Morbidity Abstract 323M-1

STROKE IN THE ELDERLY TREATED FOR SYSTOLIC HYPERTENSION (SHEP)

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References

1. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1991; 265: 3255-64.

2. Shurtleff D (ed.). Some characteristics related to the incidence of cardiovascular disease and death: Framingham Study, 18-year follow-up (Section 30). Washington, DC: DHEW Pub No (NIH) 74-599, 1974.

Objective

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

Patients Studied

This was a multicenter, randomized, placebo-controlled clinical trial of a stepped antihypertensive regimen in selected screenees age 60 years and older, drawn from a community-based ambulatory population in 16 tertiary care centers in the U.S. From the pool of 447,921 potential candidates, 4,736 were selected as suitable candidates for the trial, and these were randomized, 2,365 to active treatment, 2,371 to placebo. Selection criteria included confirmed systolic blood pressure readings (SBP) of 160-219 mm and diastolic blood pressure readings (DBP) under 90 mm, and informed consent. Screenees were excluded on the basis of a history or examination findings of specified major cardiovascular diseases or non-CV diseases, such as cancer, alcoholic liver disease, and impaired renal function. Randomization by the Coordinating Center (in the National Heart Lung and Blood Institute, Bethesda, Maryland) was stratified by clinical center and any antihypertensive medication used prior to randomization. The standard regimen of antihypertensive medication consisted of chlorthalidone, 12.5 or later 25 mg per day to achieve a reduction in SBP to below 160 mm, or a reduction of at least 20 mm if the intial SBP was under 180 mm. If this regimen did not result in the desired reduction in SBP, atenolol, 25 mg per day, was added. When atenolol was contraindicated, reserpine, 0.05 mg per day, was substituted as the Step 2 drug for supplementary antihypertensive medication. Matching placebo tablets were used for all patients in the placebo group. Demographic and other attributes of the treatment and placebo groups are given in Table 1A. Mean age was 71.6 years, 13.9% of the total group were black, and 56.8% were female. The entry period for recruitment was between March 1, 1985, and January 15, 1988.

Follow-up

The cutoff date is not given in the article, but was probably in 1990, as the minimum FU appears to have been in excess of 2 years, and the end of the entry period was in January 1988. Follow-up was by means of quarterly visits from the date of randomization. In addition to stroke, the SHEP study defined other nonfatal cardiovascular endpoints, such as transient ischemic attack (TIA), myocardial infarction (MI), bypass surgery, angioplasty, left ventricular heart failure, etc., and collected confirmed incidence data on all of these events. Data for endpoints were collected by each clinic staff. Death certificates and any available autopsy reports were obtained on patients who died. All study events were confirmed by a coding panel of three physicians who were unaware of the allocation to treatment or placebo group. Blood pressure readings, side effects, and changes in medication were also recorded. From Table 4 of the article it appears that only five patients were lost to FU in each group.

Expected Stroke Rates

"Expected" rates for stroke incidence have been derived from independent age-matched data of the Framingham Study.[2] The tables in Section 30 take account of characterizations on all of the first nine biennial examinations (1950-1968), and relate each characteristic to the average annual incidence rate of 14 different events by sex and age. Data have been combined for exposure to risk, E, in person-years, and number of events, n, from all biennial periods by sex and three different attained age groups at the date of each examination. The incidence rate, r, is derived as the quotient, n/E. With nine biennial examinations the tables of Section 30 cover an 18-year FU period in the Framingham Study. Table 8-10 provides results on incidence rates of cerebrovascular accident (stroke) to the characteristic, hypertension. The three classes for this characteristic were defined as normotension (blood pressure under 140/90), borderline, and definite hypertension. These rates, in strokes per 1000 exposed to risk per year, are shown in Table 1B, for men and women combined. As one would anticipate, the rates increase with age and extent of the hypertension. The decennial age groups of the Framingham Study do not correspond to those of the SHEP Study, and data are not available for patients over age 74 years. As a consequence it has been necessary to adjust for age, and these adjustments are given in Table 1C. The ratio of Framingam *normotensive* incidence rates, ages 65-74 to ages 55-64 is 4.1/1.2, or 3.4. This covers a 10-year age period, so the geometric mean of 3.4, or 1.13, represents the average annual increase factor for r'. The assumption has

been made that this factor may be used throughout the age range 60 and up in the SHEP Study. Estimates for mean r' have thus been derived as 2.6 per 1000 per year for the age group 60-69 years, 8.8 for the age group 70-79, and 30 for the age group 80 and up. Given the age distribution of subjects in the SHEP Study, the weighted mean incidence rate for *normotensive* subjects is 9.1 strokes per 1000 per year in the first year after entry into FU. A constant 13% per year increase has been used for r' after the first year of FU, in accordance with the Framingham results.

