Cause-Specific Mortality After First Cerebral Infarction
A Population-Based Study

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Background and Purpose—Mortality after cerebral infarction (CI) has remained unchanged during the past 20 years, despite advances in neurologic care. Key factors affecting survival may be underrecognized. The purpose of this study was to determine the rate and cause of mortality after first CI.

Methods—In this case-control, population-based study, all available medical records were reviewed for Rochester (Minnesota) residents with a first CI between 1985 and 1989 to identify morbidities and cause of death. Predictors for mortality were analyzed.

Results—First CI was recorded for 444 patients. Survival was 83% at 1 month, 71% at 1 year, and 46% at 5 years. The most frequent causes of death were cardiovascular events (22%), respiratory infection (21%), and initial stroke complications (14%). Recurrent stroke and cancer accounted for 9% and 7.5% of deaths, respectively. In the first month after CI, 51% of deaths were attributed to the initial CI, 22% to respiratory infections, and 12% to cardiovascular events. During the first year, 26% of deaths resulted from respiratory infections and 28% from cardiovascular disease. Mortality was higher among patients than controls for at least 2 years after CI. Age, cardiac comorbid conditions, CI severity, stroke recurrence, seizures, and respiratory and cardiovascular morbidities were independent predictors of death.

Conclusions—In the first month after CI, mortality resulted predominantly from neurologic complications. Later mortality remained high because of respiratory and cardiovascular causes. To improve long-term survival after CI, aggressive management of pulmonary and cardiac disease is as important as secondary stroke prevention. **(*Stroke*. 2003;34:1828-1832.)**

Key Words: cerebral infarction ■ epidemiology ■ heart disease ■ mortality ■ pneumonia

Stroke is a major cause of morbidity and the third leading cause of death in the Western world. In Rochester, Minn, the incidence of stroke has remained essentially unchanged since 1980 after a steady decline in stroke incidence during the previous decades.[1–3] Although mortality after intracranial hemorrhage has decreased, mortality after cerebral infarction (CI) plateaued.[3,4] These findings are somewhat disturbing, given the advances in neuroimaging, intensive care, and rehabilitation technology during the past 2 decades.[5] One explanation may be that potentially avoidable medical complications and treatable comorbid conditions contribute to mortality but are not managed aggressively in clinical practice.

Although much attention is paid to secondary prevention of stroke, other preventable medical sequelae of CI may also be important sources of long-term morbidity and mortality.[6,7] Attention to potential medical complications and treatable comorbid conditions after stroke may reduce mortality and disability, at least in the acute-care setting. Patients randomly assigned to specialized rehabilitation units after stroke had a decreased incidence of secondary complications (specifically, aspiration, chest infection, and urinary tract infection), and these patients less often required long-term institutionalization than their counterparts treated on general medical services. This improved outcome was believed to be attributable to improved surveillance for and prevention of medical complications and not a difference in acute-stroke treatment.[8]

A population-based ascertainment of the cause of death after CI might identify important causes of death after stroke and potentially lead to changes in the focus of poststroke rehabilitation and medical care. Autopsy series of early stroke fatality indicate that death within the first week after stroke is attributable primarily to the direct effects of stroke, such as brain edema with transtentorial herniation.[9–11] Subsequent mortality in the first month probably is attributable to potentially preventable causes, such as pulmonary embolism and respiratory infections.[9–11]

Most previous clinical epidemiological studies of survival after CI have not evaluated specifically the cause of mortality.[3,4,12] Although a recent study of mortality after stroke did

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evaluate cause of death longitudinally, this study used a mixture of hospital-based and random-sampling methods rather than a true population-based sample.[13] The early mortality rate after first stroke (5% at 1 month) was much lower than that in previous studies, and the study lacked the power to assess independent risk factors for mortality.

To examine cause of death after first CI in a population-based, case-control study, we determined the timing and cause of death in all Rochester residents with a first CI between 1985 and 1989 and predictors of mortality after CI in these patients.

