

Sex Differences in First-Ever Acute Stroke

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Background and Purpose—There are few studies analyzing stroke in women, taking into account the vascular risk factors, cause of stroke, clinical picture, and outcome. The purpose of this study was to analyze possible sex differences in patients suffering first-ever acute stroke.

Methods—From December 1995 to January 2002, 1581 patients with first-ever acute stroke were analyzed, taking into account sex, age, risk factors, clinical presentation, stroke subtype, treatment, and outcome data.

Results—Mean age was higher in women than in men ($P<0.001$). Hypertension ($P=0.0027$) and cardioembolic disease ($P=0.0035$) were independent factors related to women. Alcohol overuse ($P<0.001$), smoking ($P<0.001$), and vascular peripheral disease ($P=0.031$) were related to the male sex. Women more often suffered aphasic disorders ($P<0.001$), visual field disturbances ($P<0.05$), and dysphagia ($P<0.01$) than men. There were no differences in hemorrhagic and ischemic strokes according to sex. Women suffered more cardioembolic strokes ($P<0.001$); men suffered more atherothrombotic ($P<0.001$) and lacunar strokes ($P<0.05$). Women who survived remained more disabled than men ($P<0.001$).

Conclusions—Sex determines some clear differences in patients suffering a first-ever stroke. Women were, on average, 6 years older than men and had a different profile of vascular risk factors and a different distribution of stroke subtypes. Women had a longer hospital stay and remained more disabled than men. The amelioration of hypertension control and increase in anticoagulant treatment in patients with atrial fibrillation would be the best options for preventing stroke, especially in women. (*Stroke*. 2003;34:1581-1585.)

Key Words: gender ■ outcome ■ stroke ■ women

Cerebrovascular disease is the second cause of death worldwide, and all projections indicate that this will remain in the year 2020.^{1,2} The greater prevalence of stroke in men is well known, but recent issues emphasize the importance of stroke in women.³ Nowadays, in the United States, it is estimated that 1 in 6 women will die of stroke, whereas 1 in 25 will eventually die of breast carcinoma,⁴ and over the entire lifetime, $\approx 16\%$ of women but only 8% of men will die of stroke.⁵ In Europe, the figures are similar. For instance, the most frequent cause of death among women in Spain is stroke, which claimed 1 of 7 deaths in women in 1998.⁶ Moreover, stroke severity is greater in women than in men,^{7,8} and there is a clear influence of sex on the possibility of being discharged home after acute stroke.⁹ Differences in vascular risk factors, subtypes of stroke, and medical or surgical management have also been described.¹⁰⁻¹⁷

Knowledge of sex differences might be of interest in improving preventive strategies and the in-hospital management of stroke patients.

Patients and Methods

From December 1995 to January 2002, 1630 consecutive patients with first-ever acute stroke were admitted to our hospital, which receives almost all the neurological emergencies of 2 districts (Sant

Martí and Ciutat Vella) of Barcelona, which had a total of 282 951 inhabitants in 1996. All patients fulfilled a clinical protocol, which included epidemiological data, vascular risk factors, clinical data, stroke subtype classification according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria,¹⁸ outcome data, medical complications, and modified Rankin score at discharge. Patients with incomplete data ($n=49$) were excluded. In the remaining 1581 patients separated by sex, we analyzed the following data: age; length of hospitalization; alcoholism (history of alcohol intake >80 g/d); current smoking; past history of hypertension (evidence of at least 2 blood pressure measurements $>160/95$ mm Hg recorded on different days before the stroke); diabetes (at least 2 determinations of glucose levels >126 mg/dL); hypercholesterolemia (serum cholesterol concentration >220 mg/dL); cardiac ischemia (angor pectoris or myocardial infarct); arterial peripheral disease; atrial fibrillation; valvular heart disease; clinical data (presence of aphasia, motor deficit, sensorial deficit, visual field disturbances [hemianopsia/quadrantanopsia] and dysphagia); stroke subtype according to the TOAST classification; stroke severity at admission according to Canadian Score Scale (CSS); medical complications during hospitalization; need for rehabilitation; functional outcome (modified Rankin scale); and treatment. During hospitalization, we considered a standard neurovascular protocol to be complete when the following studies were performed: CT scan or brain MRI plus extracranial duplex or transcranial and extracranial Doppler plus cardiological study (at least 1 ECG plus a chest radiography), as well as routine blood sample analysis. Echocardiography was performed in 259 patients (transthoracic in 237, transesophageal in 22 patients). A

