Sex Differences in Stroke Survival: 10-Year Follow-up of the Copenhagen Stroke Study Cohort

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Background: Although diverging, most studies show that sex has no significant influence on stroke survival. *Methods:* In a Copenhagen, Denmark, community all patients with stroke during March 1992 to November 1993 were registered on hospital admission. Stroke severity was measured using the Scandinavian Stroke Scale (0-58); computed tomography determined stroke type. A risk factor profile was obtained for all including ischemic heart disease, hypertension, diabetes mellitus, atrial fibrillation, previous stroke, smoking, and alcohol consumption. Date of death was obtained within a 10-year follow-up period. Predictors of death were identified using a Cox proportional hazards model. *Results:* Of 999 patients, 559 (56%) were women and 440 (44%) were men. Women were older (77.0 *v* 70.9 years; $P < .001$) and had more severe strokes (Scandinavian Stroke Scale: 36.1 *v* 40.5; $P < .001$). Age-adjusted risk factors showed no difference between sexes for ischemic heart disease, hypertension, atrial fibrillation, diabetes mellitus, and previous stroke. Men more often were smokers and alcohol consumers. Unadjusted survival in men and women did not differ: 70.3% versus 66.7% (1-year), 40.0% versus 38.9% (5-year), and 17.4% versus 18.7% (10-year), respectively. Adjusting for age, stroke severity, stroke type, and risk factors, women had a higher probability of survival at 1 year (hazard ratio 1.47, 95% confidence interval 1.10-2.00); 5 years (hazard ratio 1.47, 95% confidence interval 1.23-1.76); and 10 years (hazard ratio 1.49, 95% confidence interval 1.28-1.76). Before 9 months poststroke, no difference in survival was seen. Severity of stroke had the same effect on sex. *Conclusion:* Stroke is equally severe in men and women. Short-term survival is the same. Having survived stroke, women, however, live longer. **Key Words:** Stroke—sex—mortality—prognosis.

Sex has no significant influence on survival after stroke in most studies.[1-21] In a minority of studies, survival is significantly better for men than women[22-25] and vice versa.[26-29] This finding is surprising because women, because of their markedly longer life expectancy,[30] would be anticipated to encompass at least a better long-term survival. Controversies about the influence of sex on stroke outcome may reflect diversity among studies in respect to design, sample size, and follow-up.

Current recommendations usually support equal treatments for men and women, but recent research increasingly points to the need of individualization.[31,32] A clarification of possible differences in outcome between sexes is, therefore, still needed.

We hypothesized that a better survival of women would emerge if initial stroke severity measured by a validated stroke scale and a cardiovascular risk factor evaluation were encountered in a sizable study with a lengthy follow-up.

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In a community-based cohort of 999 patients hospitalized with acute stroke, we recorded prospectively data on 10-year survival from the acute admission on March 1992 until November 1993. Based on initial stroke severity measured by a validated stroke scale and a thorough cardiovascular risk factor profile, we studied the influence of sex on short- and long-term stroke survival.

Methods

The study was community-based and prospective. In a well-defined area of Copenhagen, Denmark, with 240,000 inhabitants, all having a stroke were admitted to a 62-bed stroke department at the same hospital. The inclusion period was March 1992 to November 1993. No preselection of patients was performed, as all who had a stroke in the area were brought to the stroke department of our hospital, regardless of age, stroke severity, or comorbid diseases. In our community, all who experience symptoms of a stroke or transient ischemic attack (including nursing home residents) are urged to go to the hospital immediately. General practitioners are instructed to hospitalize all patients with stroke or transient ischemic attack. Hospital care is free, and a very high proportion (88%)[33] of the patients with stroke in the area were admitted to this hospital during the time of inclusion. On admission, all underwent a standardized program including computed tomography scan, electrocardiography, and a cardiovascular risk factor evaluation using a standardized questionnaire. Information was obtained from relatives or caregivers if needed.

Stroke was defined according to the World Health Organization (WHO) criteria.[34] Transient ischemic attack or subarachnoid hemorrhage was not included. On admission, the Scandinavian Stroke Scale (SSS) was used to assess stroke severity. SSS evaluates level of consciousness; eye movement; power in arm, hand, and leg; orientation; aphasia; facial paresis; and gait on a total score from 0 (worst) to 58 (best).[35] Computed tomography determined stroke type (hemorrhage/infarct).

The following prognostic factors were investigated in the statistical analyses: age, sex, initial stroke severity (SSS), diabetes mellitus (DM), atrial fibrillation (AF), ischemic heart disease (IHD), hypertension, previous stroke, pre-existing disability, alcohol consumption, and smoking.

