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Original Paper

Is the Efficacy of Endovascular Treatment for Acute Ischemic Stroke Sex-Related?

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Keywords
Endovascular treatment · Females · Ischemic stroke · *Real-world* setting · Sex differences

Abstract
Background: Several reports refer to differences in stroke between females and males, namely in incidence and clinical outcome, but also in response to treatments. Driven by a recent analysis of the MR CLEAN trial, which showed a higher benefit from acute stroke endovascular treatment (EVT) in males, we intended to determine if clinical outcomes after EVT differ between sexes, in a *real-world* setting. ***Methods:*** We analyzed 145 consecutive patients submitted to EVT for anterior circulation large-vessel occlusion, between January 2015 and September 2016, and compared the outcomes between sexes. ***Results:*** Our population was represented by 81 (55.9%) females, with similar baseline characteristics (pre-stroke disability, baseline NIHSS, and ASPECTS), rate of previous intravenous thrombolysis, time from onset to recanalization, and rate of revascularization; with the exception that women were on average 4 years older and had more hypertension, and men in turn had more tandem occlusions and atherosclerotic etiology (all $p < 0.05$). Even after adjusting for these statistically significant variables and for intravenous thrombolysis (as some studies advocate a different response to this treatment between sexes), there were no differences in intracranial hemorrhage, functional independence (mRS ≤2 in 60.9% males vs. 66.7% in females, $p = 0.48$; adjusted $p = 0.36$), or mortality at 3 months. ***Conclusion:*** In a *real-world* setting, we found no sex differences in clinical and safety outcomes after acute stroke EVT. Our results support the idea that women are equally likely to achieve good outcomes as men after acute stroke EVT.

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Introduction

The existence of sex-related differences in ischemic stroke has already been questioned, not only in terms of incidence and prevalence but also in terms of clinical outcome. The data are somewhat contradictory, some attributing a worse prognosis to females [1]. This difference can result from the longer life expectancy in females and an older age at the time of stroke [2].

The divergence between sexes has also been described in relation to response to treatments. Previously, it was thought that females had higher benefit from intravenous thrombolysis [3], pointing out the role of gonadal hormone exposure on coagulation and fibrinolysis systems as a possible underlying factor [2, 3]; however, a recent report by Hametner et al. [4] has questioned that idea, showing an equal response in females and males. Regarding endovascular treatment (EVT) of acute ischemic stroke, there is also controversy about the effect of sex [5–7]. Data from carotid artery stenting suggest that females may have higher periprocedural risk, in part attributed to technical difficulties related to the length of internal carotid arteries [8]. Is there a similar phenomenon in EVT of acute ischemic stroke?

Driven by a recent analysis of the MR CLEAN trial [7], which showed a higher benefit from EVT in males, we intended to determine if clinical outcomes after this treatment differ between sexes, in a *real-world* setting.

Methods

We analyzed data from our prospective database of acute stroke EVT, including all consecutive patients with anterior circulation large-vessel occlusions, treated between January 2015 and September 2016.

Our database comprises information relative to baseline and demographic characteristics, interventional procedure data, stroke etiology, and outcome and safety parameters. These include some known outcome predictive factors like age, vascular risk factors, namely diabetes, baseline National Institutes of Health Stroke Scale (NIHSS) score (assessed by a trained neurologist), Alberta Stroke Program Early CT Score (ASPECTS) at admission, arterial occlusion site, intravenous thrombolysis, time from symptom onset to recanalization, and successful recanalization (defined as modified treatment in cerebral infarction [mTICI] ≥2b and calculated from the last angiographic control images) [9–11].

Patients with a clinical suspicion of stroke were admitted to the emergency room, their neurological deficits were quantified by the NIHSS score and, without delays, a nonenhanced cranial computed tomography (CT) and a CT angiography were performed. A vascular neurologist and an interventional neuroradiologist analyzed the clinical and image data and shared the decision of selection to EVT, according to the European Stroke Organisation consensus [12]. Patients had to have pre-stroke autonomy (modified Rankin Scale [mRS] <2) independently of age, a standard nonenhanced cranial CT with an ASPECTS >5, and a CT angiography documenting large-vessel occlusion (intracranial internal carotid artery, M1 or proximal M2 segments of the middle cerebral artery, including tandem occlusions). When eligible, they were submitted to concomitant intravenous thrombolysis. EVT was performed with stent retrievers – Trevo (Stryker, Kalamazoo, MI, USA) – or thromboaspiration devices (Penumbra, Alameda, CA, USA), according to the interventional neuroradiologist's preference.