Methods

The healthcare environment in Rochester, Minnesota, is unique because almost all care for Rochester residents is provided by the Mayo Clinic, a local group practice (Olmsted Medical Center), and their affiliated hospitals. Mayo Clinic maintains inpatient and outpatient medical records as well as a master index of all diagnoses and procedures. This index includes a geographic code that identifies Rochester residents who receive care at Mayo Clinic or its affiliated hospitals. The Rochester Epidemiology Project[14] supplements this system with a similar index of medical contacts by Rochester residents at the Olmsted Medical Center and all other providers of medical care to the Rochester population. Nursing home evaluations by nurse practitioners and physicians are included in the record. Use of this extended index enables identification of all patients with specific medical disorders. The index also permits accumulation of extended longitudinal data for the high proportion of patients who remain residents of Rochester.

This study was performed by means of a population-based, retrospective medical record review. The Mayo Foundation Institutional Review Board reviewed and approved the methods. The records of all patients with a first CI between 1985 and 1989 were reviewed by 1 of the authors. The cases had been previously identified as described.[3] All available medical record information was reviewed to establish cause of death, including autopsy data if available. In the event autopsy was not performed, cause of death was determined from review of all available clinical data. Death certificate diagnoses were noted but not used as evidence of cause of death. If available data were insufficient and no medical disorder was documented immediately before death, sudden unexpected death was recorded. In addition to mortality, premorbid patient characteristics, medical morbidities, and medical events occurring after CI were identified and recorded (Table 1). Detailed definitions of risk factors and stroke subtype assessment have been published previously.[15]

An age- and sex-matched group of Rochester residents without CI was identified from the same time period, as described previously.[15] Accurate survival data from this control group are available through 8 years of follow-up.

Statistical Methods

The cohort under study was enumerated completely. Follow-up data were collected until death or the time of migration from Rochester. Follow-up data were available for 100% at 30 days, 99% at 1 year, and 98% at 5 years after CI.

The Kaplan-Meier product-limit method was used to estimate rates of survival after first CI.[16] The Cox proportional-hazards model[17] was used to predict risk factors for mortality after first CI. Multivariate proportional-hazards regression analyses were performed to identify risk factors that contributed independently to mortality after CI. This was done by stepwise forward and backward variable-selection procedures involving the basic variables and their interactions.

Results

Stroke incidence rates during this period and 1-year survival have been reported previously.[3] From 1985 through 1989, there were 444 cases of first CI in Rochester. The average patient age was 75.3 years, and 41% were men.

TABLE 1. Variables Recorded for All Patients With First CI

Patient characteristics	Sex; age; history of smoking, diabetes mellitus, hypertension, angina, myocardial infarction, atrial fibrillation, CHF, peripheral vascular disease, COPD, malignancy, GI, tract bleeding, arthritis, joint replacement, dementia, seizures, psychiatric disorder.
CI characteristics	CI subtype, location, and severity
Stroke treatment	Use of acute anticoagulation, aspirin, or oral anticoagulation; carotid endarterectomy; physical therapy; nursing home care; feeding tube; tracheostomy
Medical events after first CI	CI recurrence; intracranial hemorrhage; complication of stroke evaluation or treatment; myocardial infarction; new or worsening CHF; peripheral arterial event (including limb ischemia, arterial aneurysm, or arterial occlusion); cardiac arrhythmia; deep venous thrombosis; dehydration; pulmonary embolism; exacerbation of COPD; pulmonary infection; urinary tract infection; skin breakdown or decubitus ulcers; GI tract bleeding; falls; seizures; dementia; psychiatric disorders (including depression); limb and joint pain

CHF indicates congestive heart failure; CI, cerebral infarction; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal.

Survival

Survival after first CI (Figure 1) was 92% at 1 week, 83% at 30 days, 77% at 6 months, 71% at 1 year, 46% at 5 years, and 28% at 10 years. After CI, patients had a higher mortality rate than the age- and sex-matched population. The majority of this excess mortality occurred within the first 3 months after CI. However, the mortality rate remained higher even among patients who survived 2 years after first CI (risk ratio, 1.25; $P=0.009$).