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transesophageal study was performed mainly in large-artery stroke patients <50 years of age with no atherosclerotic disease. Results of these studies were taken into account when the stroke was subtyped.

Univariate and multivariate analyses were performed with the SPSS package 7.5 for Windows. Univariate analysis was performed with the χ^2 test for dichotomous variables. Continuous variables were tested by the *t* test or the Mann-Whitney test if normality was difficult to assume. Values of $P < 0.05$ were considered significant. Multivariate analysis was carried out with a logistic regression model. Results of the logistic regressions are presented through the use of 95% confidence intervals (CIs).

Results

The mean \pm SD age of the 772 women (48.3%) was greater than that of men (74.6 ± 11.4 versus 68.8 ± 11.9 years; $P < 0.001$). On the basis of the neurovascular protocol applied, the following differences in vascular risk factors were established according to sex. Predominant risk factors in women were the presence of arterial hypertension ($P < 0.001$; odds ratio [OR], 1.68; 95% CI, 1.37 to 2.05) and cardioembolic diseases ($P < 0.001$; OR, 1.96; 95% CI, 1.56 to 2.45), mainly because of the higher frequency of atrial fibrillation in women (30.8%) than in men (18.7%) ($P < 0.001$; OR, 1.94; 95% CI, 1.53 to 2.45). On the other hand, the following vascular risk factors were less predominant in women: arterial peripheral disease ($P < 0.001$; OR, 0.46; 95% CI, 0.29 to 0.66), current smoking ($P < 0.001$; OR, 0.05; 95% CI, 0.04 to 0.07), and active alcohol overuse ($P < 0.001$; OR, 0.10; 95% CI, 0.06 to 0.14). No differences were found for diabetes, history of cardiac ischemic disease, or hypercholesterolemia. Multivariate analysis demonstrated that hypertension ($P = 0.0027$; 95% CI, 1.24 to 1.97), cardioembolic diseases ($P = 0.0035$; 95% CI, 1.10 to 1.82), vascular peripheral disease ($P = 0.031$; 95% CI, 0.32 to 0.82), current smoking ($P < 0.001$; 95% CI, 0.05 to 0.11), and alcohol overuse ($P < 0.001$; 95% CI, 0.15 to 0.41) were different in both sexes.

Clinical Data

Women suffered aphasic disorders ($P < 0.001$; OR, 1.47; 95% CI, 1.17 to 1.85), visual field disturbances ($P < 0.05$; OR, 1.35; 95% CI, 1.02 to 1.78), and dysphagia ($P < 0.01$; OR, 1.53; 95% CI, 1.17 to 2.00) to a greater extent than men did, with no differences in motor or sensory deficits.

Stroke Subtypes

There were no statistical differences between hemorrhagic and ischemic strokes according to sex (16.3% of spontaneous intracerebral hemorrhage in men versus 14.5% in women ($P = \text{NS}$; OR, 1.17; 95% CI, 0.89 to 1.54). Subtypes of ischemic stroke according to the TOAST classification varied according to sex. There were more undetermined strokes in women than in men (48.2% versus 44.8%), but the difference was not statistically significant. Women suffered more cardioembolic strokes (27.9% versus 14.9%; $P < 0.001$; OR, 2.21; 95% CI, 1.68 to 2.90) but fewer atherothrombotic strokes (13% versus 25.3%; $P < 0.001$; OR, 0.44; 95% CI, 0.30 to 0.53) and lacunar strokes (8.9% versus 12.6%; $P < 0.05$; OR, 0.67; 95% CI, 0.48 to 0.95). Causes of possible cardioembolic sources were analyzed, taking into account clinical, ECG, and echocardiographic data. Among the 286

