Cause-specific Mortality after Stroke: Relation to Age, Sex, Stroke Severity, and Risk Factors in a 10-Year Follow-up Study

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We investigated cause-specific mortality in relation to age, sex, stroke severity, and cardiovascular risk factor profile in the Copenhagen Stroke Study cohort with 10 years of follow-up. In a Copenhagen community, all patients admitted to the hospital with stroke during 1992-1993 (n = 988) were registered on admission. Evaluation included stroke severity, computed tomography scan, and a cardiovascular risk profile. Cause of death within 10 years according to death certificate information was classified as stroke, heart/arterial disease, or nonvascular disease. Competing-risks analyses were performed by cause-specific Cox regression after multiple imputation of missing data, assuming that values were missing at random. Death was due to stroke in 310 patients (31%), to heart/arterial disease in 209 patients (21%), and to nonvascular diseases in 289 patients (29%); 180 patients were still alive after 10 years (18%). Stroke was the dominant cause of death during first year, with an absolute risk of 20.2% versus 5.2% for heart/arterial disease and 6.5% for nonvascular disease. The subsequent absolute risk of death per year was 2.8% for stroke, 4.5% for heart/arterial disease, and 5.2% for nonvascular disease. Death after stroke was associated with older age, male sex, greater stroke severity, and diabetes regardless of the cause of death. Previous stroke and hemorrhagic stroke were associated with death by stroke, ischemic heart disease was associated with death by heart/arterial disease and atrial fibrillation was associated with death by cardiovascular disease (stroke or heart/arterial disease). Hypertension, smoking, and alcohol consumption were not associated with cause-specific death. **Key Words:** Cerebrovascular disease—cardiovascular disease—cause of death—predictor.

Stroke carries a high risk of death. According to the World Health Organization, it is the second-leading cause of death worldwide, accounting for 6 million deaths annually.[1] Therefore, measures to reduce mortality after stroke have high priority. Knowledge of predictors of death after stroke is of great importance for reducing the risk of death after stroke.

Causes of death after stroke are well known, most prominently the index stroke, recurrent stroke, and other cardiovascular diseases.[2] At present, knowledge of predictors of poststroke mortality is related primarily to all-cause mortality; information on predictors of cause-specific mortality is unavailable in the literature.[2] In the present study, we identified the primary causes of death through a review of the death certificates of 988 patients with acute stroke included in the Copenhagen Stroke Study (COST) cohort. We focused on identifying predictors of cause-specific mortality by stroke, heart/arterial disease, and nonvascular causes.

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Received December 15, 2011; revision received April 10, 2012; accepted April 11, 2012.

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1052-3057/$ - see front matter

doi:10.1016/j.jstrokecerebrovasdis.2012.04.006

Patients and Methods

Patients

This study is based on data from the COST, which has been described in detail elsewhere.[3,4] In brief, the COST cohort included all patients who sustained stroke between March 1992 and November 1993 within a well-defined area of Copenhagen with 240,000 inhabitants and were admitted to our hospital's 62-bed stroke unit. Patients were not preselected; all patients within the study area who sustained a stroke were brought to the hospital's stroke unit regardless of age, stroke severity, or comorbid diseases.

In our community, all persons who experience symptoms of a stroke or transient ischemic attack (TIA), including nursing home residents, are urged to seek immediate hospital care. General practitioners are instructed to hospitalize all patients with stroke or TIA. Hospital care is free, and a very high proportion (88%) of the patients with stroke in our area were admitted to our hospital during enrollment period.[5] On admission, all patients were offered a standardized evaluation program, including a computed tomography (CT) scan, electrocardiography, and a cardiovascular risk factor evaluation using a standardized questionnaire. Information was obtained from relatives or caregivers if necessary. The type of stroke (ie, hemorrhagic or ischemic) was identified by CT scan.

Stroke was defined on clinical grounds according to the World Health Organization criteria.[6] Patients with TIA or subarachnoid hemorrhage were not included in our analysis, and patients who had a neurologic deficit on hospital admission that resolved within 24 hours after onset were subsequently excluded as well.

Evaluation

On admission, the Scandinavian Stroke Scale (SSS) was used to assess stroke severity.[7] The SSS evaluates level of consciousness; eye movement; power in the arms, hands, and legs; orientation; aphasia; facial paresis; and gait, with a total score ranging from 0 (worst) to 58 (best). The National Institutes of Health Stroke Scale (NIHSS)[8] score can be converted to the SSS score using the following equation: $SSS = 50 - 2 \times NIHSS$.[9]

The following prognostic factors were investigated in the statistical analysis: age, sex, initial stroke severity (based on SSS score), diabetes, atrial fibrillation (AF), ischemic heart disease, stroke type (hemorrhagic or ischemic), hypertension, previous stroke, preexisting disability, alcohol consumption, and smoking. Diabetes was considered present if a patient had known diabetes on admission or a plasma glucose concentration >11 mmol/L measured on admission or during the hospital stay. AF was diagnosed if detected on the admission electrocardiogram. Information on other disabling diseases other than previous stroke (eg, amputation, multiple sclerosis, severe dementia, heart failure, latent or persistent respiratory insufficiency) was obtained on admission. Ischemic heart disease was defined as a history of ischemic heart disease or ischemic heart disease diagnosed during the hospital stay. Hypertension was defined as receipt of antihypertensive treatment before admission or hypertension diagnosed during the hospital stay by repeated blood pressure measurements ≥160/95 mmHg. Smoking was defined as smoking of any kind of tobacco product on a daily basis. Ex-smokers were coded as nonsmokers. Alcohol intake was coded as present if consumed daily.

Data on prognostic factors were not available for all items in all patients for various reasons, including the patient's inability to communicate (due to, eg, aphasia or altered consciousness), absence or poor knowledge of reporting family members, and lack of information from previous admissions. The study was conducted at a time (1992-1993) when CT scan capacity was still rather low in Denmark. The average time from admission to CT scanning was 8 days. CT scan results were not available in 188 patients who died or were discharged before a CT scan could be performed. Missing risk factor values were imputed by multiple imputation (see *Statistical Methods*) under the assumption of values missing at random. Causes of death were obtained from the Danish National Registry on Causes of Death and classified into the following 3 groups: stroke, heart and arterial diseases (including ischemic heart disease, other heart diseases, and arterial diseases), and nonvascular diseases (including cancer and other nonvascular disorders).

Follow-Up

For the patients who had died, information on date of death within 10 years after the index stroke was obtained from the Danish Central Registry of Persons. Follow-up was performed until November 3, 2003 (censoring date). Six patients had immigrated to another country and were lost to follow-up.

The study was approved by the Ethics Committees of Frederiksberg and Copenhagen cities, (approval nos. KF/V.100.2263/91 and KF 01-287/98).

Statistical Methods

Cause-specific Cox regression analyses were used to study the influence of prognostic factors on death caused by stroke, heart/arterial diseases, and nonvascular diseases in a competing-risks framework.[10] For all analyses, the time origin was the date of the index stroke. The Aalen-Johansen method was used to estimate cumulative incidences (absolute risks).[11] Cox regression was used to analyze associations between prognostic factors and cause-specific hazards. The prognostic factors were entered additively into the linear predictor. The nonlinearity of the effects of the continuous prognostic factors age and stroke severity was tested using restricted smoothing splines.[12]