Sex Differences and Functional Outcome After Intravenous Thrombolysis

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Background and Purpose—Women have a worse outcome after stroke compared with men, although in intravenous thrombolysis (IVT)–treated patients, women seem to benefit more. Besides sex differences, age has also a possible effect on functional outcome. The interaction of sex on the functional outcome in IVT-treated patients in relation to age remains complex. The purpose of this study was to compare outcome after IVT between women and men with regard to age in a large multicenter European cohort reflecting daily clinical practice of acute stroke care.

Methods—Data were obtained from IVT registries of 12 European tertiary hospitals. The primary outcome was poor functional outcome, defined as a modified Rankin scale score of 3 to 6 at 3 months. We stratified outcome by age in decades. Safety measures were symptomatic intracranial hemorrhage and mortality at 3 months.

Results—In this cohort, 9495 patients were treated with IVT, and 4170 (43.9%) were women with a mean age of 71.9 years. After adjustments for baseline differences, female sex remained associated with poor functional outcome (odds ratio, 1.15; 95% confidence interval, 1.02–1.31). There was no association between sex and functional outcome when data were stratified by age. Symptomatic intracranial hemorrhage rate was similar in both sexes (adjusted odds ratio, 0.93; 95% confidence interval, 0.73–1.19), whereas mortality was lower among women (adjusted odds ratio, 0.83; 95% confidence interval, 0.70–0.99).

Conclusions—In this large cohort of IVT-treated patients, women more often had poor functional outcome compared with men. This difference was not dependent on age. **(*Stroke*. 2017;48:699-703. DOI: 10.1161/STROKEAHA.116.014739.)**

Key Words: age distribution ■ female ■ registries ■ stroke ■ thrombolytic therapy

There is a growing recognition of importance of sex in stroke outcome. More women are affected by stroke because of their longer life expectancy and have a worse functional outcome and a lower quality of life after stroke compared with men.[1–3]

In patients with acute stroke, previous research has also shown sex to affect outcome after intravenous thrombolysis (IVT) treatment; although outcome was similar between men and women treated with placebo, outcome was better in women after IVT.[4] The biological explanation for this difference remains unclear.

A possible explanation could be the difference in recanalization. Women have more cardioembolic strokes, with uniform fibrin-rich clots and therefore a higher affinity of alteplase, resulting in more frequent, faster, and complete recanalization.[5–7]

Another suggested mechanism could be a difference in endogenous fibrinolysis because of differences in sex hormones between men and women. Estrogen has an indirect influence on the controlling of the fibrinolytic system, as well as a direct neuroprotective activity.[8–11] However, there are no convincing data to support these hypotheses.

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Besides the sex differences, some studies suggest an age-related difference among IVT-treated patients: young patients (18–50 years) possibly benefit more from IVT compared with older patients (51–80 years).[12–15] The interaction of sex on the functional outcome in IVT-treated patients in relation to age is not clear.

Patients in randomized trials somehow differ from those in daily practice, and such an interaction may not be present outside of a trial setting.

The aim of this study was to compare outcome after IVT between women and men with regard to age in a large multicenter European cohort reflecting daily clinical practice of acute stroke care.

Methods

Study Population, Procedures, and Outcomes

As a joint initiative of 12 European tertiary stroke centers, the Thrombolysis in Ischemic Stroke Patients investigators performed a large prospective observational clinical cohort study.

All participating centers treated patients with acute ischemic stroke with IVT according to the current guidelines (http://eso-stroke.org/eso-guideline-directory/).

Data from individual consecutive patients were collected using a standardized form with predefined variables as is described in previous studies.[16–19] Local study investigators completed the forms using prospectively ascertained in-hospital IVT registries. Completed forms from all centers were compiled in the coordinating center in Amsterdam, where data were pooled and analyzed as described previously.[16,17]

Each center reported on the period for which they collected data up to July 2014. This period was different for each center. The first data were collected in June 1995. Patients were excluded if data on sex or 3-month outcome were missing.

The following baseline characteristics and medical history were used: age, initial stroke severity assessed by National Institutes of Health Stroke Scale, independency before index stroke, defined as a modified Rankin scale (mRS) score of 0 to 2 previous index stroke, hypertension, atrial fibrillation, coronary artery disease, hyperlipidemia, diabetes mellitus, antithrombotic medication use before stroke, current smoking, and stroke-to-needle time. Outcome measures were poor functional outcome defined as an mRS score of 3 to 6 at 3 months follow-up and ordinal mRS scores. mRS scores were obtained by the local center through a telephone interview or by outpatient clinic visit with the patient or caregiver, as described in previous research.[16–19] Safety measures were symptomatic intracranial hemorrhage and mortality at 3 months. Symptomatic intracranial hemorrhage was defined according to the criteria of the European Cooperative Acute Stroke Study II: any hemorrhage with neurological deterioration, indicated by a National Institute of Health Stroke Scale score ≥4 than the value at baseline or the lowest value within 7 days, or any hemorrhage leading to death.[20]

Statistical Analyses

Clinical characteristics were summarized and compared between women and men. All values were presented as mean (±SD) or median (interquartile range) for continuous variables and counts (percentage) for categorical variables. Percentage proportions were calculated by dividing the number of events by the total number of patients, excluding missing or unknown cases. For the comparison of categorical and continuous variables, χ^2 and Student t tests were used, respectively.