cases of cardioembolic stroke according to the TOAST criteria, the embolic source was accounted for by the following types of cardiac dysfunction: isolated atrial fibrillation, 227; atrial fibrillation plus valve dysfunction or dilated cardiomyopathy, 21; isolated valve dysfunction, 13; recent myocardial infarction, 5; akinetic left ventricular segment, 5; dilated cardiomyopathy, 4; patent foramen oval, 2; infective endocarditis, 2; and other, 7. During hospitalization, 66.7% of women and 79.6% of men were assessed with the standard neurovascular protocol ($P < 0.001$; OR, 0.51; 95% CI, 0.39 to 0.63). There were no differences in need for rehabilitation during hospitalization (54.9% in women, 50.4% in men; $P = \text{NS}$; OR, 1.17; 95% CI, 0.96 to 1.43).

Outcome

Severity at admission according to the CSS was greater in women than in men (6.60 ± 3.12 versus 7.37 ± 3.78 , $P < 0.001$). Comparing stroke subtypes, we found a greater severity in cardioembolic strokes than in atherothrombotic strokes (CSS, 5.93 ± 3.32 versus 7.26 ± 2.73 ; $P < 0.001$). However, no differences were seen in severity of cardioembolic (5.7 ± 3.34 in women versus 6.32 ± 3.27 in men) or atherothrombotic (7.27 ± 2.72 in women versus 7.26 ± 2.74 in men) stroke according to sex. Mortality was greater in women (12.1% versus 10.6%), but data did not reach the threshold of statistical significance. Women who survived remained more disabled (modified Rankin scale, 3 to 5) than men ($P < 0.001$; OR, 1.87; 95% CI, 1.50 to 2.35). In-hospital medical complications were more frequent ($P < 0.01$; OR, 1.36; 95% CI, 1.10 to 1.68) and hospitalization was longer (15.4 ± 14.5 versus 13.5 ± 11.3 days, $P < 0.005$) in women than in men. Treatment during hospitalization or at discharge showed no differences in antiaggregant or anticoagulant use compared with no treatment in patients suffering ischemic strokes (96.4% in women, 96.0% in men; $P = \text{NS}$; OR, 1.10; 95% CI, 0.63 to 1.93). Antiaggregant treatment was slightly more frequent in men (79.8% versus 76.3%, $P = \text{NS}$), whereas anticoagulant treatment was predominant in women (20.2% versus 16.2%, $P = \text{NS}$).

Discussion

The overall prevalence of stroke is higher in men than in women and increases with age in both sexes.¹⁹ Interest in and knowledge about the importance of stroke in women are increasing because of the demonstration of a higher mortality, higher disability, and higher incidence of dementia in women who survive a stroke.³ Previous studies have documented sex differences in the management and outcome of patients with cardiovascular disease^{20,21} and in stroke patients.^{10–17} In stroke patients, however, few data clearly differentiate between the sexes. Many risk factors for ischemic stroke in both men and women have been consistent in epidemiological studies. These include hypertension, smoking, diabetes mellitus, ischemic heart disease, atrial fibrillation, and transient ischemic episodes. Recent studies have provided some discordant vascular risk factors according to sex.^{10–16} Some studies have shown that hypertension was more frequent in women,^{10,16} whereas others found no such differences.^{14,17} Diabetes has been considered more frequent in women,¹⁶ but

