# SEX DIFFERENCES IN RISK FACTOR DISTRIBUTION, SEVERITY, AND OUTCOME OF ISCHEMIC STROKE

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SUMMARY - The aim of the study was to identify differences in baseline characteristics and outcomes of men and women with acute ischemic stroke. Ischemic stroke was confirmed by CT scan or autopsy in patients admitted to the 2<sup>nd</sup> Department of Neurology, Institute of Psychiatry and Neurology in Warsaw, Poland from 1995 to 2007. Male and female patients were compared for risk factors, state of activity prior to stroke, stroke type according to Oxfordshire Community Stroke Project classification, diagnostic test findings, and early 30-day outcome. Data on 1379 women and 1155 men admitted with ischemic stroke were analyzed. The mean age of female and male patients was 74.3 and 68.8 years, respectively. Women were more often disabled prior to stroke, hypertensive, diagnosed with atrial fibrillation or heart failure, and had impaired consciousness at admission, whereas men were more likely to smoke, abuse alcohol and have a history of myocardial infarction or transient ischemic attack. A higher percentage of female stroke patients suffered from total anterior circulation syndrome than males (21.2% and 14.0%, respectively). Internal carotid artery stenosis over 70% was reported in 10.8% of women and 19.1% of men. The 30-day mortality and poor outcome rates were significantly higher in women than men (17.2% vs. 13.1% and 59.9% vs. 46.2%). After adjusting for casemix in multivariate analysis, female sex was independently associated with a higher risk of an early poor outcome. In conclusion, the risk factor distribution, clinical characteristics, diagnostic test findings, and early outcomes were different between female and male ischemic stroke patients. Female sex was associated with poorer prognosis, indicating that more intensive acute and long-term global care may be needed to improve the outcome among female stroke patients.

Key words: Brain ischemia; Stroke; Sex factors; Risk factors

## Introduction

Stroke is the third leading cause of death in women, the fourth leading cause of death in men, and the most common cause of disability in adults over 40 years of age<sup>1-4</sup>. The National Center for Health Statistics has published an age-adjusted stroke mortality rate that is slightly higher in males than females, but women have a higher overall crude stroke mortality rate (68.2 *vs.* 44.2 *per* 100,000 in 2002)<sup>1</sup>. When

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younger than 70 years, stroke incidence is uniformly higher, by up to 70%, in men than women<sup>5-9</sup>. The risk of cerebral infarction increases with age in both sexes, especially in women<sup>10,11</sup>. Several studies found women having survived stroke to have less favorable outcomes than men do. Also, women were less likely to be discharged home and were more likely to have impairments and activity limitations at follow-up<sup>11-16</sup>. Women may experience more mental impairment, depression and fatigue, and they also have a lower overall quality of life than men after stroke<sup>12,17-22</sup>. The International Stroke Trial (IST) found many differences in the clinical stroke course, outcome, and prognostic factors between male and female patients in a very large cohort of stroke patients<sup>23</sup>. In various tri-

als, the severity of stroke was different between men and women; some studies showed females to suffer from a serious type and heavy course of stroke more frequently than males<sup>23-25</sup>. However, other reports do not identify sex differences<sup>3,14,21</sup>. Differences in stroke management between men and women have also been reported. Gargano and Reeves report that women received significantly less thrombolysis with alteplase than men in studies of 2566 patients with acute ischemic stroke<sup>25</sup>.

The aim of the present study was to establish and compare the risk factor distribution, severity, type of stroke, and 30-day outcomes in a very homogeneous group of male and female ischemic stroke patients from one center in middle-east Europe (Warsaw, Poland) during the 1995-2007 period. The large sample, its homogeneous nature, and the long period provided

an opportunity for relevant results for our country as well as other similar countries.

# Patients and Methods

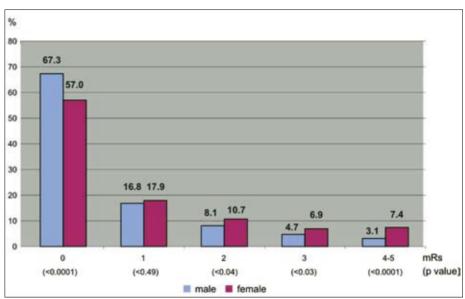
Study population consisted of 2534 patients with ischemic stroke confirmed by computed tomography (CT) scan and treated at the 2<sup>nd</sup> Department of Neurology, Institute of Psychiatry and Neurology in Warsaw from 1995 to 2007. Male and female patients were compared according to risk factors; modified Rankin scale (mRs) prior to stroke; the worst state of consciousness and neurologic deficit level during the first 24 hours after admission; the Oxfordshire Community Stroke Project (OCSP) categories of total anterior circulation syndrome (PACS), posterior circulation syndrome (PACS), posterior circulation syndrome