In addition to comparing stroke rates with independent source data, we have used the internal controls available from the study design. The active treatment group, with the lower FU blood pressure and mortality, has been designated for "expected" mortality, and the placebo group for "observed" (excess) mortality.

Results

Systolic blood pressure was substantially reduced in FU examinations, to about 143 mm in the treatment group, and about 155 mm in the placebo group (Table 1D). At 5 years 46% of the treatment group were receiving Step 1 drugs, 23% were receiving Step 2 drugs, 23% were receiving other antihypertensive medication, and 9% were receiving no antihypertensive medication. The prescribed alternative drugs were stopped in 13% of the treatment group because of side effects ("side effects" were the reason for stopping placebo in 7% of that group). In the placebo group most of the subjects continued to receive placebo throughout the study, but the proportion who also received antihypertensive medication rose from 13.1% at the end of the first year to 44.1% at the end of the fifth year. Despite these deviations from the regime prescribed at the time of randomization, the mean blood pressure readings were remarkably stable, and the lower systolic level in the treatment group represented a highly significant difference from the level in the placebo group ($p = 0.0003$). The blood pressure status of the treatment group may be fairly characterized as one of borderline systolic hypertension, but near-normal systolic pressure. Diastolic pressure was normal in both groups at the start and remained so. Another finding of note is the success of the treatment plan in reducing the systolic pressure to a normal or near-normal level (below or not far above 140 mm) in the majority of the subjects in that group, with significant reduction in the incidence of stroke, to be described below.

Table 4 of the article provides data for number of subjects alive at the start of each year of FU, number of total strokes during the year, and cumulative incidence of stroke (R) with standard deviation. From these data exposures to risk (E) have been derived, together with the *annual* stroke incidence rates (r), and these are shown in Table 1E for the placebo and treatment groups. Numbers of strokes (n') expected from the Framingham annual rates (r') have been added beside observed data, and the corresponding morbidity ratios and excess stroke rates have been calculated. The mean annual morbidity ratio is 93% for the treatment group, and 144% for the placebo group, with an excess stroke rate of 4.9 per 1000 per year. When strokes between 60 and 70 months are included, the totals observed in FU were 103 events in the treatment group (10 fatal), and 159 events in the placebo group (14 fatal). The "relative risk" of stroke, treatment group compared with placebo group, was 0.64, with $p = 0.0003$, a highly significant difference. The use of an independent source for stroke incidence rates in Table 1E shows close correspondence between the rates for the normotensive Framingham subjects and the rates for the treatment group in the SHEP study, these subjects having a near-normal systolic and a normal diastolic pressure. Failure to reduce systolic pressure in the placebo group below an average of about 155 mm has resulted in an incidence of about five extra strokes per 1000 exposed to risk per year (SHEP vs. Framingham rates). Maximum FU was 70 months, so the total events cited above are slightly in excess of the 5-year totals in Table 1E.

A different method of comparison has been used in Table 1F for event rates with total strokes, transient ischemic attacks (TIAs), and cardiovascular events of all types (definition in last footnote of the table). All event rates were lower in the active treatment group as compared with the placebo group. The "risk ratios" used in the article are thus decimal values less than 1.00. Since it is a customary convention in tables of comparative mortality and morbidity to describe results in terms of *excess rates*, or ratios *greater than 100%*, the comparison has been reversed: rates in the active treatment group, with near-normal mean systolic pressure, have been used as the expected rates, and the higher rates in the placebo group have been regarded as the observed rates. The morbidity ratios are therefore the inverse on the decimal risk ratios given in the article. This does not affect the statistical significance of the difference in rates, as given in the article, either as a P value or 95% confidence limits (CL). Since the exposures in the two groups are not identical, the data used in derivation of the expected (active treatment) rates have been given in the upper part of Table 1F. The comparative results appear in the lower part of the table, with E and n for the placebo group, and n' calculated from E and the expected r', for the active treatment group. This provides automatic adjustment for the slight differences in exposure between active treatment and placebo groups.