TABLE 1. Vascular Risk Factors According to Sex

	Women	Men	<i>P</i>	OR (95% CI)
Total cases, n	772	809		
Mean age, y	74.6±11.4	68.8±11.9	0.001	
Hypertension, n (%)	502 (65.0)	425 (52.5)	0.001	1.68 (1.37–2.05)
Diabetes mellitus, n (%)	215 (27.8)	218 (26.9)	NS	
Hypercholesterolemia, n (%)	191 (24.7)	189 (23.4)	NS	
Cardioembolic diseases, n (%)	263 (34.1)	169 (20.9)	0.001	1.96 (1.56–2.45)
Atrial fibrillation, n (%)	238 (30.8)	151 (18.7)	0.001	1.94 (1.53–2.45)
Ischemic heart disease, n (%)	79 (10.2)	102 (12.6)	NS	
Peripheral arterial disease, n (%)	36 (4.7)	76 (9.4)	0.001	0.46 (0.29–0.66)
Current smoking, n (%)	42 (5.4)	416 (51.5)	0.001	0.05 (0.04–0.07)
Alcohol overuse, n (%)	24 (3.1)	198 (24.5)	0.001	0.10 (0.06–0.14)

After logistic regression analysis adjusted for age, hypertension ($P=0.0027$; 95% CI, 1.24–1.97), cardioembolic diseases ($P=0.0035$; 95% CI, 1.10–1.82), vascular peripheral disease ($P=0.031$; 95% CI, 0.32–0.82), current smoking ($P<0.001$; 95% CI, 0.05–0.11), and alcohol overuse ($P<0.001$; 95% CI, 0.15–0.41) were different in both sexes. Proportions between groups were compared by use of the χ^2 test. Continuous variables are expressed as mean \pm SD and were compared by use of Student's *t* test.

other studies found it to be more frequent in men,¹⁰ and even other studies could not establish any significant differences.^{14,17} Greater concordance exists regarding the higher prevalence of atrial fibrillation in women^{10,16} and a higher prevalence of current smoking and daily alcohol consumption in men.^{11,15,16}

Our study shows some sex differences in patients suffering first-ever acute stroke (Table 1). First, age of first-ever stroke is significantly higher in women than in men, with an average difference of ≈ 6 years. This finding has been documented previously^{15,22} and seems to be widely accepted. According to our data, the risk factor profile varies, depending on sex (Table 1). Predominant risk factors in women are arterial hypertension and cardioembolic diseases, mainly because of the higher frequency of atrial fibrillation in women (30.8%) than in men (18.7%) (OR, 1.94). In men, active alcohol overuse, current smoking, and history of arterial peripheral disease predominate. No differences were found concerning diabetes, history of ischemic heart disease, or hypercholes-

terolemia. After logistic regression analysis adjusted for age, hypertension ($P=0.0027$; 95% CI, 1.24 to 1.97), cardioembolic diseases ($P=0.0035$; 95% CI, 1.10 to 1.82), vascular peripheral disease ($P=0.031$; 95% CI, 0.32 to 0.82), current smoking ($P<0.001$; 95% CI, 0.05 to 0.11), and alcohol overuse ($P<0.001$; 95% CI, 0.15 to 0.41) were different in both sexes. Interestingly enough, we found some clinical differences related to sex in patients suffering a first-ever stroke: Women experienced more aphasic disorders, visual field disturbances, and dysphagia than men, with no differences in motor or sensory deficits (Table 2). Aphasia was present in 28.9% of women and 21.6% of men. This aphasic predominance in women was reported by Hier et al,²³ who noted that aphasia was present in 22.5% of women and 19.4% of men. They found that aphasia was more frequent among women with infarcts (37.0%) than men (28.3%), and when stroke mechanism was controlled for, there was an excess of aphasia among women with stroke caused by cardiac embolism. They concluded that the infarct lesions producing

TABLE 2. Clinical Data and Stroke Subtypes According to TOAST Classification and Sex

