

Ten-Year Prognosis of Stroke and Risk Factors for Death in a Japanese Community

The Hisayama Study

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Background and Purpose—There have been very few population-based cohort studies of long-term prognosis and risk factors for death after stroke. We examined the 10-year prognosis, causes, and risk factors of death after stroke in a Japanese cohort.

Methods—During a 26-year follow-up of a cohort of 1621 subjects ≥ 40 years of age, 333 subjects developed first-ever stroke and were prospectively followed up for 10 years after onset. During these 10-year follow-up periods, 268 of the 333 stroke patients died. Of those, 239 (89.2%) underwent autopsy.

Results—The risk of death was greatest in the first year after first-stroke onset in both sexes (men, 40.3%; women, 43.7%). Thereafter, the survival curves decreased gradually, and risk of death reached 80.7% for men and 80.2% for women by the end of the 10-year follow-up. The 30-day case fatality rate was substantially greater in patients with cerebral hemorrhage (63.3%) or subarachnoid hemorrhage (58.6%) than in patients with cerebral infarction (9.0%). The risk of dying after the first stroke was twice the risk for stroke-free subjects. The most common cause of death was the index stroke in the first year. Thereafter, the impact of the first stroke gradually decreased, while that of recurrent stroke increased. Multivariate analysis revealed that age, lower body mass index, and hemorrhagic stroke were significant risk factors for death after stroke.

Conclusions—Our findings suggest that the risk of death after first-ever stroke is high, in part because of the larger proportion of hemorrhagic stroke in Japanese relative to stroke victims in Western countries. (*Stroke*. 2003;34:2343-2348.)

Key Words: cause of death ■ cohort studies ■ risk factors ■ stroke ■ survival

In Japan, stroke is the third-leading cause of death.¹ Stroke is also a major cause of disability² and cognitive dysfunction in the elderly.^{3,4} Because the elderly population in Japan has been increasing rapidly, stroke-related problems in Japanese health care have become important in recent years. Information on the risk of death after stroke and on stroke predictors would be helpful in coping with these problems. Although the literature concerning fatal prognosis after stroke is extensive, most studies are based on selected series of patients referred to a hospital.⁵⁻⁹ Such patients are often not representative of all stroke cases, because patients with the most severe stroke die quickly, before reaching the hospital, and patients with mild stroke may not go to the hospital at all. A prospective study of a defined population can clearly assess this problem, but very few population-based cohort studies have been able to define accurately the pathological type of stroke and evaluate its long-term prognosis.¹⁰⁻¹²

Since 1961, we have been carrying out a prospective cohort study of cardiovascular disease in the town of Hisayama,

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Japan.^{13,14} The most outstanding features of this study are that causes of death were verified by autopsy and that brain lesions of most stroke patients were examined morphologically during autopsy or by brain imaging such as CT and MRI. The purposes of this study are to determine the 10-year survival rate after first-ever stroke in the community of Hisayama; to compare the observed risks of death after first-ever stroke with those of age- and sex-matched stroke-free subjects selected from the same community; to determine the major causes of death during different time periods up to 10 years after a stroke; and to determine risk factors for death during this period.

Subjects and Methods

Follow-Up Survey

Hisayama is a suburb of Fukuoka on Kyushu Island in southern Japan. In 1961, a total of 1621 men and women ≥ 40 years of age

Received April 17, 2003; final revision received June 4, 2003; accepted June 25, 2003.

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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000091845.14833.43

who had never suffered a stroke were recruited from the residents (88.1% of the total population of this age range) as a cohort. These subjects were then followed up for 26 years, until 1987. A detailed description of the study methods was published previously.¹²⁻¹⁴ Briefly, we collected information about new cardiovascular events through a daily monitoring system established by the study team, local practitioners, and the town government. When we suspected new neurological symptoms, the study physicians carefully evaluated the subject and tried to obtain information by further diagnostic examination, including lumbar puncture, cerebral angiography, or recent brain CT or MRI. During the 26-year study period, only 2 subjects were lost to follow-up, and 852 subjects died. Of those who died, 704 (82.6%) underwent autopsy examination.

