Survival and Recurrence Following Stroke
The Framingham Study

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SUMMARY Survival and recurrences after stroke were assessed prospectively in a general population sample of 5184 subjects followed biennially for 26 years. Initial strokes occurred in 198 men and 196 women. There were 84 second and 27 third strokes and 223 deaths reported. Thirty-day case-fatality rates for initial strokes were: 15% (33/222) for brain infarction, 16% (10/63) for cerebral embolus, 46% (18/39) for subarachnoid hemorrhage, and 82% (14/17) for intracerebral hemorrhage.

Cumulative, age-adjusted 5-year survival rates for brain infarction were reduced by pre-stroke cardiac disease (coronary heart disease and/or congestive heart failure) and hypertension prior to initial stroke from .85 to .35 in men and .70 and .56 in women. Hypertension alone reduced survival from .85 to .51 in men, but not in women.

Recurrences were primarily of the same type as the initial stroke. Cumulative 5-year recurrence rate for brain infarction was .42 for men, almost double that for women. Rates were reduced by excluding hypertensives and those with combined cardiac comorbidity and hypertension. Thus, risk of death or recurrence after stroke is substantial and profoundly influenced by sex and by cardiac comorbidity and hypertension present prior to the initial event.

STROKE RANKS THIRD as a cause of death in the United States. Among survivors, recurrence is common with cumulative disability among those affected. The impact of stroke as a force of mortality can be most clearly assessed by prospective epidemiologic study of a defined population. In this way possible contributing factors measured systematically prior to the stroke may be compared in survivors of the initial stroke and in decedents. These identified precursors of stroke and of stroke survival may also be compared among those prone to stroke recurrences. As a result, the candidates for stroke, for death from stroke, and for stroke recurrence can be identified and possible preventive measures recommended.

Methods

The Heart Disease Epidemiology Study, comprised of a stratified general population sample of residents of the town of Framingham, Massachusetts, began in 1949 with an initial cohort of 5209 men and women, aged 30 to 62 years at entry. Extensive evaluations including physical examination, laboratory testing, and personal history taking were conducted biennially. A population of 5184 men and women found to be free of stroke at Exam I have been followed prospectively for 26 years for disease occurrence including stroke and death. Sampling procedure, criteria, and methods of examination have been described elsewhere.

By applying uniform criteria, each stroke was classified by type as either Atherothrombotic Brain Infarction (ABI), Cerebral Embolism (CE), Intracerebral Hemorrhage (IH), Subarachnoid Hemorrhage (SH), Transient Ischemic Attack only (TIA), or Other. Follow-up has been good with 81% taking each exam and only 3% completely lost to follow-up after 26 years. On each of the 14 biennial examinations, the subjects were routinely questioned by a physician concerning habits, medications, and illnesses during the preceding two years. Subjects were systematically queried about the occurrence of transient monocular blindness, episodic vertigo, focal numbness, tingling or muscle weakness, double vision or speech disturbance. Details surrounding all interim illnesses were sought.

For stroke, including transient ischemic attacks (TIA), surveillance was maintained by the daily monitoring of all admissions to the only general hospital in town. If a stroke or TIA was suspected, the patient was seen in the hospital by the study neurologist (P.A.W.), usually within a few days of the ictus. Neurological symptoms or signs noted by the study physician at biennial examination, including TIA diagnosed by the patient's private physician, were followed by a detailed evaluation in the Neurology Clinic. The circumstances surrounding all illnesses and the death of each study subject were also investigated by scrutiny of all available medical information, including hospital and physician records and postmortem data. For all illnesses under study and upon the death of each subject, all data were reviewed by a panel of physicians to determine the stroke status and underlying cause of death. A neurologist has participated in reviews of suspected stroke cases for the past 18 years. During the past ten years, most subjects have been admitted to the hospital by their personal physicians when stroke or TIA was suspected. Most had lumbar puncture, brain scan, EEG and skull radiographs. Cerebral arteri-
raphy was performed on some patients with stroke and computerized axial tomography was done in recent years. Forty percent of decedents in the cohort were autopsied; in half of these the brain was examined.

Life table analysis was carried out to evaluate survival using the initial stroke as the common starting point. Cumulative survival rates were calculated for the ABI group alone and for all strokes combined. Each case was classified as to whether the patient had associated congestive heart failure (CHF), coronary heart disease (CHD), both combined, or no heart disease prior to the initial stroke, and cumulative survival rates were calculated. Because of the similarity in survival rates for the cardiac comorbidity groups, the CHD and CHF groups were combined. Realizing that age at stroke has a definite impact on survival, summary relative odds were used to compute age-adjusted survival curves. A further reclassification of the cases accounting for hypertension prior to stroke was then carried out. Definite hypertension prior to stroke was designated when on two separate examinations prior to the stroke the patient was found to have a blood pressure of 160/95 or greater. This resulted in four categories: 1. hypertension only; 2. CHD and/or CHF alone; 3. hypertension with CHD and/or CHF; and 4. no comorbidity prior to the initial stroke. Age-adjusted cumulative survival rates were subsequently calculated for all subgroups except the second category because of the small number of cases. Standard survival rates were also calculated using a segment of the Framingham population with an average age similar to the stroke cohort.