	Women, n (%)	Men, n (%)	<i>P</i>	OR (95% CI)
Motor deficit	553 (71.6)	579 (71.6)	NS	
Sensory deficit	302 (39.1)	319 (39.4)	NS	
Aphasic disorder	223 (28.9)	175 (21.6)	0.001	1.47 (1.17–1.85)
Visual deficit	133 (17.2)	111 (13.7)	0.05	1.35 (1.02–1.78)
Dysphagia	154 (19.9)	113 (14.0)	0.01	1.53 (1.17–2.00)
Cerebral hemorrhage	110 (14.2)	132 (16.3)	NS	
Ischemic stroke	662 (85.8)	677 (83.7)	NS	
Atherothrombotic	86 (13.0)	171 (25.3)	0.001	0.44 (0.30–0.53)
Lacunar	59 (8.9)	85 (12.6)	0.05	0.67 (0.48–0.95)
Cardioembolic	185 (27.9)	101 (14.9)	0.001	2.21 (1.68–2.90)
Unusual	14 (2.1)	17 (2.5)	NS	
Unknown/undetermined	318 (48.2)	303 (44.8)	NS	
Standard neurovascular protocol	515 (66.7)	644 (79.6)	0.001	0.51 (0.39–0.63)

Proportions between groups were compared by use of the χ^2 test.

TABLE 3. Outcome and Treatment Data According Sex

	Women	Men	<i>P</i>	OR (95% CI)
Rankin score, 0 to 2, n (%)	400 (51.8)	527 (65.1)	0.001	0.53 (0.44–0.68)
Rankin score, 3 to 5, n (%)	279 (36.1)	196 (24.2)	0.001	1.87 (1.5–2.35)
Death, n (%)	93 (12.1)	86 (10.6)	NS	
In-hospital medical complications, n (%)	287 (37.2)	244 (30.2)	0.01	1.36 (1.10–1.68)
Length of hospitalization, d	15.4±14.5	13.5±11.3	0.005	
Antiaggregant treatment, n (%)	505 (76.3)	540 (79.8)	NS	
Anticoagulant treatment, n (%)	133 (20.2)	110 (16.2)	NS	
No treatment, n (%)	24 (3.6)	27 (4.0)	NS	
Rehabilitation needed, n (%)	424 (54.9)	408 (50.4)	NS	

Proportions between groups were compared by use of the χ^2 test. Continuous variables are expressed as mean \pm SD and were compared by use of Student's *t* test.

aphasia in men were more posteriorly placed and the infarct lesions in women were more anteriorly placed, suggesting possible sex differences in the positioning of the language zone in the brain. We did not analyze specifically the relationship between sex and aphasia, but the higher frequency of visual field disturbances in women than men in our series (17.2% versus 13.7%) does not support the Hier et al²³ conclusion. We believe that the differences seen in the presence of aphasic and visual field disturbances and dysphagia in our patients could be the consequence of the greater severity of stroke in women than in men (CSS, 6.60 ± 3.12 versus 7.37 ± 3.78 ; $P < 0.001$). As in our study, a greater incidence of swallowing difficulties with a clear relationship with longer in-hospital stay has been observed in women in a Stroke Rehabilitation Center.²⁴

In analyzing the stroke subtypes, we did not find any difference between hemorrhagic and ischemic strokes according to sex (16.3% of spontaneous intracerebral hemorrhage in men versus 14.2% in women). However, we noted some clear differences in the ischemic stroke subtypes according to the TOAST classification (Table 2): More men than women were affected by atherothrombotic and lacunar strokes, whereas women suffered more cardioembolic strokes than men. The male preponderance of large-artery atherosclerosis has been reported by some authors,^{11,14} and the greater frequency of cardioembolic strokes in women has been observed by others.¹⁵ The predominance of atherothrombotic strokes in men in our series is congruent with the greater frequency of well-known atherosclerotic risk factors found in men (current smoking and arterial peripheral disease), whereas in women, it seems clear that the higher frequency of atrial fibrillation was responsible for the high percentage of cardioembolic strokes. Interestingly, only 11.2% of women and the same percentage of men who suffered cardioembolic stroke were under anticoagulant treatment, 19.8% and 17.8% were under antiplatelet treatment, and 69% of women and 71% of men did not receive any preventive therapy.