Stroke Cases and Controls

Stroke, defined as a sudden onset of a nonconvulsive and focal neurological deficit persisting for >24 hours, was classified as cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, or undetermined type.^{14,15} The diagnosis of stroke and determination of its pathological type were based on clinical history, neurological examination, all available clinical data (including brain CT or MRI), and autopsy findings. During follow-up, we identified 340 new stroke events and divided them into 244 cases of cerebral infarction (120 men, 124 women), 60 cases of cerebral hemorrhage (40 men, 20 women), 29 cases of subarachnoid hemorrhage (6 men, 23 women), and 7 cases of undetermined type (3 men, 4 women). After exclusion of the 7 cases of undetermined type, 333 were enrolled in the study (166 men, 167 women; mean age, 73 ± 10 years; range, 46 to 97 years). As a reference group, we randomly selected individuals free from stroke at baseline among residents of Hisayama who participated in health checkups in 1973 or 1974, which was the middle of the study period. Each stroke case had 2 sex- and age-matched (± 2 years) controls. The reference group consisted of 666 individuals (332 men, 334 women; mean age, 72 ± 8 years; range, 46 to 97 years).

Follow-Up

We followed up the stroke patients from the onset of the stroke until death or 1997 and the reference group for 10 years from 1973 or 1974 to 1983 or 1985. No cases or controls were lost to follow-up.

During the 10-year follow-up, 268 of the 333 stroke patients died; of them, 239 (89.2%) underwent autopsy examination. We reviewed all the available clinical information and interviewed the attending physicians and the families of the deceased subjects. For each individual, the underlying disease was chosen as the cause of death. Diseases linked to the underlying cause of death were classified into the following 4 categories established in the Oxfordshire Community Stroke Project.⁷ First-stroke deaths were due to the direct effects of a brain lesion or to complications of immobility resulting from the first stroke. These included deaths from bronchopneumonia even years after the stroke if stroke-related impairments were thought to be in some way responsible and there was no other, more likely, cause of death. Recurrent stroke deaths were attributed directly to brain lesions or complications of immobility after a recurrent stroke (ie, with symptoms that led to early death and were associated with an increase in disability). If a death from stroke-related impairments occurred after a recurrent stroke, it was attributed to the recurrent stroke rather than the first stroke. Cardiovascular deaths were due to definite or probable cardiac causes, ruptured aortic aneurysms, or peripheral vascular disease. Sudden deaths were regarded as cardiovascular unless an alternative explanation was found at autopsy. Nonvascular deaths were those unrelated to any stroke disability and clearly were due to a nonvascular cause, eg, cancer, bronchopneumonia, accidents, or suicide.

Risk Factors for Death

To elucidate the risk factors for death in stroke cases, we collected the following data from the regular health checks performed within 2 years before the onset of stroke: age at onset; sex; alcohol consumption; smoking habits; glucose intolerance; average of 3

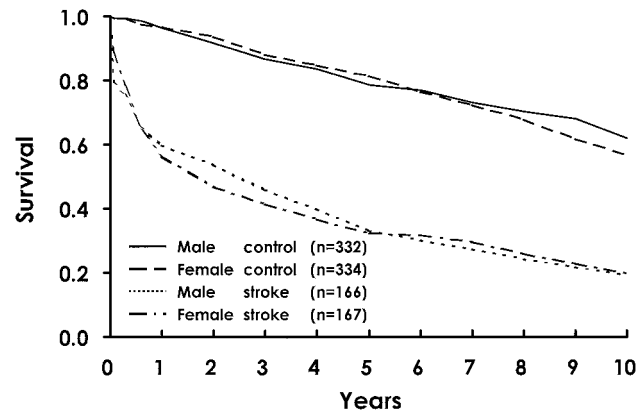


Figure 1. Kaplan-Meier survival curves by sex showing probability of survival after first-ever stroke vs a reference group free from stroke at baseline.

systolic and diastolic blood pressures; hypertension ($\geq 140/90$ mm Hg or use of antihypertensive agents); body mass index; abnormal ECG findings, including left ventricular hypertrophy (Minnesota code 3-1) and/or ST depression (Minnesota code 4-1, 4-2, 4-3); atrial fibrillation (Minnesota code 8-3); and serum total cholesterol. The categories used in the definition of glucose intolerance were described in a previous report.¹⁶

Statistical Analysis

SAS software (version 6.12) was used for the statistical analysis. Survival curves within the 10 years were calculated with the Kaplan-Meier product limit technique. The odds ratio and 95% confidence intervals (CIs) for stroke cases compared with reference subjects were calculated by the χ^2 test. We estimated the age-adjusted and multivariate relative risk (RR) of each potential risk factor for death by using the β coefficients available in the Cox proportional-hazards analysis.