The main analysis was a comparison of poor outcome as a crude odds ratio (OR) and the ordinal mRS scores between women and men using Mann–Whitney U and χ^2 tests, respectively. We additionally compared poor outcome between women and men stratified by age in decades (<40, 40–49, 50–59, 60–69, 70–79, and ≥80 years). Crude comparisons were adjusted for clinical characteristics that significantly differed (P<0.05) between women and men in a multivariate logistic regression analysis (adjusted OR). Second, mortality and symptomatic intracranial hemorrhage rates were compared between women and men (crude and adjusted OR).

Results

Demographic and baseline characteristics according to sex are presented in Table 1. Of the 9495 patients treated with IVT, 4170 (43.9%) were women. Compared with men, women were older, had more severe strokes, were less often functionally independent before index stroke, and had a longer stroke-to-needle time. Atrial fibrillation and hypertension were more prevalent among women, whereas men more often reported hyperlipidemia, diabetes mellitus, and coronary artery disease and were more often current smokers.

The 3-month outcome was available for 9070 (95.5%) patients. Overall, 50% of the women had a poor outcome, compared with 41% among men (mRS score of 3–6: crude OR,

Table 1. Clinical Characteristics of Women Compared With Men

	Women (n=4170)	Men (n=5325)	*P* Value
Age, y (SD)	71.9±14.5	67.0±13.2	<0.001*
Median NIHSS on admission (IQR)	11 (6–17)	9 (5–16)	<0.001†
Previous mRS score of 0–2 before index stroke, n/N (%)	3071/3390 (90.6)	4164/4334 (96.1)	<0.001‡
Previous ischemic stroke, n/N (%)	631/4150 (15.2)	798/5199 (15.3)	0.847‡
Hypertension, n/N (%)	2888/4162 (69.4)	3420/5210 (65.6)	<0.001‡
Atrial fibrillation, n/N (%)	1354/4155 (32.6)	1250/5208 (24.0)	<0.001‡
Coronary artery disease, n/N (%)	584/4106 (14.2)	1095/5147 (21.3)	<0.001‡
Hyperlipidemia, n/N (%)	1597/4138 (38.6)	2263/5199 (43.5)	<0.001‡
Diabetes mellitus, n/N (%)	716/4162 (17.2)	1026/5208 (19.7)	<0.002‡
Antithrombotics use before stroke, n/N (%)	1626/4035 (40.3)	2012/5065 (39.7)	0.597‡
Current smoking, n/N (%)	499/3414 (14.6)	1144/4170 (27.4)	<0.001‡
Median stroke-to-needle time, min (IQR)	135 (101–178)	140 (105–180)	
Mean stroke-to-needle time, min	149.5±63.3	145.8±63.3	<0.009*
STN <90 min, n (%)	510 (14.1)	719 (16.1)	
STN 90–180 min, n (%)	2293 (63.4)	2819 (63.0)	
STN 180–270 min, n (%)	701 (19.4)	777 (17.4)	
STN >270 min, n (%)	113 (3.1)	159 (3.6)	

Variables were included in a multivariate regression model if P<0.05. IQR indicates interquartile range; mRS, modified Rankin scale; n/N, number of patients divided by total of patients excluding missing data; NIHSS, National Institutes of Health Stroke Scale; and STN, stroke-to-needle time.

*Students t test.

†Mann–Whitney U test.

‡χ^2.

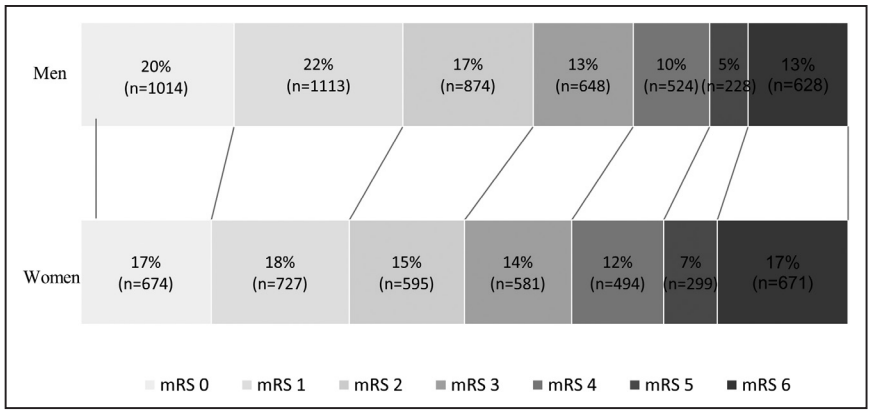

Figure 1. Univariate analysis of distribution of modified Rankin scale (mRS) score after intravenous thrombolysis in men and women (n=9070).