Cause-Specific Mortality

Among the 444 CI patients, 310 deaths were documented during 10 years of follow-up. Autopsy data were available for 19%, and cause of death was determined from review of

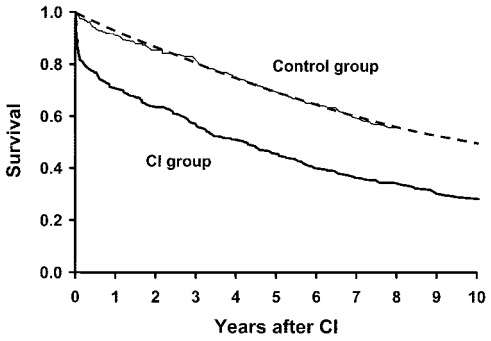

Figure 1. Kaplan-Meier 10-year survival curves for 444 patients with first CI (CI group). The observed 8-year survival of 444 age- and sex-matched control patients without CI (control group, solid line) did not differ from expected survival (community life-table data, dashed line). The mortality rate among stroke patients was highest during the first month after CI but remained increased compared with controls for at least 2 years.

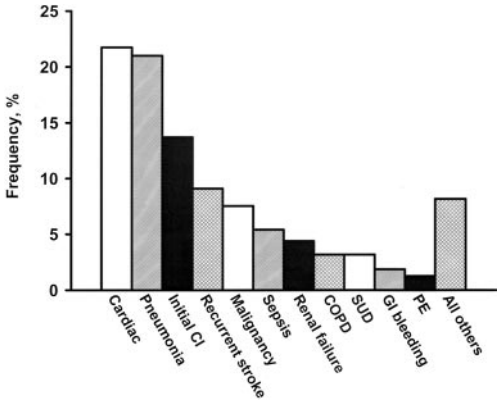

Figure 2. Cause of death after first CI. During 10 years of follow-up, 310 deaths occurred among 444 CI patients. Identified causes of death are shown in order of frequency. "Cardiac" death includes fatal myocardial infarction, fatal arrhythmia, and congestive heart failure. COPD indicates chronic obstructive pulmonary disease; SUD, sudden unexpected death; GI bleeding, fatal gastrointestinal tract bleeding; PE, fatal pulmonary embolism.

comprehensive medical records in all other cases. Overall causes of death are presented in Figure 2, and their frequency in each of several intervals appears in Figure 3. During the entire period, the most common single cause of death after first CI was respiratory infection (pneumonia), and respiratory causes as a whole (including chest infections and chronic obstructive pulmonary disease) accounted for 25% of deaths. Cardiac causes (myocardial infarction, congestive heart failure, and fatal arrhythmias) accounted for 22% of deaths. Recurrent stroke accounted directly for only 9% of deaths. Pulmonary embolism was an uncommon cause of death after CI, accounting for <2% of deaths.

Half of the deaths that occurred during the first month after CI were attributed to direct effects of the initial CI (Fig. 3). These deaths were most commonly attributed generically to

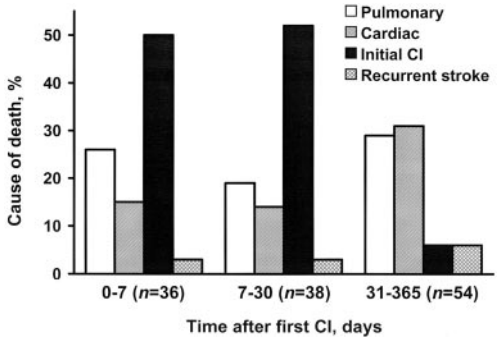

Figure 3. Cause-specific mortality during selected time intervals after first CI. During the first year, 128 deaths occurred among CI patients. More than 50% of deaths within the first month were attributed directly to the initial CI. Pulmonary deaths (due to pneumonia, chronic obstructive pulmonary disease, or pulmonary embolism) and cardiac deaths (due to myocardial infarction, congestive heart failure, or fatal arrhythmia) together accounted for 34% of the mortality during the first month after CI. In patients who survived the first month after CI, cardiac and pulmonary causes together accounted for 54% of the 1-year mortality. Mortality due to recurrent stroke accounted for only 5% of the 1-year mortality.