Results

Absolute Risks for All Patients

Figure 1 shows Kaplan-Meier survival curves by sex for all 333 stroke patients. To similar degrees in both sexes, the risk of death was greatest in the first year (men: 40.3%; 95% CI, 32.9 to 47.8; women: 43.7%; 95% CI, 36.1 to 51.2) and particularly during the first 30 days after stroke (men: 24.7%; 95% CI, 18.1 to 31.3; women: 21.6%; 95% CI, 15.3 to 27.8%). Beyond the first year, the survival curves for the patients decreased similarly to those for reference subjects in both sexes. The risk of death reached 66.9% (95% CI, 59.7 to 74.0) for men and 67.7% (95% CI, 60.6 to 74.8) for women up to 5 years and 80.7% (95% CI, 74.2 to 86.3) up to 10 years, respectively.

Absolute Risks for Subgroups

Stratification by age showed that patients <65 years of age had a worse prognosis during the early period after stroke than did older patients (Figure 2). Among other age groups, the risk of death increased the older the patient was, regardless of the poststroke period. The survival curves comparing prognoses among the different pathological types of stroke are shown in Figure 3. The fatality rate during the early period was substantially greater for patients with hemorrhagic stroke (cerebral hemorrhage: 63.3%; 95% CI, 51.1 to 75.5; subarachnoid hemorrhage: 58.6%; 95% CI, 40.7 to 76.5) than

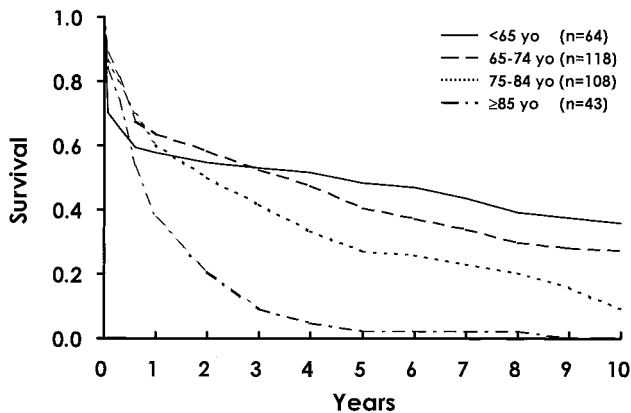


Figure 2. Kaplan-Meier survival curves stratified by age at onset showing probability of survival during 10 years of follow-up in patients with first-ever stroke.

for patients with cerebral infarction (9.0%; 95% CI, 5.4 to 12.6).

RR Compared With Controls

The risk of dying after first stroke was twice that of reference subjects (Table 1). In the first year after stroke, patients had a 12-fold RR of death, which declined to 2- or 3-fold over the subsequent years up to 5 years and to 1.6-fold in the next 5 years. Patients who survived at least 30 days had a 1.9-fold higher risk of dying over the next 10 years than reference subjects.

Cause of Death

A histogram of causes of death during different time intervals from the onset of first-ever stroke is shown in Figure 4. During the first 30 days after first stroke, 83.1% of deaths were due to the direct neurological effects of the index stroke, and another 6.5% and 2.6% were due to recurrent stroke and other cardiovascular diseases, respectively. Thereafter, the frequency of first stroke gradually decreased, whereas that of recurrent stroke increased. Over the 10-year follow-up, 41.0% of deaths were due to first stroke and 21.6% to recurrent stroke. Only 5.6% of deaths were due to other cardiovascular causes.