DM was considered present if a patient had known DM on admission or if plasma glucose level was greater than 11 mmol/L on admission or during the hospital stay. AF was diagnosed if present on admission electrocardiogram. Information concerning other disabling disease was obtained on admission and included disabling diseases other than previous stroke (e.g., amputation, multiple sclerosis, severe dementia, heart failure, latent or persistent respiratory insufficiency). IHD was present if a patient had a history of IHD, or had IHD diagnosed during the hospital stay. Hypertension was present if a patient received antihypertensive treatment before admission, or if hypertension was diagnosed during hospital stay by repeated detection of blood pressure 160/95 mm Hg or higher. Smoking was coded if a patient smoked any kind of tobacco on a daily basis. Ex-smokers were coded as nonsmokers. Intake of alcohol intake was coded if consumed daily.

Follow-up

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

Statistical Analyses

Statistical analyses were performed with the a statistical software package (SPSS, Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL). Difference in age and SSS score for sex was analysed using a standard *t* test. Logistic regression models were applied to calculate an age-adjusted estimate of the odds ratio between sex and all possible risk factors, each coded as binary variables. Independent predictors of death were identified using the Cox proportional hazards (CPH) model. Significance of predictors was based on the probability of the Wald statistic and a significance level of 5%. To assess whether the baseline hazard functions were proportional log-minus-log plots were performed for each variable. Log-linearity of age and SSS score was tested by elaborating these variables and performing a likelihood ratio test. The study was approved by the ethics committee.

Results

Of the 999 patients included, 559 (56%) were women and 440 (44%) were men. Mean age was higher in women (77.0 *v* 70.9 years; $P < .001$) and stroke severity expressed by the mean SSS score was more severe in women (36.1 *v* 40.5; $P < .001$). Table 1 shows the age-adjusted odds ratio values of potential cardiovascular risk factors for men relative to women. AF did not differ for sex (19.9 *v* 12.1; $P = .205$), but hemorrhage (9.4% *v* 5.2%; $P = .019$) was more often in women. Men were more often smokers (53.8% *v* 36.5%; $P = .014$) and had daily alcohol consumption (49% *v* 16.7%; $P < .001$). No significant difference between sexes was found for hypertension, IHD, previous stroke, DM, or AF.

Survival

Three subanalyses were done for end points 1, 5, and 10 years poststroke. Unadjusted survival in men and

Table 1. *Age-adjusted odds ratio of risk factors for men compared with women*

Variable	Women		Men		OR	95% CI
	Yes/no	Percentage	Yes/no	Percentage		
Hypertension	172/341	33.5	134/289	31.7	0.838	0.630-1.116
Known ischemic heart disease	102/404	20.2	87/329	20.9	1.165	0.836-1.623
Previous stroke	101/421	19.3	94/332	22.1	1.272	0.917-1.764
Other disabling disease	130/398	26.6	75/354	17.5	0.720	0.518-1.000
Alcohol consumption	75/375	16.7	188/196	49.0	0.962	0.949-0.976
DM	72/447	13.9	76/353	17.7	1.244	0.866-1.787
Smoking	162/282	36.5	204/175	53.8	1.463	1.081-1.982
Atrial fibrillation	109/440	19.9	53/385	12.1	0.786	0.542-1.141
Hemorrhage	42/404	9.4	19/345	5.2	0.497	0.278-0.890

CI, Confidence interval; *DM,* diabetes mellitus; *OR,* odds ratio.

women did not differ significantly: men 70.3%, women 66.7% (1-year); men 40.0%, women 38.9% (5-year); and men 17.4%, women 18.7% (10-year).

One-Year Survival

The variables in Table 2 were found significant in the CPH model for 1-year survival (*P* value, hazard ratio [HR], 95% confidence interval). Women had a significantly higher probability of survival (HR 1.465). A 10-year increase in age decreased the probability of survival (HR 1.460) whereas a 10-point increase in the SSS score increased the probability of survival (HR 0.621). DM (HR 2.085), AF (HR 1.438), and hemorrhage (HR 1.980) decreased the probability of 1-year survival.

Five-Year Survival

The variables in Table 3 were found significant in the CPH model for 5-year survival (*P* value, HR, 95% confidence interval). Women had a significantly higher probability of survival (HR 1.471). A 10-year increase in age decreased the survival probability (HR 1.649 per 10 years) whereas a 10-point increase SSS score increased the survival probability (HR 0.696 per 10 points). DM (HR 1.440), AF (HR 1.339), previous stroke (HR 1.334), and other disabling disease (HR 1.306) decreased the probability of 5-year survival.