Table 1. Demographic and clinical characteristics of ischemic stroke patients (n=2534)

	Male		Female		<i>P</i> -value
	n	(%)	n	(%)	P-value
Total	1155	(45.6)	1379	(54.4)	
Age (yrs)		, ,		, ,	
Mean (95% CI)	68.8	(68.1-69.5)	74.3	(73.6-74.9)	<0.001
Past medical history	731	(63.6)	989	(71.7)	
Hypertension	242	(21.0)	383	(27.8)	< 0.0001
Congestive heart					< 0.0002
failure	202	(17.5)	421	(30.5)	
Atrial fibrillation	237	(20.5)	147	(10.7)	< 0.0001
History of cardiac infarct	410	(35.5)	240	(17.4)	< 0.0001
Current smoker	169	(14.6)	159	(11.5)	< 0.0001
History of TIA	169	(14.6)	33	(2.4)	< 0.03
Alcohol abuse	197	(17.1)	213	(15.4)	< 0.0001
History of stroke	216	(18.7)	265	(19.2)	>0.29
Diabetes mellitus	397	(34.4)	503	(36.5)	>0.78
Coronary heart disease					>0.28
Status pre-admission - mRs	771	(67.3)	781	(57.0)	<0.0001
0	192	(16.8)	245	(17.9)	>0.49
1		(8.1)	147	(10.7)	< 0.04
2		(4.7)	95	(6.9)	< 0.03
3 4-5		(3.1)	101	(7.4)	<0.0001
Length of hospital stay Mean (95% CI)	14.8	(14.19-15.53)	15.4	(14.81-16.05)	>0.05

CI = confidence interval; TIA = transient ischemic attack; mRs = modified Rankin scale.

Fig. 1. Modified Rankin scale (mRs) values in men and women before stroke: 0 = without symptoms; 1 = symptoms not demanding lifestyle changes; 2 = slight motor disability but independent in daily activity; 3 = moderate motor disability, walking with support; 4-5 = patient needs a lot of help in daily activity, stays in bed and chair, or needs constant care during the day and night.



(POCS) and lacunar syndrome (LACS); diagnostic test findings; and early 30-day outcome, with death rate and poor outcome defined as modified Rankin scale (mRs)  $\geq 3^{26-28}$ . The information was collected in the local stroke registry.

We assessed sex differences in the distribution of the known stroke risk factors (age, atrial fibrillation (AF), hypertension, and other), state prior to stroke, and clinical status at admission (consciousness level, stroke subtype). The place of residence 30 days after stroke was classified as own home, relative's home, rehabilitation center, residential care, or other hospital department for care.

#### Statistical analysis

Comparisons between men and women with respect to categorical variables were made using chisquare analysis. Continuous variables were tested using Student's t-test, or Mann-Whitney test if normality was difficult to assume. Univariate analysis was performed with the chi-square test for dichotomous variables or Pearson's chi-square test for categorical variables. The level of significance was set at *P*<0.05. We used a logistic regression model to adjust for casemix and evaluate any independent effects of sex.

# Results

Out of 2534 registry subjects, 54% (n=1379) were female and 46% (n=1155) were male. Many demographic and clinical characteristics measured at base-

line differed by sex (Table 1). Female patients were 5.5 years older than male patients (mean age 74.3 and 68.8 years, respectively). Women were less likely to smoke, abuse alcohol, or have a history of cardiac infarct, and they were more likely to be disabled prior to stroke compared to men (14.3% vs. 7.8%) (Fig. 1). Atrial fibrillation occurred more frequently in females than males (30.5% and 17.5%, respectively), as well as congestive heart failure and hypertension. Transient ischemic attack (TIA) was less common among women compared to men (11.5% vs. 14.6%). No significant sex differences were recorded for diabetes mellitus, coronary heart disease, or prior medical history of stroke. Women were more likely to have impaired consciousness (30.7% vs. 20.4%) or severe stroke (TACS) (Table 2). Internal carotid artery (ICA) stenosis >70% was more common in men than women (19.1% vs. 10.8%) (Table 3). The intima-media thickness (IMT) was approximately 0.1 mm greater in men than women (Table 4).