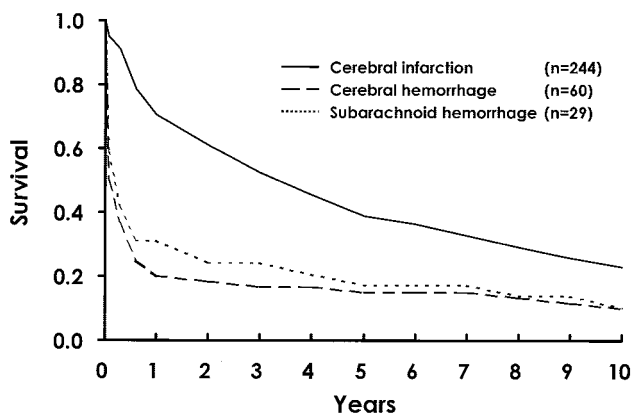


Figure 3. Kaplan-Meier survival curves stratified by pathological type of stroke showing probability of survival during 10 years of follow-up in patients with first-ever stroke.

TABLE 1. Odds Ratios of Death After a First-Ever Stroke During Different Time Intervals From Stroke Onset Compared With Controls

Interval	CVA Cases, n		Controls, n		Odds Ratio	95% CI
	At Risk	Deaths	At Risk	Deaths		
0–1 y	333	140	666	23	12.17	7.99–18.55
1–2 y	193	26	643	26	3.33	1.98–5.60
2–3 y	167	27	617	35	2.32	1.40–3.85
3–4 y	145	18	582	21	3.44	1.88–6.29
4–5 y	127	18	561	28	2.84	1.62–4.97
5–10 y	109	44	533	138	1.56	1.19–2.04
30 d–10 y	256	191	662	267	1.85	1.65–2.08
All intervals	333	268	666	271	1.98	1.78–2.20

CVA indicates cerebrovascular accident.

Risk Factors for Death Over 10 Years

Table 2 shows the multivariate prediction model for death 10 years after first-ever stroke among the 333 patients and the 244 patients diagnosed with cerebral infarction using baseline risk factors that appeared to be significant in the univariate analysis. The significant prognostic factors for death among stroke patients were age (RR for a 10-year increment, 1.55; 95% CI, 1.34 to 1.79), body mass index (RR, 0.95; 95% CI, 0.91 to 0.98), and hemorrhagic stroke, including cerebral hemorrhage and subarachnoid hemorrhage (RR, 2.84; 95% CI, 2.17 to 3.72). Among patients with cerebral infarction, significant predictors of death were age (RR, 2.03; 95% CI, 1.87 to 2.45), body mass index (RR, 0.91; 95% CI, 0.85 to 0.95), hypertension (RR, 1.57; 95% CI, 1.14 to 2.17), and atrial fibrillation (RR, 1.62; 95% CI, 1.11 to 2.36).

Discussion

The strengths of our study are that it is community based and includes almost all stroke cases developed in a cohort, thus eliminating the bias of case selection encountered in clinical series of hospital cases; a large proportion of the stroke patients underwent CT or MRI examination or autopsy to determine the pathological type; an autopsy was performed in almost 90% of deceased patients; and RRs and absolute risks of death were estimated up to 10 years after first-ever stroke.

Long-Term Prognosis

In our study, the 5-year risk of death after first stroke was 67% for men and 68% for women, exceeding the 40% to 54% rates reported in previous community-based studies.^{6–8,10} The higher fatality rates of our stroke patients are attributed to the older age of our subjects and the larger proportion (26%) of hemorrhagic stroke. These findings were similar to those of a previous study performed in another part of Japan.¹¹ In particular, our patients with subarachnoid hemorrhage showed a higher fatality rate (59%) in the early period compared with other studies in which the risks were 37% to 46%.^{6–8,10} This can be explained partly by the fact that we identified almost all instantaneous or sudden deaths by subarachnoid hemorrhage, even in cases lacking a correct diagnosis before death, because autopsies were performed in 83% of the deaths among our inception cohort.

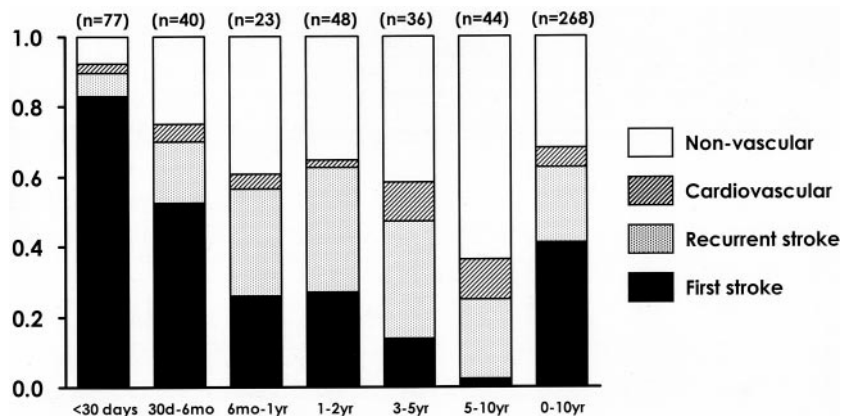


Figure 4. Histogram showing the proportion of patients dying from different causes during different time intervals from onset of index stroke.