Functional outcome (mRS) was assessed in person by neurologists at an outpatient visit at 3 months of follow-up, and the evaluation of all imaging studies was done by the same interventional neuroradiologist who performed the procedure, not blinded from the clinical data. Outcomes included functional independence (mRS ≤2), as well as mortality at 3 months and total and symptomatic intracranial hemorrhage, according to European Cooperative Acute Stroke Study criteria [13]. The study was approved by the local ethics committee.

The independent effect of sex on clinical outcomes was analyzed with a multivariate logistic regression model, that adjusted for variables with statistical significance (p values <0.05) in the univariate analysis and for intravenous thrombolysis, since some studies advocate a different response to this reperfusion treatment between sexes [3]. Statistical analysis was performed with SPSS (V.24.0; IBM Corporation, Armonk, NY, USA). We used the χ^2 test or Fisher exact test for categorical variables and the Student t test or the Mann-Whitney U test for continuous variables, according to the normality of distributions.

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Table 1. Baseline characteristics and interventional procedure data according to sex

	Male	Female	*p* value
Patients	64 (44.1)	81 (55.9)	
Age, years	67.7±13.3	72.1±13.2	0.03
Pre-stroke mRS <2	61 (95.3)	73 (90.1)	0.35
Vascular risk factors			
Diabetes	13 (21.3)	17 (21.0)	0.96
Hypertension	31 (50.8)	58 (71.6)	0.01
Dyslipidemia	28 (45.9)	40 (49.4)	0.68
Current smoking	10 (16.4)	5 (6.2)	0.05
Baseline NIHSS score	18 (13–20)	16 (14–20)	0.59
ASPECTS score	8 (7–9)	8 (8–9)	0.34
Arterial occlusion site			
Intracranial ICA	18 (28.1)	24 (29.6)	0.84
MCA M1 segment	33 (51.6)	45 (55.6)	0.63
MCA M2 segment	13 (20.3)	12 (14.8)	0.38
Tandem occlusion	17 (26.6)	5 (6.2)	0.001
Etiology			
Cardioembolism	32 (50.0)	42 (51.9)	0.83
Large-artery atherosclerosis	14 (21.9)	7 (8.6)	0.03
Other or undetermined	18 (28.1)	32 (39.5)	0.15
Prior IV thrombolysis	43 (67.2)	58 (71.6)	0.57
Process times, min			
Time from symptoms to needle	135 (88–179)	135 (96–195)	0.67
Time from onset to groin puncture	270 (205–350)	255 (191–330)	0.47
Time from groin puncture to recanalization	41 (25–65)	43 (26–66)	0.85
Time from onset recanalization	313 (250–397)	296 (235–418)	0.60
General anesthesia	2 (3.1)	2 (2.5)	1.0
Successful recanalization (mTICI ≥2b)	59 (92.2)	69 (85.2)	0.19

Quantitative variables are expressed as means ± SD or medians (interquartile range), and categorical variables are expressed as numbers (percentages). ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; IV, intravenous; MCA, middle cerebral artery; mRS, modified Rankin Score; mTICI, modified treatment in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale.

Results

Amongst 145 consecutive patients submitted to EVT, mainly with stent retrievers (98.6%), females represented 55.9% (81/145) of our population. Seventy percent (101/145) of the patients received intravenous thrombolysis.

When comparing both sexes (Table 1), females were on average 4 years older and had more hypertension (71.6 vs. 50.8%, $p = 0.01$); males had higher rates of tandem occlusions (26.6 vs. 6.2%, $p = 0.001$) and atherosclerotic etiology (21.9 vs. 8.6%, $p = 0.03$). There were no statistically significant differences between males and females in baseline NIHSS score (18 vs. 16, $p = 0.59$), pre-stroke autonomy (95.3 vs. 90.1%, $p = 0.35$), ASPECTS score (8 vs. 8, $p = 0.34$), and rate of previous intravenous thrombolysis (67.2 vs. 71.6%, $p = 0.57$).

