



Sex-related differences among ischaemic stroke patients treated with intravenous thrombolysis in Poland

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ABSTRACT

Aim of study. We investigated sex differences in ischaemic stroke patients treated with intravenous alteplase.

Clinical rationale for study. We suggest that it is necessary to improve care for women with atrial fibrillation. Our data suggests that closer evaluation of treatment for ischaemic stroke in men and women is needed, preferably in the form of a prospective study.

Materials and methods. This was a multicentre analysis of 1,830 ischaemic stroke patients treated with alteplase from 2004 to 2012. Data was prospectively collected in the Safe Implementation of Treatments in Stroke (SITS) registry. The main outcome measures were symptomatic intracerebral haemorrhage (sICH) within 36 hours of treatment, three months of functional independence, and mortality.

Results. Women were significantly older (mean age 71.3 vs 66.2 years; $p < 0.01$), more often suffered from hypertension (78.3% vs 70.1%; $p < 0.01$) and cardio-embolic strokes (34.7% vs 27.1%; $p < 0.01$), and presented heavier baseline deficits. There were no differences in sICH, but after three months fewer women were functionally independent (46.5% vs 53.3%; $p < 0.01$) and women had higher mortality (26.0% vs 19.7%; $p < 0.01$).

Conclusions: Of the ischaemic stroke patients treated with intravenous thrombolysis, women had worse long-term outcomes than men. This discrepancy may be explained by the older age and higher proportion of cardio-embolic strokes with more severe baseline deficits. However, multiple logistic analysis did not show that sex itself had an impact on the greater mortality in women after a stroke, or on the poorer prognosis.

Key words: alteplase, ischaemic stroke, sex differences, risk factors, outcome

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Introduction

In recent years, a lot of research has been published looking into ischaemic stroke's epidemiology, prognosis, risk factors, pathogenesis, clinical picture and course, as well as its treatment and sex-dependent outcomes [1]. Many studies have shown that women suffer from more severe strokes than men, and have

less favourable prognoses, something which is additionally modified by their home country's level of development [2–9].

Women also appear to be less often treated with intravenous thrombolysis [9–13]. It is uncertain if they equally benefit from intravenous and intra-arterial thrombolysis treatment [12–17]. One should also take into account specific national or regional differences in patients' profiles [18].

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Clinical rationale for the study

The aim of this study was to investigate sex-related differences in patient profiles and outcomes among Caucasian ischaemic stroke patients from Polish centres treated with intravenous thrombolysis.

Materials and methods

This is a retrospective multicentre analysis of 1,830 consecutive ischaemic stroke patients treated with intravenous alteplase (tPA) in Polish centres from 1 January 2004 to 31 December 2012. The data was prospectively recorded in the Safe Implementation of Treatments in Stroke – International Stroke Thrombolysis Registry [19]. The main outcome measures were: functional independence (0–2 in modified Rankin Scale score-mRS) at three months; sICH within 36 hours of treatment; and three-month mortality [19]. Dependency was defined as an mRS score of 3–5 [20].

Stroke events were defined according to the World Health Organisation's criteria, and stroke was confirmed in all patients by neuroimaging [21].

Stroke subtypes were classified on admission according to the Trial of Org10172 in Acute Stroke Treatment (TOAST) criteria [22]. Stroke severity was measured using the National Institutes of Health Stroke Scale score (NIHSS) on admission and at discharge. Conventional stroke risk factors, including hypertension, diabetes mellitus, atrial fibrillation (AF), hyperlipidemia and tobacco smoking, were defined as self-reported in previous medical records or newly diagnosed. Obesity was defined as a body mass index $\geq 30\text{kg/m}^2$. Pre-stroke mRS, at discharge, and three months after the stroke, were assessed during an interview with the patient or his or her proxy.

Statistical analysis

Continuous variables are presented as mean with standard deviation or median and quartiles, depending on the normality of data distribution. Categorical variables are presented as a number of observations with percentage. For comparisons between men and women, Mann-Whitney U tests and Fisher's exact tests were used, as appropriate [23]. A p value = 0.05 was considered significant. All analyses were performed in R v. 3.4.0. [24]. A multiple logistic regression model, which was adjusted for age, onset-to-door time, door-to-treatment time, presence of hypertension, diabetes, AF, smoking (currently), and baseline mRS score before stroke (0 and 1 only), was applied to identify factors contributed considerably to the main endpoints (death, mRS after three months, sICH according to SITS).