1.52; 95% confidence interval, 1.40–1.65; Figure 1). Ordinal mRS score differed between men and women ($P<0.001$; Figure 1). Women still had more often a poor functional outcome after adjustment for age, stroke severity, functional independency before index stroke, hypertension, atrial fibrillation, coronary artery disease, hyperlipidemia, diabetes mellitus, current smoking, and stroke-to-needle time (OR, 1.15; 95% confidence interval, 1.02–1.31; Table 2). When age was stratified per decade and for adjustments, there was no association between sexes and functional outcome. A suggestion of a turning point from a poor functional outcome toward a good functional outcome among women was at approximately the age of 40 years, but it did not reach statistical significance (Table 3; Figure 2).

Symptomatic intracranial hemorrhage rates were similar between women and men. Whereas about mortality, female sex was associated with a higher mortality rate (OR, 1.40; 95% confidence interval, 1.24–1.57) in crude analysis, but markedly, in multivariate analysis, women had a lower mortality rate (OR, 0.83; 95% confidence interval, 0.70–0.99; Table 2). The change in mortality rate was mostly determined by age and atrial fibrillation.

Discussion

In this large European multicenter cohort study of consecutive ischemic stroke patients receiving IVT, women more often had a poor functional outcome after IVT than men. This finding was not dependent on age and could not be explained by a higher bleeding risk or mortality rate in women.

This study provides evidence for a interaction between sex and outcome after IVT: women more often have a worse functional outcome after IVT than men. This is in contrast to what has been previously reported.[4,21]

Conflicting results come from several studies investigating the relation between sex and functional outcome after IVT. For example, the secondary analysis of the GAIN (Glycine Antagonist in Neuroprotection for Patients With Acute Stroke) Americas trial showed that female sex was associated with a worse functional outcome after IVT, which is in line with our findings.[22] However, in the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register (SITS-ISTR), sex did not show influence on the functional outcome after IVT, though there was a higher bleeding risk among men. This could be a possible explanation for the worse functional outcome among men in contrast to our study.[23] A pooled analysis of randomized IVT trials found no appreciable effect of sex on outcome after IVT and concluded that women seem to benefit from IVT because of the worse functional outcome among women in the placebo-treated group.[4]

Table 2. Outcome Measures After Intravenous Thrombolysis in Women Versus Men

Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Main outcome measures		
mRS score of 3–6 at 3 mo	1.52 (1.40–1.72)	1.15 (1.02–1.31)
Safety outcome measures		
$SICH_{ECASS-II}$	1.01 (0.83–1.22)	0.93 (0.73–1.19)
Mortality	1.40 (1.24–1.57)	0.83 (0.70–0.99)

CI indicates confidence interval; ECASS II, European Cooperative Acute Stroke Study II; mRS, modified Rankin scale; OR, odds ratio; and SICH, symptomatic intracerebral hemorrhage.

*Adjusted baseline variables: age, National Institutes of Health Stroke Scale on admission, previous mRS score of 0–2 before index stroke, hypertension, atrial fibrillation, coronary artery disease, hyperlipidemia, diabetes mellitus, current smoking, and stroke-to-needle time.

Table 3. Poor Functional Outcome After Intravenous Thrombolysis in Women Versus Men According to Age Category

Age Group	Women (n/N)	Men (n/N)	mRS Score of 3–6 Unadjusted OR (95% CI)	mRS Score of 3–6 Adjusted OR (95% CI)*
<40	27/158	30/179	0.95 (0.49–1.83)	0.80 (0.35–1.83)
40–50	66/216	118/393	1.27 (0.82–1.96)	1.55 (0.91–2.63)
50–60	111/378	263/885	1.09 (0.79–1.51)	1.19 (0.82–1.73)
60–70	286/746	466/1309	1.20 (0.94–1.52)	1.17 (0.89–1.54)
70–80	663/1299	687/1533	1.25 (1.04–1.50)	1.04 (0.84–1.30)
>80	890/1242	463/727	1.35 (1.07–1.71)	1.21 (0.92–1.58)

CI indicates confidence interval; mRS, modified Rankin scale; n/N, number of patients divided by total of patients excluding missing data; and OR, odds ratio.