TABLE 2. Univariate Analysis of Risk Factors for Mortality After First CI

Risk Factor	RR	*P* Value, χ^2
Patient characteristics and medical disorders present on the date of CI		
Male	0.73	0.006, 7.50
Age	1.06 per year	<0.001, 102.71
Prior myocardial infarction	1.85	<0.001, 21.28
Prior angina	1.53	0.001, 11.44
Diabetes mellitus	1.37	0.02, 5.67
Past or present smoker	0.68	0.001, 12.02
Hypertension	1.37	0.02, 5.84
Atrial fibrillation	2.47	<0.001, 56.57
Dementia	2.32	<0.001, 36.83
Prior CHF	3.29	<0.001, 82.99
Stroke characteristics		
Subtype		
Large artery stenosis/occlusion	0.36	<0.001, 61.03
Lacunar	0.32	Non-cardioembolic vs
Ischemia	0.48	cardioembolic
Other	0.27	
Location		
Posterior circulation	0.78	0.008, 13.80
Brain stem	0.55	Non-anterior circulation
Uncertain	1.14	vs anterior circulation
Combined	1.66	
CI severity		
Moderate	1.31	<0.001, 113.05
Severe (maximal Rankin score of 4 or 5)	3.91	Moderate or severe CI vs mild CI
Events after first CI		
Chest infection	8.08	<0.001, 320.78
Skin breakdown	5.74	<0.001, 156.93
Other arrhythmia	5.39	<0.001, 24.58
CHF	3.71	<0.001, 80.15
Falls (requiring evaluation)	3.03	<0.001, 65.49
GI tract bleeding	2.74	<0.001, 26.38
Myocardial infarction	2.72	<0.001, 34.71
Recurrent stroke	2.72	<0.001, 58.74
Atrial fibrillation	2.63	<0.001, 25.46
Urinary tract infection	2.50	<0.001, 57.41
Peripheral vascular event	2.39	<0.001, 15.84
New-onset seizure	2.30	<0.001, 16.88
Pulmonary embolism	1.78	0.164, 1.94
Limb and joint pain	1.51	0.02, 5.52
Deep venous thrombosis	1.39	0.270, 1.22
Depression	0.94	0.77, 0.09
Medical and surgical interventions		
Acute anticoagulation	0.62	<0.001, 13.82
Aspirin	0.55	<0.001, 26.07
Carotid endarterectomy	0.33	0.01, 6.21

CHF indicates congestive heart failure; CI, cerebral infarction; GI, gastrointestinal; RR, relative risk.

TABLE 3. Multivariate Analysis of Risk Factors for Mortality After First CI

Risk Factor	RR*	*P* Value
Patient characteristics and medical disorders present on the date of CI		
Age	1.03 per year (1.02–1.04)	<0.001
Prior myocardial infarction	2.22 (1.53–3.23)	<0.001
Prior angina	0.66 (0.47–0.92)	0.01
Atrial fibrillation	1.71 (1.22–2.39)	0.002
Prior CHF	1.50 (1.09–2.06)	0.01
Stroke characteristics		
Subtype		
Large artery stenosis/occlusion	0.68 (0.44–1.06)	00.1
Lacunar	1.39 (0.86–2.26)	Non-cardioembolic
Ischemia	1.19 (0.82–1.71)	vs cardioembolic
Other	0.45 (0.18–1.13)	
CI severity		
Moderate	1.00 (0.69–1.43)	<0.001
Severe (maximal Rankin score of 4 or 5)	1.84 (1.29–2.63)	Moderate or severe CI vs mild CI
Events after first CI		
Chest infection	4.88 (3.80–6.27)	<0.001
Myocardial infarction	2.80 (1.92–4.08)	<0.001
Skin breakdown	2.56 (1.89–3.55)	<0.001
Peripheral vascular event	2.51 (1.51–4.03)	<0.001
Recurrent stroke	2.31 (1.74–3.06)	<0.001
CHF	2.11 (1.53–2.90)	<0.001
New-onset seizure	1.81 (1.16–2.83)	0.009
GI tract bleeding	1.75 (1.15–2.67)	0.009
Falls (requiring evaluation)	1.56 (1.17–2.08)	0.002
Limb and joint pain	0.65 (0.45–0.95)	0.03
Medical interventions		
Acute anticoagulation	0.63 (0.47–0.85)	0.002
Aspirin	0.69 (0.53–0.90)	0.006

