25 mg/d, or, if atenolol was contraindicated, low-dose reserpine, 0.05 mg/d—was added as needed, and the dosage of either drug could have been doubled. High-level adherence to this regimen was maintained throughout the 5 years of the trial. Based on the effects of this regimen (plus regression to the mean and adaptation to clinic assessment), the average SBP of the active treatment group was lower during the trial by about 26 mm Hg, and it was about 11 mm Hg lower than the placebo group SBP. The average DBP of the active treatment group was about 3 to 4 mm Hg lower than the placebo group DBP. These data demonstrate an ability to achieve and sustain control of ISH in older persons with a low-dose, stepped-care drug regimen. This regimen was associated with only an infrequent excess of adverse effects and no evidence of increase in dementia or depression.

Also, the SHEP results may have implications for current uncertainties about optimal drug treatment regimens for diastolic hypertension, especially "mild" hypertension. The SHEP findings are congruent with the combined results of previous trials of drug treatment for diastolic hypertension in efficacy of preventing not only stroke but also coronary heart disease and all cardiovascular disease.[45] In all these trials an oral diuretic was the step 1 treatment drug. The SHEP was unique in two respects: it used low-dose chlorthalidone, and its participants were older people with ISH. The favorable SHEP results suggest that a low-dose oral diuretic, particularly chlorthalidone, may be as efficacious for step 1 drug treatment of high blood pressure as any other drug available. Data from large-scale, long-term randomized trials are not available—such data are needed.[46] The importance of this question is underscored by data on the comparative costs of oral diuretics and newer drugs.[49]

In conclusion, SHEP demonstrated significant efficacy of active antihypertensive drug treatment in preventing stroke in persons aged 60 years and older with ISH. This result was achieved (1) with use of stepped-care treatment, starting with low-dose chlorthalidone as the step 1 medication; (2) with the majority of participants assigned to active drug therapy being at or below the goal blood pressure; (3) with a low-order excess of adverse effects; and (4) with no excess incidence of depression or dementia. Favorable findings were demonstrated for multiple secondary end points of the trial, including the incidence of major cardiac and cardiovascular events. These findings indicate a considerable potential for decreasing morbidity and disability by effective sustained drug treatment of ISH, given its prevalence and the high rates of cardiovascular diseases in those aged 60 years and older.

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SHEP COOPERATIVE GROUP INVESTIGATORS

Investigators at the 16 clinical centers and coordination and service centers of the SHEP Cooperative Group are listed below. For full membership in all SHEP subcommittees see Black et al.[51]

Albert Einstein College of Medicine, Bronx, NY.—M. Donald Blaufox, MD, PhD (*Principal Investigator*); William H. Frishman, MD; Gail Miller, RN; Maureen Magnani, RN; Sylvia Smoller, PhD; Zirel Sweezy.

Emory University School of Medicine, Atlanta, Ga.—W. Dallas Hall, MD (*Principal Investigator*); Sandy Biggio, RN, BSN; Margaret Chiappini, RN, BSN; Cori Hamilton; Margaret Huber, RN, BSN; Gail McCray; Deanne J Unger, RNC, BSN; Gary L. Wollam, MD.

Kaiser Permanente Center for Health Research, Portland, Ore.—Thomas M. Vogt, MD, MPH (*Principal Investigator*); Merwyn R. Greenlick, PhD; Stephanie Hertert; Patty Karlen, RN; Marlene McKenzie, RN, MN; Marcia Nielsen, RN, MN; Kathy Reavis, RN; Vicki Wegener, RN, FNP.

Medical Research Institute of San Francisco, Calif.—William McFate Smith, MD, MPH (*Principal Investigator*); Geri Bailey, RN; Philip Frost, MD; Jean Maier, RN; Ann Slaby; Jacqueline Smith, RN.

Miami (Fla) Heart Institute.—Fred Walburn, PhD (*Principal Investigator*); Maria Canosa-Terris, MD; Garcia Garrison, RN; Melissa Jones; Jeff Raines, PhD; Naldi Ritch; Avril Sampson, MD; Elisa Serantes, MD; Susan Surette.

Northwestern University Medical School, Chicago, Ill.—David Berkson, MD (*Principal Investigator*); Flora Gosch, MD; Joseph Harrington; Patricia Hershinow, RN; Josephine Jones; Angeline Merlo; Jeremiah Stamler, MD.

Pacific Health Research Institute, Honolulu, Hawaii.—Helen Petrovitch, MD (*Principal Investigator*); Sandra Akina, RN; J. David Curb, MD, MPH; Fred I. Gilbert, MD; Mary Hoffmeier, RN; Lei Honda-Sigall, RN.

Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway.—John B. Kostis, MD (*Principal Investigator*); Nora Cosgrove, RN; Susan Krieger, RN; Clifton R. Lacy, MD.