We were surprised by the sex differences seen in the percentages of lacunar infarcts because the main risk factor for this stroke subtype is hypertension, which is overrepresented in women. However, other studies report the same findings.^{15,17} The low percentage of lacunar strokes in our series (8.9% in women, 12.6% in men) was due to strict

application of the TOAST criteria (so patients with CT- or MRI-proven lacunar infarcts associated with atrial fibrillation, those with large-artery atherosclerosis, and those with incomplete neurovascular studies were placed in the undetermined group of the TOAST classification). This fact, however, was not the responsible for the sex differences because, when we analyzed only the radiological data (lacunar infarcts proven by CT or brain MRI), the statistical difference persisted: 138 female and 190 male patients had radiological lacunar infarcts ($P < 0.01$; OR, 0.71; 95% CI, 0.20 to 0.90).

A higher in-hospital mortality in women has been reported,¹⁵ and a large recent study shows a higher age-specific rate of stroke death in women ≥ 65 years of age.²⁵ In our series, despite the greater stroke severity in women, mortality was only slightly greater in women than in men (12.1% versus 10.6%) with no statistical differences. However, the surviving women remained more disabled than men (Table 3). Wyller et al⁹ found that the odds for a man to have a higher Barthel score than a woman was 3.1 in the subacute phase and 3.3 after 1 year and that men had a lower likelihood to be permanent nursing home residents after 1 year. Other studies found that men were more likely than women to be discharged home and less likely to be discharged to long-term care facilities.¹⁰ Why more women than men are incapacitated after a stroke is not well understood, but we believe that some facts such as older age, greater stroke severity, and higher rate of in-hospital medical complications in women might be, at least in part, responsible. Another interesting difference was that the standard neurovascular protocol during hospitalization was incomplete in 33.3% of women and 20.4% of men. The greater severity of stroke in women may have made many of the required diagnostic procedures unusable or unavailable. It seems reasonable that this fact also affected the accuracy of stroke subtyping in women, which should be considered a limitation of our results.

To date, recommendations for treatment of stroke in women and men appear to be the same. In fact, previous studies show that the postdischarge use of aspirin, ticlopidine, and warfarin was similar in male and female stroke survivors, but among stroke survivors ≥ 85 years of age, men were more likely than women to receive aspirin and ticlopidine.¹⁰ In our patient series, no differences were found during hospitalization or at discharge concerning antiaggregant or anticoagulant

use versus no treatment. However because of the different stroke subtypes, anticoagulation therapy was slightly more frequent in women (20.2% versus 16.2%) and antiplatelet treatment in men (79.8% versus 76.3%). These differences, however, did not reach statistical significance.

In the Holroyd-Leduc et al¹⁰ study, no sex differences were found concerning the usage of in-hospital rehabilitative services. We obtained the same results.

Study Limitations

Echocardiograms were performed in <20% of patients, so cardioembolic strokes may have been underestimated. The role of other potential stroke risk factors such as obesity and low- and high-density lipoprotein cholesterol could not be assessed.

Conclusions

This study shows that sex determines some clear differences in patients suffering first-ever strokes and supports the great importance of stroke in women because of their greater severity, mortality, and morbidity. Although no sex differences were seen in the therapeutic decisions, women undergo fewer diagnostic procedures than men. The preventive strategies to decrease stroke in women would include the improvement of hypertension control and the amelioration of the preventive treatment in patients with atrial fibrillation. Stroke prevention with anticoagulation in atrial fibrillation is a priority in both men and women; however, women obtain the most benefit from it.

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