Cause of Death

Our data confirm that the RR of death in the year after first-ever stroke for which the index stroke is mainly responsible is very high (odds ratio, 12.2; 95% CI, 7.99 to 18.55), and patients continue to die with a 2- to 3-fold excess risk in subsequent years up to 10 years. These late deaths are not due mainly to the index stroke but to recurrent stroke. Compared with Western populations,^{7,8} our subjects are characterized by a relatively small proportion of other cardiovascular events among causes of death during the late period after stroke. This probably reflects the lower risk of atherosclerotic diseases such as coronary heart and peripheral vascular diseases in Japanese.

Risk Factor for Death

As in previous studies,^{7,8,11} we found that advanced age was associated with a greater risk of death in the long-term period after stroke. This suggests that older patients may have more advanced underlying diseases. Meanwhile, in our subjects, the risk of death during the early period was worse in younger patients (<65 years of age) than in older patients. This phenomenon was attributed to a larger proportion of hemorrhagic stroke in this younger age group than among older patients.

In our study, the survival curves of hemorrhagic stroke dropped rapidly during the course of the first year after index stroke, particularly during the early period, and almost reached a plateau during the period after 1 year, whereas during the 10 years overall, the risk of dying from hemor-

rhagic stroke was 2.8-fold higher than the risk of dying from cerebral infarction. These findings imply that the risk of death from hemorrhagic stroke was determined in the acute period but that its adverse effect on fatal prognosis remained for the full 10-year follow-up period.

There are conflicting reports of the impact of hypertension on survival after stroke.^{8-11,17,18} In most of those reports,^{8,9,17} blood pressure was taken after the stroke; thus, the measurements may have been influenced by the acute event and thereby may be difficult to evaluate accurately. As in our study, prospective cohort studies in Framingham (Mass)¹⁰ and Manitoba (Canada)¹⁸ demonstrated a significant association between hypertension before stroke and increased risk of subsequent death.

Among our subjects, lower body mass index was a significant risk factor for death among patients with cerebral infarction and among total stroke patients. Our previous study showed that low body mass index was a risk factor for death from pneumonia in the elderly.¹⁹ Thus, being lean may reflect insufficient nourishment and decreased resistance to bacterial infection. Several previous reports have indicated excess mortality rates from cardiovascular disease among lean hypertensive subjects.²⁰⁻²² Lean hypertensive individuals tend to have more severe end-organ damage²⁰ and may suffer from higher peripheral vascular resistance than those who are obese²¹ and may well carry stronger genetic determinants of cardiovascular disease than obese hypertensive subjects.²²

Atrial fibrillation was another independent risk factor for death among our patients with cerebral infarction, as in other population-based studies.^{17,23} Atrial fibrillation often induces congestive heart failure and cerebral embolism, leading to early death.

Study Limitations

There are several potential limitations to the findings in our study. First, we collected stroke cases that developed among an inception cohort during 26 years of follow-up. Thus, their prognoses may have changed during the long-term observation period. Secular trends in the prognosis of stroke patients should be taken into account, and we will do so in another study. Second, the severity of the index stroke was not taken into account in the evaluation of risk factors for fatality. Thus, our estimates of the effects of risk factors are probably conservative. Finally, we could not provide information on

TABLE 2. Final Multivariate Analysis of Risk Factors at Baseline for Death After First-Ever Stroke During the 10-Year Follow-Up Period

Variable	All Stroke		Cerebral Infarction	
	RR	95% CI	RR	95% CI
Age (10 y)	1.55*	1.34-1.79	2.03*	1.87-2.45
Body mass index (1 kg/m ²)	0.95*	0.91-0.98	0.91*	0.86-0.95
Hemorrhagic stroke	2.84*	2.17-3.72	NI	
Hypertension	NI		1.57*	1.14-2.17
Atrial fibrillation	NI		1.62†	1.11-2.36

NI indicates not included in the model.