About one third of the subjects in each group were receiving antihypertensive medication just prior to the randomization procedures, and the SHEP authors have provided data on stroke rates for the subgroups with and without such prior treatment. These are included in Table 1F, and show higher event rates for those with such a treatment history than for those without: morbidity ratios of 146% and 196%, respectively. For total strokes the overall morbidity ratio of 162% was significantly greater than 100%, and this was true also for nonfatal strokes (149 events in the placebo group vs. 96 in the active treatment group). However, the excess of fatal strokes (14 vs. 10) was not significant at the 95% level, and the TIA ratio of 132% also did not achieve statistical significance. The excess event rate was 5.8 per 1000 per year for total strokes, and 2.1 per 1000 per year for TIAs. A much higher excess event rate of 23 per 1000 was observed for all CV events, and the morbidity ratio of 145% had a high statistical significance, because of the large numbers of events, 414 in the placebo, and 289 in the active treatment groups.

Incidence data for various indicators of coronary heart disease and cause of death results have been considered to be of sufficient importance to warrant presenting in a future morbidity abstract. For side effects of treatment and other details pertinent to stroke and TIA, the reader is referred to the source article.[1]

Comment

The oral diuretic drug chlorthalidone proved to be effective in reducing the mean systolic pressure to a near-normal level of about 143 mm, and there were significant reductions in the incidence rates for stroke and all CV events. In the 1979 Blood Pressure Study, men at ages 60-69 years with a diastolic pressure < 83 mm had a mortality ratio exceeding 220% when the systolic pressure was 158 mm or higher, but a ratio of only 112% or less when the systolic pressure was below 158 mm. These ratios were for all durations to 22 years combined. For durations 0-5 years a mortality ratio of 185% was found in men age 40-69 in rated systolic hypertension group G (BP 148-167/78-87 mm). For all durations in men age 40-69 the mortality ratio by cause of death was also significantly elevated at 242% for "Vascular Lesions of CNS," based on 161 death claims (Table S21). Systolic hypertension results in increased stroke mortality as well as morbidity even though stroke deaths were too few in the SHEP study to achieve significance (14 in the placebo group and 10 in the active treatment). As noted, CV mortality results will be developed in a future abstract.

Table 1A

Selected Characteristics for SHEP Placebo and Active Treatment Groups

Characteristic	Placebo		Active Treatment	
	No.	%	No.	%
Total Group	2371	100.0	2365	100.0
Age 60-69	992	41.9	972	41.1
70-79	1061	44.7	1062	44.9
80 up	318	13.4	331	14.0
Race - Black	332	14.0	326	13.8
Sex - Male	1012	42.7	1034	43.7
Sex - Female	1359	57.3	1331	56.3
Current Smoker	306	12.9	298	12.6
Exsmoker	891	37.6	866	36.6
Never Smoked	1174	49.6	1201	50.8
History of Stroke	31	1.3	35	1.5
History of MI	116	4.9	116	4.9
Baseline ECG Abnormal	1439	60.7	1450	61.3

Table 1B

Mean Blood Pressure by Follow-up Duration

Duration of FU	Placebo	Active Treatment
0 (at entry)	170/76	170/77
1 year	156/73	142/70
2 years	154/72	142/68
3 years	155/72	142/68
4 years	155/71	143/67
5 years	155/71	144/68

Table 1C

Stroke Incidence Rates, Framingham Study Experience 1950-1968, by Age and Blood Pressure Group at Biennial Exams 1-8, Male and Female Combined

Age	Normotensive*			Borderline Hypertensive*			Definite Hypertensive*		
	Exposure Pers Yrs.	No. of Strokes	Inc. Rate per1000	Exposure Pers Yrs.	No. of Strokes	Inc. Rate per1000	Exposure Pers Yrs.	No. of Strokes	Inc. Rate per1000
	E	n	r	E	n	r	E	n	r
45-54	17318	11	0.6	9314	16	1.7	5048	16	3.2
55-64	9738	12	1.2	8226	21	2.6	6082	31	5.1
65-74	2658	11	4.1	3476	27	7.8	3746	37	13.5
60-69			2.6†			5.2†			9.3†

* Normotensive: BP < 140/90. Borderline Hypertensive: BP 140-159/< 95 or (< 160)/(90-94). Definite Hypertensive: systolic BP 160/90 or higher.

† Estimated as arithmetic mean of rates in age groups 55-64 and 65-74.