Rates of successful recanalization (mTICI ≥2b) were also similar (92.2 vs. 85.2%, $p = 0.19$), with identical time from onset to recanalization (313 vs. 296 min, $p = 0.60$) and time from groin puncture to recanalization (41 vs. 43 min, $p = 0.85$).

There were no differences in intracranial hemorrhage, both for total (12.5 vs. 13.6%, $p = 0.85$; adjusted $p = 0.83$) and symptomatic (4.7 vs. 2.5%, $p = 0.66$; adjusted $p = 0.90$) cases,

Table 2. Clinical and safety outcomes according to sex

	Male	Female	*p* value	Adjusted *p* value	Adjusted OR (95% CI)
Functional independence (mRS ≤2) at 3 months	39 (60.9%)	54 (66.7%)	0.48	0.36	0.70 (0.33–1.50)
Mortality at 3 months	7 (10.9%)	8 (9.9%)	0.84	0.20	0.47 (0.15–1.50)
ICH	8 (12.5%)	11 (13.6%)	0.85	0.83	1.12 (0.38–3.28)
Symptomatic ICH	3 (4.7%)	2 (2.5%)	0.66	0.90	0.87 (0.10–7.67)

Adjustment was performed for statistically significant variables (age, hypertension, tandem occlusion, and large-artery atherosclerosis) and for intravenous thrombolysis, using a multivariable logistic regression model. CI, confidence interval; ICH, intracranial hemorrhage; mRS, modified Rankin Score; OR, odds ratio.

functional independence (60.9 vs. 66.7%, $p = 0.48$; adjusted $p = 0.36$), or mortality (10.9 vs. 9.9%, $p = 0.84$; adjusted $p = 0.20$) at 3 months, even after controlling for potential confounding factors (Table 2).

Discussion

In our series, although females were older and had more hypertension, in accordance with previous reports [1, 5], the rate of successful recanalization was similar and we found no sex differences in clinical and safety outcomes after EVT. Despite the prior suggestion that EVT may present higher technical difficulties in females than males [8], our results did not support this idea, at least in terms of time from groin puncture to recanalization, which showed no statistically significant difference between sexes.

In 2012, Lutsep and Hill [5] reported the effect of gender in EVT outcomes. They analyzed 305 patients included in the MERCI and MultiMERCI trials and found that rates of revascularization, functional independence, and mortality at 3 months were similar between males and females. Though these results came from EVT trials that used first-generation devices, comprised not only anterior circulation but also vertebrobasilar occlusions, and the MERCI trial only included patients ineligible for intravenous thrombolysis.

Two of the randomized clinical trials that firstly demonstrated the superiority of EVT in anterior circulation large-vessel occlusions [14, 15] performed a subgroup analysis by sex, also showing an equal benefit in functional independence at 3 months in both sexes ($p = 0.78$ in SWIFT-PRIME) [14]. However, outcome was not adjusted for possible differences in baseline characteristics, which were not specified by sex. On the opposite side, a recent analysis of the MR CLEAN trial showed that, comparing to controls of the same sex, males have a greater benefit from EVT, with a treatment effect (adjusted common odds ratio for a shift in the direction of better outcome on the mRS) of 2.39 (95% confidence interval 1.55–3.68) opposing to 0.99 (95% confidence interval 0.60–1.66) in females, and a statistically significant interaction between sex and treatment effect ($p_{\text{interaction}} = 0.016$). In addition, women also had higher rates of mortality than their counterparts in the control group and higher rates of severe adverse events than men submitted to EVT. However, this fact does not seem to justify the lack of treatment effect in females. The authors did not find a reliable clinical or biological fundament to explain this difference and eventually consider that their results may be “a play of chance” [7].

Our findings are in accordance with a recent work by Sheth et al. [6], including almost 400 patients from a prospective multicenter randomized cohort, which showed no sex differences in successful recanalization and functional independence at 3 months.