Ten-Year Survival

The variables in Table 4 were found significant in the CPH model for 10-year survival. The results of this analysis are almost identical to the 5-year survival analysis and still display a significantly higher probability of survival for women (HR 1.490).

Fig 1 illustrates the sex-specific CPH survival plot for 10-year survival.

To identify the cut-off point in the Cox regression analysis (i.e., the survival censoring point where sex becomes a significant explanatory variable) we increase the censoring by 1 month starting with a 1-month censoring. The analysis showed that sex became significant using 9-month censoring.

Separate models have been applied to analyze whether there is an interaction between sex and SSS score. The results of this analysis are shown in Table 5. It is seen that there is no significant interaction between sex and SSS score (i.e., severity of the stroke has the same effect on each sex).

Table 2. *Significant variables in 1-year survival Cox proportional hazards regression model*

	Parameter estimate, B	*P* value	Hazard ratio, Exp(B)	95% CI for Exp(B)	
				Lower	Upper
Age (units of 10 years)	0.378	<.001	1.460	1.234	1.728
SSS (units of 10 points)	−0.476	<.001	0.621	0.567	0.680
Diabetes	0.735	<.001	2.085	1.458	2.981
Atrial fibrillation	0.363	.053	1.438	0.996	2.077
Hemorrhage	0.683	.005	1.980	1.224	3.201
Sex	0.382	.016	1.465	1.075	1.999

CI, Confidence interval; *SSS,* Scandinavian Stroke Scale.

Table 3. *Significant variables in 5-year survival Cox proportional hazards regression model*

	Parameter estimate, B	*P* value	Hazard ratio, Exp(B)	95% CI for Exp(B)	
				Lower	Upper
Age (units of 10 years)	0.500	<.001	1.649	1.492	1.822
SSS (units of 10 points)	−0.362	<.001	0.696	0.661	0.733
Previous stroke	0.288	<.005	1.334	1.090	1.631
Other disabling disease	0.267	.009	1.306	1.069	1.594
Diabetes	0.365	.001	1.440	1.151	1.802
Atrial fibrillation	0.292	.008	1.339	1.080	1.661
Sex	0.386	<.001	1.471	1.228	1.762

CI, Confidence interval; *SSS,* Scandinavian Stroke Scale.

Discussion

Two main findings emerged from this study. Men and women are at the same risk of dying from a stroke. Having survived the stroke, however, women live longer than men. In other words, short-term stroke survival is the same for men and women whereas long-term stroke survival is markedly better for women.

Women and men differed in respect to important confounders. Women were older and had more severe strokes. This explains that short-term survival at a first glance appears to be significantly better for men and that long-term survival looks equal for both sexes. Moreover, women more often had other disabling diseases and hemorrhagic strokes whereas men more often were consumers of alcohol and tobacco. The lack of adjustment for one or more of these variables explains much of the diverging conclusions among studies. However, as we found no interaction between stroke severities and sex, our study shows that severity of stroke is not influenced by sex per se and differences in survival between men and women are determined by other factors.

The strength of this study is that it is prospective and community-based including all patients in a well-defined community hospitalized with stroke regardless age, stroke severity, or other complicating diseases. Moreover, the stroke admittance rate in the area is high and close to the incidence reported in population-based studies. A limitation is that patients who die at home are not included and this may underestimate mortality. However, the small number of patients with minor strokes not being admitted to hospital may counterbalance it. Finally, as a multivariate analysis was applied and because we had a sizeable study population and a lengthy follow-up, we consider bias to be of no major importance for the main conclusion of this study.

The difference in survival between sexes became significant at 9 months poststroke. However, it appears from the sex-specific survival plots that a difference in survival between sexes takes effect much earlier. On the other hand, it is also evident from these plots that there is no difference between sexes in the very acute state. Thus, our study does not point to the presence of a sex-specific ability to survive stroke per se. Findings from other large-scale studies on short-term survival are diverging: in the WHO MONICA populations the age-adjusted 28-day case fatality is higher among women.[24] Stroke severity and other prognostic confounders are, however, not recorded in these studies. In several studies the level of consciousness or degree of paresis were used as markers of stroke severity and no difference in 1- to 3-month

Table 4. *Significant variables in 10-year survival Cox proportional hazards regression model*

	Parameter estimate, B	*P* value	Hazard ratio, Exp(B)	95% CI for Exp(B)	
				Lower	Upper
Age (units of 10 years)	0.481	<.001	1.618	1.490	1.757
SSS (units of 10 points)	−0.299	<.001	0.742	0.709	0.776
Previous stroke	0.248	.006	1.281	1.072	1.531
Other disabling disease	0.283	.002	1.328	1.114	1.583
Diabetes	0.357	<.001	1.429	1.178	1.734
Atrial fibrillation	0.290	.003	1.336	1.100	1.622
Sex	0.398	<.001	1.490	1.278	1.736

CI, Confidence interval; *SSS,* Scandinavian Stroke Scale.