Results

The studied population included 1,830 consecutive ischaemic stroke patients treated with alteplase between January

2004 and December 2012 in many centres in Poland. The analysed group included 819 women (44.8%). Women were significantly older (mean age 71.3 vs 66.2 years), were more frequently dependent before a stroke (9.3% vs 3.1%), were more often burdened with AF (35.8% vs 26.3%) and hypertension, but were less often smokers (13.3% vs 33.9%) (Tab. 1). Women suffered more severe strokes (median baseline NIHSS score 13 vs 11). Stroke aetiology in women was more often cardioembolic (34.7% vs 27.1%) (Tab. 1), although they used anticoagulants less often (3.8% vs 4.2%).

Women had significantly longer onset-to-door time (ODT) (median 70 vs 62 min) and longer onset-to-treatment time (OTT) (median 160 vs 154 min), with a borderline difference in door-to-treatment time (DTT) (median 75 vs 80 min, $p = 0.05$). Their stroke unit stay was significantly shorter (median 8.7 vs 9.1 days). There were no significant differences in the prescription rates of hypotensive medications, aspirins, vitamin K antagonists or new oral anticoagulants, but women were less likely than men to be prescribed statins on discharge from hospital (83.4% vs 90.1%).

Women had significantly higher mortality, both at day 7 (15.5% vs 9.6%) and three months after the onset of symptoms (26.0% vs 19.7%) (Tab. 2). This discrepancy was not modified by the presence of AF, hypertension or diabetes. There were no significant differences in the occurrence of sICH according to the ECASS (European Cooperative Acute Stroke Study) or the SITS definition (Tab. 2) [19]. However, a tendency towards a higher occurrence of sICH according to ECASS in women was particularly marked in subgroups of patients with diabetes, with heart failure, with aspirin use before stroke, and with disability before stroke (Tab. 3).

Multiple logistic analysis did not confirm that sex itself had an impact on greater mortality in women after a stroke or a worse prognosis (Tab. 4).

Discussion

In line with data from other cohorts, we found that women with acute ischaemic stroke treated with tPA are older than men and more often suffer from strokes of cardioembolic aetiology [7, 9, 17, 25–29]. However, the mean age at stroke onset among Polish women was seven years lower than in Sweden (mean age 71.3 vs 78.4 years). In other words, female Polish patients experienced a stroke seven years earlier than female Swedish patients [30]. Female Polish patients, despite a higher proportion of pre-stroke AF, used oral anticoagulants as frequently as men (3.8% vs 4.2%). Similarly to Swedish patients [30], no differences were found in the prescription rate of anticoagulants after an ischaemic stroke. Higher proportions of AF and hypertension in women have also been reported in other cohorts [9, 28, 29, 31].

Probably because of all the abovementioned reasons, the neurological condition on admission of women was significantly worse than men [30, 32, 33]. We observed that the ODT,

Table 1. Sex differences in risk factors and clinical characteristics among patients with ischaemic stroke treated with intravenous thrombolysis

Characteristics	Men	Women	p-value
Cases, n (%)	1011 (55.2)	819 (44.8)	< 0.01
Age, years, mean (SD)	66.2 (11.0)	71.3 (11.6)	< 0.01
Atrial fibrillation, n (%)	262 (26.3)	289 (35.8)	< 0.01
Congestive heart failure, n (%)	214 (21.5)	151 (18.8)	0.16
Hyperlipidemia, n (%)	317 (33.4)	254 (32.6)	0.76
Hypertension, n (%)	700 (70.1)	637 (78.3)	< 0.01
Diabetes mellitus, n (%)	184 (18.4)	171 (21.1)	0.15
Previous stroke, n (%)	138 (13.8)	107 (13.2)	0.78
Smoking – previous, n (%)	189 (28)	47 (6.8)	< 0.01
Smoking – current, n (%)	324 (33.9)	106 (13.3)	< 0.01
Baseline NIHSS score, median (Q1-Q3)	11 (7–16)	13 (7.5-18)	< 0.01
SBP mean, mm Hg (SD)	151.4 (20.8)	152.4 (20.4)	0.18
DBP mean, mm Hg (SD)	85.7 (13.1)	83.7 (12.9)	< 0.01
Glucose, mg/dl, (SD)	131.1 (47.3)	135.5 (49.3)	0.01
Large-vessel disease, CAS, n (%)	155 (16.6)	69 (9.3)	< 0.01
Large vessel disease, other, n (%)	301 (32.2)	249 (33.4)	0.64
Cardio-embolic, n (%)	253 (27.1)	259 (34.7)	< 0.01
Lacunar stroke, n (%)	57 (6.1)	57 (7.6)	0.24
Other/unusual n (%)	35 (6.0)	56 (4.7)	0.28
Unknown, n (%)	111 (11.9)	76 (10.2)	0.31

SBP — systolic blood pressure; DBP — diastolic blood pressure

Table 2. Sex differences in outcomes at three months after ischaemic stroke treated with alteplase