*Adjusted baseline variables: National Institutes of Health Stroke Scale on admission, previous mRS score of 0–2 before index stroke, hypertension, atrial fibrillation, coronary artery disease, hyperlipidemia, diabetes mellitus, current smoking, and stroke-to-needle time.

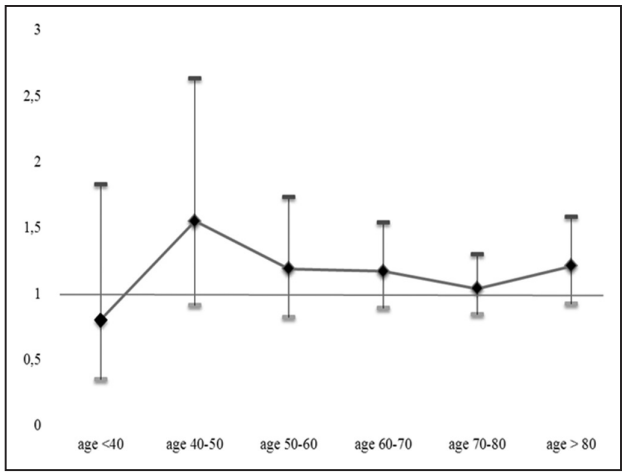

Figure 2. Adjusted odds ratio with 95% confidence intervals for poor functional outcome after intravenous thrombolysis in women vs men according to the age category. Adjusted baseline variables: National Institutes of Health Stroke Scale on admission, previous modified Rankin scale score of 0 to 2 before index stroke, hypertension, atrial fibrillation, coronary artery disease, hyperlipidemia, diabetes mellitus, current smoking, and stroke-to-needle time.

A possible explanation for the contrasting findings in our study could be that patients in randomized control trials tend to have less comorbidities, while in the daily practice, frail women are the most affected by stroke. And age was not taking into account in these studies.

With regard to age, we did not find a significant difference in functional outcome after IVT between men and women in the different age groups.

In contrast to our study, a recent single-center cohort study found that women were more likely to have a favorable outcome; although male sex was associated with a favorable outcome in the older age group, women had a better functional outcome in the middle age group compared with men.[24] However, this study was limited by relatively small number of patients compared with our cohort and included fewer elderly patients.

Interestingly, our study suggests of a turning point from good functional outcome to a poor functional outcome around the age of 40 years, which suggest a possible benefit from IVT in young women. However, because of small numbers of patients in this subgroup, this finding lacked statistical significance.

In previous publications, there is some evidence that age is related to functional outcome in IVT-treated patients: young patients (18–50 years) have possibly more benefit from IVT compared with older patients (51–80 years) and an increase in mortality and lower functional independence with increasing age, with age ranges ≤30, 31 to 40, 41 to 50, and >50 years.[12–15]

A possible explanation for the poor functional outcome after IVT in women, especially the older women, could be the change in endogenous estrogen levels. In animal studies, changes in estrogen levels were inversely associated with the severity of ischemia and brain injury, and the longer the animals were estrogen depleted the higher the incidence of stroke.[25] In humans, studies showed that the sooner the hormone replacement therapy was started after menopause and at younger age, the lower was the incidence of vascular events, suggesting a neuroprotective effect from higher estrogen levels.[26] Thus, with increase of age, the estrogen levels diminish in women and thereby decreasing the suggested neuroprotective effect of estrogen.

Estrogen also has an indirect influence on the alteplase, by lowering the level of platelet activator inhibitor 1, a serine protease inhibitor which decreases the effectiveness of IVT.[8–10] One might suggest that as women's estrogen levels decline during life, the benefit from IVT for women declines with increasing age by higher levels of platelet activator inhibitor 1.

Besides biological hormonal status differences, sex aspects such as living situation (alone or with spouse), family support, and social background also contribute to long-term functional outcome and are largely not included in studies on functional outcome after stroke.[7]

Our study has some limitations: this is a retrospective analysis of prospectively collected data from a joint initiative of 12 European stroke centers, and the possibility of under-reporting might exist. Because of the absence of a comparison group lacking IVT, we were not able to study potential differences of effectiveness of IVT in a real-life setting. Moreover, there were many baseline differences between women and men, which we corrected for, but might have resulted in overcorrection. Estrogen levels and living situation and social background were not assessed, which might differ between male and female sexes and could influence the functional outcome.

Thus, our key findings must be interpreted with caution and must not lead to withholding IVT in the treatment of women with acute ischemic stroke.

Summary/Conclusions

In this large European multicenter consecutive, explorative cohort study, representing daily clinical practice, women more often have a poor functional outcome after IVT compared with men. This difference was not dependent on age. More research on potential reasons for these findings is required.

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