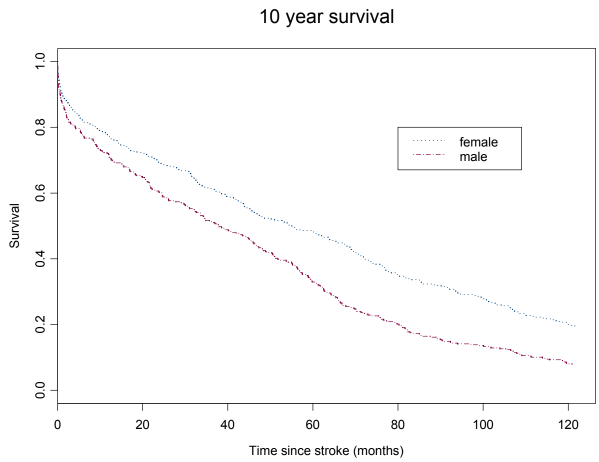

Figure 1. *Sex-specific survival curve for 10-year mortality.*

survival between sexes was observed when adjusting for these and other confounding variables.[1-7] In a study using the National Institutes of Health Stroke Scale as marker of stroke severity there was no sex-specific difference in 3-month survival when adjusting for this and other relevant confounders as done also in our study. In the Rochester, Minn, population stroke severity was determined retrospectively from hospital records and no sex-specific difference in 3-month survival was found.[10] On the other hand, in a Dutch study using Glasgow Coma Scale as marker of stroke severity women had a better 6-month survival,[26] whereas in a Polish study using level of consciousness as marker of stroke severity 2-week survival was poorer in women.[23]

In our study survival is markedly better in women 9 months poststroke and onward. Women continuously have a 1.5 better chance of being alive up to 10 years after the stroke. Several large-scale studies did not find any sex-specific difference in stroke mortality in studies with 1,[9] 10,[10] and even 20[17] years follow-up, but these studies, except for age, did not adjust for stroke severity or other confounders of importance for stroke survival. Two Swedish studies[13,19] used validated stroke severity scores and did not find any sex-specific difference in 1-year[13] and 3-year[19] survival when adjusting for stroke severity and other relevant confounders. In other studies stroke severity was estimated on the basis of consciousness or various neurologic deficits; 1-year[11,12,14] and 3-year[20,21] survival did not differ between sexes. In the Rochester, Minn, population[10,18] sex did not influence 5-year stroke survival whereas in the Framingham population[28] 5-year survival was better among women.

Table 5. *Test for interaction between sex and Scandinavian Stroke Scale scores*

	SSS (female) parameter estimate, B_1	SSS (male) parameter estimate, B_2	Wald test statistics	*P* value
1 y	0.622	0.619	0.0326	.97
5 y	0.728	0.757	−0.4601	.65
10 y	0.770	0.785	−0.2749	.78

SSS, Scandinavian Stroke Scale.

Our study is the first large-scale study with a follow-up as long as 10 years where stroke severity at stroke onset and a thorough cardiovascular risk factor profile were determined prospectively using a validated stroke severity scale. Other studies with a long follow-up either did not measure stroke severity, stroke severity was determined retrospectively from hospital records, or stroke severity was estimated without using a stroke scale. There was no interaction between stroke severity and sex, but stroke severity was a strong predictor not only of short-term survival, but of long-term survival as well. Information of stroke severity is, thus, important for analyzing predictors of stroke survival.

In the industrialized world women live 5 to 7 years longer than men,[30] which is in agreement with the result of our study. Women experienced stroke on average 6 years later than men. This is undoubtedly the key to the understanding of the better long-term survival of women with stroke. Women also experience myocardial infarction several years later than men.[36] Women, therefore, experience fatal cardiovascular diseases later than men and, hence, live longer than men even if they have had a stroke. Higher consumption of tobacco and alcohol further contributes to earlier occurrence of cardiovascular disease in men. The great diversity among studies in respect to design, sample size, follow-up, and results calls, however, for further study.

In conclusion, stroke is equally severe in men and women and short-term survival is the same for men and women. Having survived stroke, women, however, live longer than men, most certainly because of their lower risk of a subsequent cardiovascular event.

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