Recurrences were identified and comparisons made between the type of initial stroke and the type of second stroke. Third and fourth strokes were also recorded. Using the time interval from first to second stroke and accounting for withdrawals and deaths, a cumulative recurrence rate was calculated for the ABI group. The recurrences were classified according to associated hypertension, CHD, and CHF prior to the initial stroke and cumulative recurrence rates were recalculated.

Results

At the end of twenty-six years of follow-up 394 strokes had occurred: 198 in men, 196 in women. ABI was the commonest type of stroke accounting for 57% of all strokes; CE accounted for 16%, SH and IH for 10% and 4%, respectively, while other strokes occurred in 3%, and TIA only in 10% of the total (table 1). Type of initial stroke was distributed similarly in men and women and most occurred in the seventh decade.

Case Fatality Rate

The thirty-day case fatality rate varied dramatically by type of stroke with a 22% rate overall (fig. 1). ABI rates were equal in men and women at about 15%, but appeared to be higher in men than women for SH with an average of 46%. The case fatality rate for IH was 82%. These higher case fatality rates were clearly related to the virulence of the disease and were not merely an age effect, since the hemorrhage cases were, on the average, younger than either cerebral embolism or brain infarction events. Age, however, had a definite impact on the case fatality rate for ABI (table 2). The rate in men increased from 8% for ABI occurring below the age of 60 to 23% for those above the age of 70. The rates in women were quite similar. The disparity in case fatality rates in cerebral embolism between men and women is perplexing. The discrepancy of 23% in men versus 9% in women cannot be accounted for by age since the average age at stroke was 67 in men and 69.5 in women. Neither can it be explained by the nature of the underlying cardiac disease, since rheumatic heart disease is more common in younger women in Framingham.

Survival

Survival was assessed after the initial stroke. At the end of ten years of follow-up the cumulative survival rate for all strokes combined was 35%. Survival was better for women than men continuing a trend established within the first few years following the stroke. This superior survival experience in females was not due to age differences since the average ages of the two sexes were similar. At 5 years the cumulative survival rate was about 89% for the standard population; for stroke victims survival were 60% for women and 52% for men. For ABI, survival results were similar to all strokes combined (fig. 2). Their cumulative five-year survival rates were 56% and 64% for men and women, respectively. Since the majority of the strokes (57%) were ABIs and death was usually immediate (within the first month of stroke) for the hemorrhages, long term survival was determined largely by the ABI group. Henceforth, survival results will only be reported for the ABIs.

Determinants of survival were studied by examining the effect of cardiac comorbidity on survival. Survival was found to be worse in the presence of either CHD or CHF than in those free of these conditions (fig. 3). Five-year cumulative survival rates for ABIs were substantially reduced from 69% to 41% in men but only reduced from 68% to 65% in women. The rate of decrement in survival for the standard population and that for ABIs without heart disease appears similar.

| Table 1 Distribution of Initial Stroke by Type, 26 Year Follow-up |
|----------------|----------------|----------------|
|                | Number of cases | Percent of all strokes |
|                | Men | Women |                  |
| Atherosclerotic brain infarction | 111 | 111 | 57% |
| Cerebral embolus | 30 | 33 | 16% |
| Intracerebral hemorrhage | 10 | 7 | 4% |
| Subarachnoid hemorrhage | 16 | 23 | 10% |
| Transient ischemic attack only | 25 | 16 | 10% |
| Stroke from other causes | 6 | 6 | 3% |
| Total | 198 | 196 | 100% |
suggesting that after the first three months the difference in survival between these two groups is largely a consequence of the immediate stroke mortality.

To assess the impact of hypertension, the major determinant to stroke occurrence, on survival these rates were recalculated for three groups: those with hypertension associated with CHD and/or CHF, those with hypertension only, and those free of these conditions. For ABIs, there is a definite impact of hypertension and cardiac comorbidity on survival (fig. 4). This is most striking in men. Cardiac comorbidity and hypertension together exert a marked adverse impact on survival, reducing the cumulative five-year survival rate from 85% to 35%; those with hypertension alone occupy an intermediate position at 51%. Survival in the five years after ABI is quite good in men free of hypertension and cardiac comorbidity. For women, the five-year cumulative survival rate was reduced from 70% to 55% by the presence of prior hypertension and cardiac comorbidity. However, prior hypertension alone had little adverse impact on survival after ABI in women. The presence of cardiac comorbidity had a greater adverse impact on survival in men than women. Hypertension also exerts greater adverse effect in men than in women. For men and women free of hypertension or cardiac comorbidity prior to the ABI survival is quite comparable.