The incidence of poor 30-day outcome and case fatality was significantly higher among women than men (59.9% vs. 46.2% and 17.2% vs. 13.1%, respectively) (Fig. 2). Women were discharged to residential homes or institutional care more often than men were (9.4% vs. 3.4%; P<0.001) (Table 5).

The logistic regression model revealed that sex was not an independent predictor of death at 30 days, but it was independently associated with a higher risk of early poor outcome (Table 6). However, age, mRs,

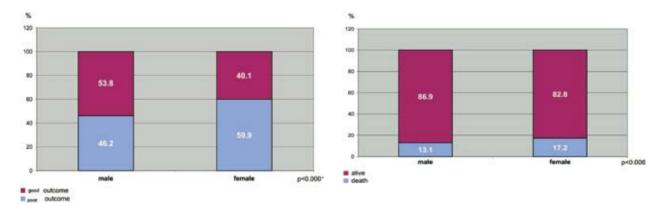


Fig. 2. 30-day outcome and mortality of ischemic stroke. Top = the modified Rankin scale defined good outcome as 0-2: without symptoms, symptoms not demanding lifestyle changes, or slight motor disability but independent in daily activity. The modified Rankin scale defined poor outcome as 3-6: moderate motor disability, walking with support; needs a lot of help in daily activity; needs constant care during the day and night; or death.

Table 2. Patient characteristics at admission

Marker	Male	(N=1151)	Female	Female (N=1374)	
Wiarker	n	(%)	n	(%)	<i>P</i> -value
Consciousness level					
Alert	917	(79.7)	953	(69.4)	< 0.0001
Drowsy	146	(12.7)	236	(17.2)	< 0.003
Stupor	63	(5.5)	118	(8.6)	< 0.004
Coma	25	(2.2)	67	(4.9)	<0.0006
Stroke subtype Total anterior circulation syndrome Partial anterior circulation syndrome Posterior circulation syndrome Lacunar circulation syndrome Unclassified stroke	161 505 317 140 28	(14.0) (43.9) (27.5) (12.2) (2.4)	289 566 353 97 59	(21.2) (41.5) (25.9) (7.1) (6.1)	<0.0001 >0.24 >0.37 <0.0001 <0.02
Total cholesterol Mean (mg%) (95% CI)	198.9 (19	6.0-201.7)	206.2 (203.	4-208.9)	<0.0004

CI = confidence interval.

Table 3. Internal carotid artery (ICA) state on Doppler sonography of the stroke side in ischemic stroke patients

Sex	Occlusion n (%)	Stenosis 70%-99% n (%)	Stenosis <70% n (%)	Arteriosclerotic changes n (%)	Normal state n (%)
Male (n=1115)	131 (11.7)	83 (7.4)	177 (15.9)	250 (22.4)	474 (42.5)
Female (n=1308)	76 (5.8)	65 (5.0)	169 (12.9)	339 (25.9)	659 (50.4)
P-value	< 0.0002	< 0.05	< 0.02	< 0.0001	>0.05

TIA, hypertension prior to stroke, and consciousness at admission were significantly associated with 30-day outcome (Table 6). The 30-day case fatality was sig-

nificantly higher among older patients and those who smoked, had congestive heart failure or a history of stroke (Table 7).

Table 4. Carotid artery intima-media thickness in ischemic stroke patients

Sex	Intima-media thickness				
	Right side (mm)	Left side (mm)			
Male (n=1102)	0.99±0.38	1.06±0.41			
Female (n=1298)	0.90±0.32	0.94±0.27			
P-value	<0.0001	< 0.0001			

Table 5. Place of discharge after ischemic stroke

Location	Male n (%)		Female n (%)		P-value
Family home	604	(74.8)	658	(71.5)	>0.14
Rehabilitation department	132	(16.3)	120	(13.0)	0.06
Residential home	72	(8.9)	142	(15.4)	<0.0002
Total	808	(100.0)	920	100.0)	