University of Alabama, Birmingham.—Richard M. Allman, MD (*Principal Investigator*); Ralph E. Allen, PA-C; Donna M. Bearden, MD; Lisa Carlisle; Vanessa P. Cottingham; Laura Farley, RN; Julia Hall; Glenn H. Hughes, PhD; Phillip Johnson; Linda Jones, CRNP; Laverne Parr; Pat Pierce; Harold W. Schnaper, MD.

University of California, Davis.—Nemat O. Borhani, MD, MPH (*Principal Investigator*); Patty Borhani; Alfredo Burlando, MD; Frances LaBaw, RN; Marshall Lee, MD; Sheila Lamé; Susan Pace, RN.

University of Kentucky Medical Center, Lexington.—Gordon P. Guthrie, Jr, MD (*Principal Investigator*); Jenny Brown; Jimmie Brumagen, RN; Ellen Christian, PA-C; Lynn Hanna, PA-C; Arlene Johnson, PhD; Jane Kotchen, MD; Theodore Kotchen, MD; William Markesbery, MD; Rita Schrodt, RN; John C. Wright, MD.

University of Minnesota, Minneapolis.—Richard H. Grimm, MD, PhD (*Principal Investigator*); Julie Levin; Mary Perron, RN; Alice Stafford.

University of Pittsburgh, Pa.—Lewis H. Kuller, MD, DrPH (*Co-Principal Investigator*); Robert McDonald, MD (*Co-Principal Investigator*); Shirley Arch (deceased); Gale Rutan, MD; Betsy Gahagan, RN; Jerry Noviello, PhD.

University of Tennessee, Memphis.—William B. Applegate, MD, MPH (*Principal Investigator*); Laretha Goodwin, RN, MBA; Stephen T. Miller, MD; Amelia Rose, RN; Alice Wallace, RN.

Washington University, St Louis, Mo.—H. Mitchell Perry, Jr, MD (*Principal Investigator*); Greta H. Camel, MD; Sharon Carmody; Jerome Cohen, MD; Judith Jensen, RN; Elizabeth Perry.

Yale University, New Haven, Conn.—Henry R. Black, MD (*Principal Investigator*); Diane Christianson, RN; Janice A. Davey, MSN; Charles K. Francis, MD; Linda Loesche.

School of Public Health, University of Texas Health Science Center at Houston (Coordinating Center).—C. Morton Hawkins, ScD (*Principal Investigator*); Barry R. Davis, MD, PhD; William S. Fields, MD; Darwin R. Labarthe, MD, PhD; Lemuel A. Moyé, MD, PhD; Sara Pressel, MS; Richard B. Shekelle, PhD.

Program Office, National Heart, Lung, and Blood Institute, Bethesda, Md.—*Project Officer:* Jeffrey L. Probstfield, MD; *Deputy Project Officer:* Eleanor Schron, RN, MS; *Former Project Officers:* Jeffrey A. Cutler, MD, MPH; Curt Furberg, MD, PhD; *Biostatistics Officers:* Edward Lakatos, PhD; Janet Wittes, PhD; *Contracting Officer:* C. Eugene Harris; *Contract Specialist:* Linda Gardner; *Other Key Personnel:* Thomas P. Blaszkowski, PhD; Clarissa Wittenberg, MSW.

National Institute on Aging, Bethesda, Md.—Evan Hadley, MD; J. David Curb, MD, MPH; Jack Guralnik, MD, PhD; Lot Page, MD (deceased); Teresa Radebaugh, ScD; Stanley Slater, MD; Richard Suzman, PhD.

Steering Committee.—Kenneth G. Berge, MD, Mayo Clinic, Rochester, Minn (*chair*).

Behavioral Assessment Subcommittee.—William B. Applegate, MD, MPH, (*chair*).

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Drug Selection Working Group.—Robert McDonald, MD (*chair*).

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Health Care Financing Administration, Washington, DC.—William Merashoff.

Drug Distribution Center, Perry Point, Md.—Richard Moss.

Central Chemical Laboratory (MetPath Laboratories, Teterboro, NJ).—S. Raymond Gambino, MD; Arlene Gilligan; Joseph E. O'Brien, MD; Nicholas Scalfratto; Elana Sommers.

Electrocardiographic Laboratory (University of Minnesota, Minneapolis).—Richard Crow, MD; Margaret Bodellan; Ronald J Prineas, MBBS, PhD.

Computed Tomogram Reading (University of Maryland, Baltimore).—L. Anne Hayman, MD; C. V. G. Krishna Rao, MD.

Consultants.—Marilyn Albert, PhD, Harvard Medical School and Massachusetts General Hospital, Boston; Lisa F. Berkman, PhD, Yale University, New Haven, Conn; Judith Challop-Luhr, PhD, Floral Park, NY; Debra Egan, MS, MPH, Washington, DC; June Gregonis, Duke University Medical Center, Durham, NC; Thomas R. Price, MD, University of Maryland Hospital, Baltimore; Ronald J. Prineas, MBBS, PhD, University of Miami, Fla; Kenneth A. Schneider, MD, Duke University Medical Center, Durham, NC; Philip Weiler, MD, University of California, Davis; Janet Wittes, PhD, Washington, DC.