Recurrence

There is a substantial recurrence rate among stroke survivors. In men, there were 43 second strokes and 15 third strokes. In women there were 41 second strokes and 12 third strokes and one fourth stroke. The majority of recurrences were of the same type as the preceding stroke. Sixty-five percent of the recurrent strokes were ABIs. This is due to the high case fatality rates among the hemorrhage cases, and the great frequency of ABI as the initial stroke. For second stroke after ABI, men experienced a 42% five-year cumulative recurrence rate and women a 24% rate (fig. 5). This excess risk of recurrences among men was not due to age since the age composition of the two groups was quite similar.

After removing cases with hypertension prior to the initial ABI, the cumulative recurrence rate falls, particularly in men. A further reduction in recurrence occurs in men when those cases with prior hypertension and CHD and/or CHF are excluded. After ABI in men, five-year cumulative recurrence rates were re-
with no additional reduction by excluding those with cardiac comorbidity and hypertension.

Discussion
The least distorted picture of survival and recurrence, and of the natural history of stroke may be discerned through prospective epidemiologic study. Study of a general population sample eliminates the bias of case selection encountered in clinical series of
Concerning survival, intracranial hemorrhage, both intracerebral and subarachnoid hemorrhage, are highly lethal and account for the major portion of the thirty-day case fatality rate. ABI, accounting for the majority of the cases, has a better immediate survival. After surviving the initial event, those ABIs free of hypertension and cardiac comorbidity survive nearly as well as the general population. In men, documented hypertension prior to the stroke has an adverse effect on

FIGURE 4. Survival Following ABI, Effect of Prior Hypertension and Cardiac Comorbidity.

FIGURE 5. First Recurrence of Stroke Following ABI.
survival. When combined with CHF or CHD survival after stroke is poorer still. In women, however, hypertension prior to the ABI has little adverse impact on survival and only in the presence of CHF or CHD does hypertension exert an adverse influence. Hypertensive women in the Framingham cohort are more likely to comply with antihypertensive therapy and to achieve better blood pressure control than men. Possibly, this better control of hypertension following stroke in women places them at nearly the same blood pressure level and thus at the same survival level as the general population.

Recurrence is common, particularly following ABI and is usually of the same type as the initial stroke. It is more frequent in men. This is not due to an age effect since the age composition of the two groups is quite similar. Recurrence in men, as in survival, is strongly influenced by the presence of cardiac comorbidity prior to the initial stroke, and by the presence of hypertension as well. Recurrence in women, however, is not as strongly influenced by these antecedent conditions, again probably as a result of better blood pressure control in women.

Immediate mortality following stroke varies in different series. In Rochester, Minnesota, the thirty-day case fatality rate for cerebral infarction was 28%, for intracerebral hemorrhage 84%, and for subarachnoid hemorrhage it was 52%. Surprisingly low immediate mortality figures, as seen in some studies, may be due to an excess of mild cases, while high case fatality rates could reflect older stroke patients or the predominance of intracranial hemorrhages in the population sample.

Other studies have also examined survival after stroke. It has been generally found that the long term survival of a stroke victim is shorter than that of the general population. Survival is adversely affected by the age at stroke and diverges more sharply from expected in the first several months after stroke. Most reports indicate long term survival to be greater in women than men; a few observe better survival in men. There are conflicting reports of the impact of hypertension on stroke survival. Most use blood pressure elevation seems to hold the key to treatment. Hypertensive patients with CHF or CHD exerts its impact on immediate as well as on long term survival.

Reported rates of stroke recurrence range from 13% to 53%. In Rochester, Minnesota, the recurrence rate was 10% in the first year, and 20% by the fifth year after stroke. Differences in the recurrence rates reflect the varying time periods of follow-up and the definition of stroke recurrence. When recurrence is defined as a worsening of existing symptomatology, rates can be expected to be higher than when documented evidence of a new event is required.

Preventive Implications
The stroke itself is the most common underlying cause of death within the first 30 days after stroke. Among long term survivors, however, cardiovascular disease is the leading cause of death. Cardiovascular disease and hypertension are also important factors favoring stroke recurrence, particularly in men. These findings have important therapeutic and preventive implications.

Treatment of elevated blood pressure and early and vigorous treatment of CHF and impaired cardiac function may exert a beneficial impact on survival. Treatment of hypertension following recovery from stroke is thought by some to be hazardous for fear of further compromising the cerebral circulation. Prospective study suggests that the benefits might outweigh the hazards. Treatment of hypertension clearly prevents the initial stroke and vigorous and sustained treatment of blood pressure elevation seems to hold the key to stroke prevention.

After hypertension, impaired cardiac function is the most potent precursor of stroke and ABI incidence. Stroke recurrence, like death following ABI, is related to hypertension and to the presence of CHD and CHF. Early diagnosis and vigorous treatment of these cardiac impairments may offer an opportunity to prevent recurrence and to improve longevity among stroke survivors.

References
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