Table 6. Logistic regression analysis for poor 30-day outcome

Factor	ß	P-value	OR	95% CI
Sex	-0.4	0.001	0.67	0.53 - 0.85
Age	0.04	< 0.0001	1.04	1.03 - 1.05
mRs before stroke	0.059	< 0.0001	1.80	1.59 - 2.04
Consciousness	1.91	< 0.0001	6.73	4.96 - 9.15
Hypertension treatment before stroke	-0.59	< 0.0001	0.55	0.41 - 0.76
Circulatory failure	0.22	0.09	1.24	0.97 - 1.60
Atrial fibrillation	0.03	0.82	1.03	0.81 - 1.30
Ischemic heart disease	0.19	0.1	1.21	0.96 - 1.53
Diabetes mellitus	0.05	0.48	1.05	0.92 - 1.21
History of stroke	-0.03	0.83	0.97	0.72 - 1.31
Smoking	0.21	0.10	1.23	0.96 - 1.57
Alcohol abuse	0.83	0.07	1.09	0.99 - 1.19

CI = confidence interval; OR = odds ratio; mRs = modified Rankin scale.

Table 7. Logistic regression analysis for 30-day mortality

Factor	ß	p-value	OR	95% CI
Sex	0.185	0.3	1.2	0.88-1.65
Age	0.045	< 0.0001	1.05	1.03-1.06
mRs before stroke	-0.018	0.8	0.98	0.87-1.10
Consciousness	1.21	< 0.0001	3.34	2.83-3.95
Hypertension treatment before stroke	-0.193	0.34	0.83	0.56-1.22
Circulatory failure	0.49	0.001	1.62	1.22-2.15
Atrial fibrillation	0.24	0.09	1.27	0.96-1.66
Ischemic heart disease	0.01	0.9	1.01	0.76-1.35
Diabetes mellitus	1.14	0.1	1.15	0.98-1.36
History of stroke	-0.51	0.01	0.6	0.41-0.89
Smoking	0.34	0.02	1.41	1.05-1.88
Alcohol abuse	0.06	0.3	1.06	0.95-1.17

CI = confidence interval; OR = odds ratio; mRs = modified Rankin scale.

# Discussion

In our cohort, female acute ischemic stroke patients had a higher early case fatality rate than male patients. However, on an average, females had a higher incidence of more AF, hypertension and congestive heart failure, with AF being 1.7-times more common among females than males. Thus, female patients generally had more severe strokes. Disturbances of consciousness are typical for severe stroke. As more severe stroke according to OCSP classification was more common in women than men, female patients had a higher rate of altered consciousness. Similarly, the IST including 17,370 ischemic stroke patients showed females to have more AF and more severe strokes, as well as a higher early case fatality rate than men<sup>23</sup> After adjusting for differences in our study, female sex was not a significant independent predictor of early 30-day mortality, but it was associated with poorer early prognosis. The 30-day mortality appeared to be determined preliminarily by stroke severity, similar to 14-day mortality in the IST<sup>23</sup>. An excess of AF in women was noted in the Framingham study and others<sup>13,24,29,30</sup>. Echocardiography was not routinely performed in our patients, but other studies found embolic events to be more frequently the cause of stroke in women than in men<sup>24,30</sup>. Roquer et al. found cardioembolic stroke to be twice as common among women as in men, and it appears to be a specific ischemic stroke predictor of in-hospital mortality, but only for women<sup>31,32</sup>.

We also found a significantly worse 30-day outcome among women with acute ischemic stroke, both in terms of overall survival and greater dependency in survivors. As a result, women were less likely to be without help for daily living compared to men, and they were more likely to be in residential or institutional care. Similarly, in the IST analysis, more women remained in residential or institutional care 6 months after stroke, and the difference in long-term outcome between men and women remained significant in multivariate analysis after adjusting for other factors<sup>23</sup>. The cause of this higher dependency in women is not clear but raises the possibility that the lack of the neuroprotective effect of estrogen in these predominantly postmenopausal women might play a role<sup>33</sup>. These findings are often also explained by the fact that, compared with men, women are older, have poorer prestroke function and more comorbidities<sup>14,23,34-36</sup>. The Kansas City Stroke Study<sup>22</sup>, IST<sup>23</sup>, and a national study from Denmark<sup>34</sup> showed this disparity between men and women to have diminished after adjustment for baseline differences in age, stroke severity, and risk factors.