Outcome	Men	Women	p-value
Death, n (%)	199 (19.7)	213 (26.0)	< 0.01
mRS 0-1, n (%)	358 (35.4)	245 (29.9)	< 0.01
mRS 0-2, n (%)	539 (53.3)	381 (46.5)	< 0.01
Intracerebral haemorrhage according to ECASS def., n (%)	45 (4.7)	50 (6.5)	0.11
Intracerebral haemorrhage according to SITS def., n (%)	14 (1.5)	16 (2.0)	0.36

ECASS — European Cooperative Acute Stroke Study; SITS — Safe Implementation of Treatments in Stroke; mRS — modified Rankin Scale score

Table 3. Frequency of symptomatic intracerebral haemorrhage (sICH) according to ECASS definition in women and men depending on presence of additional factor

Additional factor	Men sICH		Women sICH		p-value
	with factor	without factor	with factor	without factor	
Diabetes, n (%)	9 (5.3)	36 (4.6)	13 (8.0)	36 (6.0)	1.36 (CI 0.52–3.08)
Atrial fibrillation, n (%)	20 (8.2)	23 (3.3)	27 (9.9)	22 (4.5)	1.31 (CI 0.74–2.56)
Hypertension, n (%)	8 (4.8)	12 (4.2)	42 (7.0)	32 (4.8)	1.4 (CI 0.86–2.27)
Heart failure, n (%)	11 (5.5)	32 (4.3)	15 (10.9)	34 (5.5)	1.47 (CI 0.66–3.38)
Aspirin use before stroke, n (%)	12 (4.0)	28 (4.4)	21 (8.4)	28 (5.6)	1.56 (CI 0.75–3.28)
Disability before stroke, (mRS > 1) n (%)	3 (4.5)	39 (4.5)	14 (11.3)	32 (5.1)	1.28 (CI 0.78–2.05)

Table 4. Multiple regression logistic model adjusted for age, onset-to-door time (OTD), door-to-treatment time (DTT), presence of hypertension, diabetes mellitus, AF, smoking (current), score 0–1 in mRS before stroke, initial stroke severity on NIHSS scale

Variable	OR ± 97.5 CI	2.5% CI	97.5% CI
Death	1.2104	0.8752	1.6736
Intracerebral haemorrhage according to SITS def.	1.2493	0.5059	3.12222
mRS 0–1 after 3 months	1.0037	0.7803	1.2909
mRS 0–2 after 3 months	1.0137	0.7851	1.3098

OR — odds ratio; CI — 95% confidence interval; SITS — Safe Implementation of Treatments in Stroke; mRS — modified Rankin Scale score

as well as the OTT, in women was on average several minutes longer than in men. This might be caused by their older age, more frequent functional dependence, and more frequent living alone [32]. The difference may not be of major clinical importance overall, but it still deserves to be addressed. Attempts should be made to equip older women who live alone with the knowledge of how to recognise stroke and how to react. It might also be profitable to consider providing them with a special device to facilitate communication with ambulances in case of emergency. As there were no differences in DTT, we can assume that the processing of patients qualified for tPA is equal for both sexes while in hospital.

Yeo et al. [15] observed, in a group of 2,460 ischaemic stroke patients treated with intravenous alteplase, that if the outcome of women improved significantly (a 10 or more points reduction in NIHSS scale) within 2–24 hours, there was a doubled chance of regaining full independence at three months after an ischaemic stroke. This illustrates the necessity of women receiving particularly good care within the first 24 hours from the onset of an ischaemic stroke. If such care were to become standard, then the number of women with greater independence at three months would increase.

Our study has some limitations. It used data from a voluntary multicentre registry. The evaluation of control CT scan was performed on site, and the diagnosis of sICH was made at the discretion of an attending physician. It is impossible to determine how many patients were not reported, and why. Because only a fraction of Polish stroke centres participate in the SITS, one may expect that our results are generalisable to dedicated stroke units, but probably not fully to all Polish stroke units. Nonetheless, the registry provides the best available multicentre real life data.

Clinical implications/future directions

Our findings confirm that there are several important sex-related differences in ischaemic stroke patients treated with intravenous alteplase. Although women do not seem to be at a clearly increased risk of intracerebral haemorrhage, they more often have a poor long-term outcome and higher mortality. This discrepancy may be to some extent explained by the older age and higher proportion of cardio-embolic strokes with more severe baseline deficit.

One may assume that the optimisation of primary prevention, improved stroke awareness, and improved communication with ambulance dispatchers could reduce the gap between men and women. Therefore, specific central health policies should be encouraged and properly implemented.

Our data suggests that closer evaluation of the treatment of ischaemic stroke in men and women in Poland is needed, preferably in the form of a prospective study. It is also necessary to improve care for women with AF.

Conflict of interests: None

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