*95% confidence interval.
CHF indicates congestive heart failure; CI, cerebral infarction; GI, gastrointestinal.

brain ischemia; transtentorial herniation was documented in only a small proportion of deaths (4%). Respiratory infections and cardiovascular causes (myocardial infarction, congestive heart failure, and arrhythmias) accounted for large proportions of the other deaths during the first month after CI. In patients who survived 30 days after a first CI, the cause of subsequent death was divided about equally between cardiac causes (28%) and respiratory causes (26%). Recurrent stroke remained a notable but minor cause of death.

Risk Factors for Mortality After First CI

Using a Cox proportional-hazards model, we examined potential predictors of mortality after CI. The risk factors included in the model and their relative risk (RR) values are listed in Table 2 (univariate analysis). Table 3 lists the independent risk factors identified by multivariate analysis.

Advancing age and history of myocardial infarction or atrial fibrillation were strongly associated with increased mortality after first CI. Severe CI (defined as a maximal Rankin disability score of 4 or 5) was also associated with higher mortality. Moderate CI severity, however, did not predict higher mortality than did mild CI.

Major medical complications during the 10 years after first CI were recorded carefully. Several neurologic and medical complications after CI were important predictors of mortality. In particular, significant predictors of mortality after first CI, independent of other risk factors including stroke severity, were recurrent stroke (RR, 2.31 [95% confidence interval, 1.74 to 3.06]); chest infection (RR, 4.88 [3.80 to 6.27]); myocardial infarction (RR, 2.80 [1.92 to 4.08]); congestive heart failure (RR, 2.11 [1.53 to 2.90]); new-onset seizures (RR, 1.81 [1.16 to 2.83]); and skin breakdown (RR, 2.56 [1.89 to 3.55]).

Acute anticoagulation therapy (with heparin or heparinoids) and aspirin use after first CI were associated with reduced mortality. This association was independent of CI subtype, CI severity, and other factors included in the model.

Discussion

Stroke is a leading cause of death worldwide. After first CI, patients had higher mortality than did age- and sex-matched subjects without stroke. Most of the higher mortality was apparent in the first 3 months after CI. However, the mortality rate in CI survivors continued to exceed the mortality rate in matched subjects without stroke for several years after CI.

During the first 30 days after CI, deaths were primarily caused by neurologic complications of acute brain ischemia, although numerous early deaths were attributable to cardiac events and respiratory infections. In contrast to data from previous autopsy studies,[9–11] pulmonary embolism was not a major cause of death in our cohort. Patients who survived the first month after CI continued to have a higher mortality rate than controls because of cardiac and pulmonary events rather than direct effects of the initial CI. Comparatively, recurrent stroke accounted for only a small proportion of deaths (<10%) during long-term follow-up.

In multivariate analysis, a history of cardiac disease and the occurrence of medical complications after CI (particularly respiratory infections and cardiac events) were as important as recurrent stroke in predicting mortality. Interventions to reduce the risk of aspiration and respiratory infections, as well as diagnosis and management of clinical and subclinical cardiac diseases in stroke patients, are probably as important as secondary stroke prevention in reducing mortality after CI.

After a first CI, more patients die of myocardial infarction than recurrent stroke. Although the mechanism of CI is often investigated in great detail, few physicians evaluate aggressively for the presence of coronary artery occlusive disease. Whether screening CI patients for occult ischemic heart disease would reduce poststroke mortality merits further investigation.

Likewise, early evaluation of swallowing function (even in patients without overt dysphagia) may prevent aspiration, pneumonia, and death. Our data complement previous findings that suggest dysphagia is an important independent risk factor for chest infection and death in stroke patients.[18] These data should alert neurologists and others involved in the care of stroke patients. Although we must continue to intervene with aggressive prevention of secondary stroke, appropriate attention must be paid to evaluation and management of potentially fatal medical morbidities.

Acknowledgments

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