The present study had a number of methodological strengths and weaknesses that should be taken into account on considering the clinical significance of the findings. The study was prospective and the data were of high quality, but it was a single-center study. Despite this fact, the characteristics of the group of ischemic stroke patients were broadly similar to other large hospital-based stroke studies and are likely to be broadly representative. The results can be helpful for planning proper stroke prevention, taking into account the different risk factors and mortality rate in men and women. The sample was not a representative population-based sample, but one drawn from patients admitted to the hospital. However, it seems implausible that there was a sex-dependent bias in patient inclusion/exclusion in the trial. Moreover, exploratory post-hoc analyses of a large number of variables may generate associations that are highly significant, but some of them may also have clinical importance. Finally, given that the women with ischemic stroke had, on an average, more severe strokes, the female sex appearing to be an independent prognostic factor may simply be due to incomplete adjustment for stroke severity and the presence of other age-related comorbidities such as circulatory failure.

The finding that women were more likely to be living in residential homes after discharge from the hospital is most likely related to the higher dependency rate.

In conclusion, these explanatory analyses found differences in the risk factor distribution between men and women and suggested that sex may have effect on stroke outcome. Because of the different impact of cardiovascular risk factors in men and women, the strategies for prevention should be different in the two sexes<sup>34</sup>. In women, controlling blood pressure and AF should be a priority, whereas lifestyle changes are necessary in men. These results also indicate that additional studies are needed to confirm or refine these findings and to examine the underlying biological mechanisms.

In men, the following were found more often compared to women: smoking, myocardial infarction, alcohol use, and a history of TIA. In women, the following were found more often compared to men: hypertension, circulatory failure, and AF. Internal carotid artery stenosis >70% and occlusion on the cerebral infarction side was indicated more often in men than women when the most serious type of stroke was noted, whereas impaired consciousness at admission was significantly more frequent in women. Similarly, early death and poor outcome (mRs ≥3) were more frequent in females than males. Multivariate analysis yielded female sex as an independent negative prognostic factor of acute ischemic stroke.

In this study, data on 11551 men were compared with data on 13791 women with ischemic stroke. The future study will be focused on comparison in this population of women between the subjects with good and poor premorbid function and between those with and without AF.

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### Sažetak

# SPOLNE RAZLIKE U RASPODJELI RIZIČNIH ČIMBENIKA, TEŽINI I ISHODU ISHEMIJSKOG MOŽDANOG UDARA

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Cili studije bio je utvrditi razlike u osnovnim značajkama i ishodu između muškaraca i žena s akutnim ishemijskim moždanim udarom. Ishemijski moždani udar potvrđen je kompjutorskom tomografijom ili pri autopsiji u bolesnika primljenih na Drugi neurološki odjel Zavoda za psihijatriju i neurologiju u Varšavi, Poljska, od 1995. do 2007. godine. Bolesnici i bolesnice uspoređeni su u odnosu na rizične čimbenike, stanje aktivnosti prije moždanog udara, vrst moždanog udara prema klasifikaciji Oxfordshire Community Stroke projekta, nalaze dijagnostičkih pretraga i rani 30-dnevni ishod. Analizirali su se podatci za 1379 žena i 1155 muškaraca s ishemijskim moždanim udarom. Srednja dob bolesnica bila je 74,3 godine, a bolesnika 68,8 godina. Žene su češće imale invalidnost prije moždanog udara, kao i hipertenziju, atrijsku fibrilaciju ili srčano zatajenje, te poremećaj svijesti kod prijma, dok je kod muškaraca češće zabilježena navika pušenja, zlouporaba alkohola te povijest infarkta miokarda ili prolaznog ishemijskog napadaja. Bolesnice su u većem postotku patile od sindroma ukupne prednje cirkulacije nego muškarci (21,2% prema 14,0%). Stenoza unutarnje karotidne arterije veća od 70% zabilježena je u 10,8% žena i 19,1% muškaraca. Smrtnost unutar 30 dana i stope lošeg ishoda bile su značajno više u žena negoli u muškaraca (17,2% prema 13,1%, odnosno 59,9% prema 46,2%). Nakon prilagodbe za casemix u multivarijatnoj analizi ženski spol bio je neovisno udružen s većim rizikom za rani loš ishod. U zaključku, raspodjela rizičnih čimbenika, te kliničke značajke, nalazi dijagnostičkih pretraga i rani ishodi razlikovali su se između muških i ženskih bolesnika s ishemijskim moždanim udarom. Ženski spol bio je udružen s lošijom prognozom, ukazujući na potrebu intenzivnije akutne i dugoročne opće skrbi kako bi se poboljšao ishod bolesti među bolesnicama s ishemijskim moždanim udarom.

Ključne riječi: Moždana ishemija; Moždani udar; Spolni čimbenici; Čimbenici rizika