* $P < 0.01$; † $P < 0.05$.

the rehabilitation of stroke patients and evolution of the level of their functional impairment. Nonetheless, we believe that our findings contribute to a better understanding of the prognosis of stroke patients and of stroke predictors in Japanese who are considered to be at higher risk of stroke than are people in other countries.

Conclusions

Our findings confirm the importance of primary prevention of stroke, because Japanese are characterized by a larger proportion of hemorrhagic stroke and thereby a higher fatality rate after stroke. The maintenance of good nutrition may be important to improve the long-term prognosis after stroke. In addition, management of hypertension and atrial fibrillation is considered to be useful to avoid early death after cerebral infarction.

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Editorial Comment

Trends in Stroke Mortality

Stroke is a serious public health problem leading to long-term disabilities, recurrence, and death. Therefore, the prognosis of outcome is investigated in several epidemiological studies in recent years. Stroke mortality varies from country to country; an increase in mortality was observed in Eastern European countries, except in Poland, whereas mortality declined in other European population.¹ Biological, clinical, environmental, and social factors may interact to facilitate or interfere with recovery from stroke.² Barker and Lackland³ have demonstrated that within Britain and the United States there are geographic variations in poststroke mortality that are not

correlated with differences in adult lifestyle. In particular, these authors found a higher stroke mortality in areas of England and Wales characterized in the past by poor living standards. Hardie and coworkers,⁴ in a population-based study in Australia, have found that the direct effects of initial stroke and cardiovascular diseases are the major causes of death after first-ever stroke.

The present study examines the 10-year prognosis, causes, and risk factors of death after first stroke in a Japanese cohort. A total of 1261 subjects, aged >40 years and living in Hisayama on Kyushu Island in southern Japan, were enrolled

and followed from 1961 to 1987. When neurological symptoms were suspected, the patient underwent clinical and diagnostic examinations including lumbar puncture, cerebral angiography, and brain imaging. The 82.6% of patients who died underwent autopsy. To elucidate the risk factors for death, the authors have collected several clinical data: alcohol consumption, smoking habits, glucose intolerance, serum total cholesterol, body mass index, hypertension, and abnormal ECG findings. Multivariate statistical analysis indicated that age, lower body mass index, and hemorrhagic stroke were significant risk factors for death. The article describes differences between the presented findings and those obtained in previous studies from other authors. As concerns potential limitations of the study, the severity of the index stroke was not taken into account in the evaluation of risk factors for fatality.

Prospective studies on defined populations allow examination of patients representative of a broad range of cases including severe as well as very mild stroke. Therefore, these studies may better individuate and analyze parameters that may influence functional recovery, degree of disability, and stroke mortality. However, future studies have to consider in the employed statistical models also other variables related to the standards of medical care and rehabilitation, psychiatric complications, type of discharge, quality of life, and socioeconomic status.

Depression has been found to be a frequent psychiatric complication of stroke also in long-term survivors. The relationship between depression and location of brain damage is disputed, but several studies suggest that depression may impair long-term recovery in activities of daily living after stroke and can adversely affect resumption of social activities.⁵ Can mood disorders influence long-term mortality after stroke?

The role of comorbidity for recovery is debatable, however; for example, the Framingham study has demonstrated that ischemic stroke associated with atrial fibrillation leads to recurrence, higher disability, and more frequent death. Therefore, the medical care standard, including the possibility of

having adequate pharmaceutical treatments for concomitant diseases, can explain some differences in mortality trends in different countries and in different geographic areas in the same country.

According to several trials,^{2,6} home care appears to be a fruitful intervention. The familiar settings and the resumption of previous activities are probably to prompt motivation; task- and context-oriented rehabilitation approaches may improve activities of daily living, social relationships, motor dexterity, and walking. Can the benefits from a long-term personalized assistance at home reduce mortality after stroke?

To have a good understanding of the factors affecting epidemiological trends in stroke mortality as well as in long-term functional recovery, population-based studies can play a fundamental role if they are well planned considering the above-mentioned parameters, also taking into account the subtypes and the severity of cerebral vascular damages and the level of disability after the acute phase.

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