Methodological limitations of our work include the fact that the classification of recanalization (mTICI scale) was performed by the same interventionist who carried out the procedure and the clinical evaluation at 3 months was not blinded to the results of the endovascular procedure, with a potential to introduce bias. However, our recanalization rates and outcomes are similar to the report of Sheth et al. [6] that shows a successful recanalization in 87% of females versus 83% of males and functional independence at 3 months in 53% of females versus 56% of males. Besides, in our analysis, we included neither the collateral status nor the infarct volume, which are known outcome predictors [16, 17]. Our study may be underpowered to detect sex differences (145 vs. 233 patients in the MR CLEAN trial [7]), but this is probably not the case, since the abovementioned cohort of 400 patients showed results overlapping with ours [6]. Additionally, the aforementioned results are all from clinical trials and with different methodologies (e.g., MR CLEAN [7] analyzes the treatment effect comparing with controls of the same sex), which limit the comparison with data from our *real-world* series.

To our knowledge, this is the first report from the *real world*, supporting the idea that women are equally likely to achieve good outcomes as men after acute stroke EVT.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1 Ahnstedt H, McCullough LD, Cipolla MJ: The Importance of considering sex differences in translational stroke research. Transl Stroke Res 2016;7:261–273.
2 O'Reilly MR, McCullough LD: Sex differences in stroke: the contribution of coagulation. Exp Neurol 2014;259: 16–27.
3 Kent DM, Price LL, Ringleb P, Hill MD, Selker HP: Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. Stroke 2005; 36:62–65.
4 Hametner C, MacIsaac RL, Kellert L, Abdul-Rahim AH, Ringleb PA, Lees KR; VISTA Collaborators: Sex and stroke in thrombolyzed patients and controls. Stroke 2017;48:367–374.
5 Lutsep HL, Hill MD: Effects of sex on mechanical embolectomy outcome. J Stroke Cerebrovasc Dis 2012;21: 240–242.
6 Sheth SA, Warach S, Gralla J, Jahan R, Goyal M, Nogueira R, Zaidat O, Pereira V, Siddiqui A, Lutsep H, Liebeskind D, McCullough L, Saver JL: Abstract TMP7:Endovascular stroke therapy abrogates sex-related differences in recanalization in acute ischemic stroke. Stroke 2017;48:ATMP7.
7 de Ridder IR, Fransen PS, Beumer D, Berkhemer OA, van den Berg LA, Wermer MJ, et al: Is intra-arterial treatment for acute ischemic stroke less effective in women than in men? Interv Neurol 2016;5:174–178.
8 Howard VJ, Lutsep HL, Mackey A, Demaerschalk BM, Sam AD, Gonzales NR, et al: Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Lancet Neurol 2011;10:530–537.
9 Yoon W, Kim SK, Park MS, Baek BH, Lee YY: Predictive factors for good outcome and mortality after stent-retriever thrombectomy in patients with acute anterior circulation stroke. J Stroke 2017;19:97–103.
10 Linfante I, Starosciak AK, Walker GR, Dabus G, Castonguay AC, Gupta R, et al: Predictors of poor outcome despite recanalization: a multiple regression analysis of the NASA registry. J Neurointerv Surg 2016;8:224–229.

11 Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA; IMS I and II Investigators: good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology 2009;73: 1066–1072.
12 Wahlgren N, Moreira T, Michel P, Steiner T, Jansen O, Cognard C, et al: Mechanical thrombectomy in acute ischemic stroke: consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. Int J Stroke 2016;11:134–147.
13 Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al: Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245–1251.
14 Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al: Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285–2295.
15 Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al: Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019–1030.
16 Berkhemer OA, Jansen IG, Beumer D, Fransen PS, van den Berg LA, Yoo AJ, et al: Collateral status on baseline computed tomographic angiography and intra-arterial treatment effect in patients with proximal anterior circulation stroke. Stroke 2016;47:768–776.
17 Yoo AJ, Chaudhry ZA, Nogueira RG, Lev MH, Schaefer PW, Schwamm LH, et al: Infarct volume is a pivotal biomarker after intraarterial stroke therapy. Stroke 2012;43:1323–1330.