Table 1D

Estimate of Normotensive Stroke Rate, Weighted for Age Distribution in Total SHEP Series, with Allowance for Age Increase in Rate

Framingham Age Increase			Weighted Mean "Expected" r', SHEP Series					
Age Years	Rate/1000 BP < 140/90	Age Factor	SHEP Age	Initial Rate	10-year Factor	Rate for SHEP Age	SHEP Age Distrib.	Fraction of Rate
	r'	x		r'_i	x	r'	f	(r')(f)
55-64	1.2		60-69	2.6	1.0	2.6	0.415	1.1
65-74	4.1		70-79	2.6	3.4	8.8	0.448	3.9
10yr x		3.4	80 up	8.8	(3.4)	29.9	0.137	4.1
Ann. x		1.13*	All	—	—	9.1	1.000	Sum 9.1

* Geometric mean annual increase = $(3.4)^{0.1}$

Table 1E

Stroke Incidence Rates, SHEP Clinical Trial (Subjects Age 60 up), Compared with Rates in Framingham Study Subjects, 1950-1968, Adjusted to SHEP Age Distribution (See Tables 1A-1D)

FU Interval Start-End t to t + Δt	Exposure Pers.-Yrs. E	No. of Strokes Obs. n	No. of Strokes Exp.* n′	Morbidity Ratio 100n/n′	Mean Ann. Stroke Rate per 1000 Obs. r	Mean Ann. Stroke Rate per 1000 Exp. r′	Mean Ann. Stroke Rate per 1000 Excess (r-r′)	Cumulative Rate Stroke-Free Surv. P†	Cumulative Rate Stroke Incid. R
				2371 Patients on Placebo					
0-1 yr	2356.5	34	21.4	159%	14.4	9.1	5.3	.986	.014
1-2	2289.5	42	23.6	178	18.3	10.3	8.0	.968	.032
2-3	2191.0	22	25.4	87	10.0	11.6	–1.6	.958	.042
3-4	1779.0	34	23.3	146	19.1	13.1	6.0	.940	.060
4-5	1000.5	24	14.8	162	24.0	14.8	9.2	.917	.083
0-5	9616.5	156	108.5	144	16.2	11.3	4.9	.917	.083
				2365 Patients on Active Treatment					
0-1 yr	2354.5	28	21.4	131%	11.9	9.1	2.8	.988	.012
1-2	2301.0	22	23.7	93	9.6	10.3	–0.7	.979	.021
2-3	2219.0	21	25.7	82	9.5	11.6	–2.1	.969	.031
3-4	1804.5	18	23.6	76	10.0	13.1	–3.1	.960	.040
4-5	1032.0	13	15.3	85	12.6	14.8	–2.2	.948	.052
0-5	9711.0	102	109.7	93	10.5	11.3	–0.8	.948	.052

* Basis of expected stroke rate: Framingham Study 18-year FU for normotensive subjects.[2]

† $P = (p_1)(p_2) \ldots$, where $p = (1 - r)$.

Table 1F

Strokes and Other CV Events in the SHEP Study - Incidence Rates in the Placebo Group Compared with Rates in the Actively Treated Patient Group

Group	No. Alive at Start *l*	Exposure* Pers-Yrs E	No. of Events Observed† n	No. of Events Expected† n′	Morbidity Ratio 100n/n′	Mean Ann. Event Rate/1000 Observed† r	Mean Ann. Event Rate/1000 Expected† r′	Mean Ann. Event Rate/1000 Excess (r-r′)
				Actively Treated Group Used for "Expected" Rates				
No prior AHD[1]	1584	6623	—	67	—	—	10.1	—
With prior AHD[1]	781	3266	—	36	—	—	11.0	—
Total-Stroke[2]	2365	9889	—	103	—	—	10.4	—
Total-TIA[3]	2365	9889	—	62	—	—	6.3	—
Total-CV Events[4]	2365	9889	—	289	—	—	29.2	—
				Placebo Group (Mean BP 155/72) vs. Treated Group (Mean BP 142/69)				
No prior AHD[1]	1577	6509	96	65.8	146%	14.7	10.1	4.6
With prior AHD[1]	794	3277	63	32.2	196	19.2	11.0	8.2
Placebo-Stroke[2]	2371	9786	159	98.0	162	16.2	10.4	5.8
Placebo-TIA[3]	2371	9786	82	61.4	132	8.4	6.3	2.1
Placebo-CV Events[4]	2371	9786	414	286.0	145	42.3	29.2	13.1

* Derived from article data for *l* and E, annual data to 5 years plus 60 to 70 months, for Active Treatment and Placebo Groups. Estimated for subgroups (mean FU 4.13 years in Active Treatment Group and 4.18 years in Placebo Group).

† Because of higher FU systolic BP the Placebo Group has been designated "Observed" and the Actively Treated Group has been designated "Expected" with respect to incidence rates.

1 AHD - antihypertensive drug used prior to randomization.

2 Total completed strokes, fatal and nonfatal.

3 TIA - transient ischemic attack as distinct from a completed stroke.

4 All cardiovascular events, nonfatal and fatal: myocardial infarction, sudden or rapid cardiac death, coronary artery bypass graft, angioplasty, stroke, TIA, and endarterectomy.