Stroke

CLINICAL AND POPULATION SCIENCES

Sex-Related Differences in Outcomes After Endovascular Treatment of Patients With Late-Window Stroke

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BACKGROUND AND PURPOSE: Sex-related differences exist in many aspects of acute stroke and were mainly investigated in the early time window with conflicting results. However, data regarding sex disparities in late presenters are scarce. Therefore, we sought to investigate differences in outcomes between women and men treated with endovascular treatment in the late time window.

METHODS: Analyses were based on the SOLSTICE Consortium (Selection of Late-Window Stroke for Thrombectomy by Imaging Collateral Extent), which was an individual-patient level analysis of seven trials and registries. Baseline characteristics, 90-day functional independence (modified Rankin Scale score ≤2), mortality, and symptomatic intracranial hemorrhage were compared between women and men. Effect of sex on the association of age and successful reperfusion (final Thrombolysis in Cerebral Infarction 2b–3) with outcomes was assessed using multivariable logistic regression adjusted for age, National Institutes of Health Stroke Scale score, Alberta Stroke Program Early CT Score, time from onset to puncture, occlusion location, intravenous thrombolysis, and successful reperfusion, with interaction terms.

RESULTS: Among 608 patients treated with endovascular treatment, 50.5% were women. Women were older than men (median age of 72 versus 68 years, P=0.02) and had a lower prevalence of tandem occlusions (14.0% versus 22.9%, P=0.005). Workflow times were similar between sexes. Adjusted outcomes did not differ between women and men. Functional independence at 90 days was achieved by 127 out of 292 women (43.5%) and 135 out of 291 men (46.4%). Mortality at 90 days (54 [18.5%] versus 48 [16.5%]) and symptomatic intracranial hemorrhage (37 [13.3%] versus 33 [11.6%]) were similar between women and men. There was no sex-by-age interaction on functional outcomes. However, men had higher likelihood of mortality ($P_{interaction}$=0.003) and symptomatic intracranial hemorrhage ($P_{interaction}$=0.017) with advancing age. Sex did not influence the relation between successful reperfusion and outcomes.

CONCLUSIONS: In this multicenter analysis of late patients treated with endovascular treatment, sex was not associated with functional outcome. However, sex influenced the association between age and safety outcomes, with men experiencing worse outcomes with advancing age.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: Editorials ■ reperfusion ■ thrombectomy ■ sex ■ stroke

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Nonstandard Abbreviations and Acronyms

ASPECTS	Alberta Stroke Program Early CT Score
ESCAPE	Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke
ESCAPE-NA1	Efficacy and Safety of Nerinetide for the Treatment of Acute Ischaemic Stroke
EVT	endovascular treatment
HERMES	Highly Effective Reperfusion Using Multiple Endovascular Devices
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PRove-IT	Precise and Rapid Assessment of Collaterals Using Multiphase CTA in the Triage of Patients With Acute Ischemic Stroke for IV or IA Therapy
sICH	symptomatic intracranial hemorrhage
SOLSTICE	Selection of Late-Window Stroke for Thrombectomy by Imaging Collateral Extent

Sex-related differences in stroke outcomes have been a long-standing discussion in the stroke community. The existing literature does not support a modifying effect of sex on endovascular treatment (EVT) outcomes in the early time window, with conflicting results showing worse or neutral outcomes in women compared with men.[1–9] A post hoc analysis of the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) showed that women have lower chances of better functional outcomes and higher rates of mortality compared with men.[2] Conversely, in a pooled analysis of 7 clinical trials within the HERMES (Highly Effective Reperfusion Using Multiple Endovascular Devices) collaboration, sex did not influence clinical outcomes or modify EVT treatment effect among those treated within 6 hours from onset.[1,10] Data regarding sex differences in late-window patients are scarce. A substudy of the DEFUSE-3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3), which treated patients 6 to 16 hours after onset, found that women exhibited worse clinical outcomes in the EVT arm.[11] Although clinical characteristics were not stratified by sex, the DAWN trial (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) did not report any sex differences in clinical outcome in all included patients.[12]

There are some observations that support a potential role for sex in the outcome of patients with stroke in the late versus early time window and collateral flow may have contributed to this difference. Several studies reported a better collateral flow in women.[1,11,13] For instance, in the pooled analysis of Chalos et al,[1] women had higher collateral grades (100% filling of occluded area) compared with men, 46% versus 35%, $P<0.001$, despite a lack of impact on 90-day clinical outcome. Whether outcomes differ by sex is still not clearly understood in this population of late presenters. Therefore, we aimed to assess sex-related differences in stroke presentation, imaging characteristics, and outcomes in a real-world multinational cohort of patients with stroke treated with EVT between 6 and 24 hours after symptom onset or last known well.

METHODS

We used data from the SOLSTICE (Selection of Late-Window Stroke for Thrombectomy by Imaging Collateral Extent) Consortium, which was an individual-patient level analysis of data from multiple trials and registries in North America, Europe, and Korea, using collateral imaging to select patients with stroke with large vessel occlusion for EVT between 6 and 24 hours. These are the Acute Stroke Registry and Analysis of Lausanne,[14] Lausanne, Switzerland (inclusion period: 2003–2017); the Beaumont Hospital Registry,[15] Dublin, Ireland (2014–2017); ESCAPE trial (the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; 2013–2014)[16]; the ESCAPE-NA1 trial (Efficacy and Safety of Nerinetide for the Treatment of Acute Ischaemic Stroke; 2017–2019);[17] the Italian Registry of Endovascular Thrombectomy,[18] Italy (2011–2017); the PRove-IT study (Precise and Rapid Assessment of Collaterals Using Multiphase CTA in the Triage of Patients With Acute Ischemic Stroke for IV or IA Therapy; 2012–2016)[19]; and the Seoul National University Bundang Hospital Stroke Registry (2011–2016).[20] Details regarding the included studies are summarized in Table S1. The main study was registered at PROSPERO (https://www.crd.york.ac.uk/PROSPERO/; Unique identifier: CRD42020222003) and the article adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The data that support the findings of this study are available from the corresponding author upon reasonable request.

All patients underwent collateral imaging and were treated with EVT. Perfusion imaging was performed in a subset of patients according to local institutional protocols.

We classified patients into favorable or unfavorable imaging profiles. A favorable collateral profile was defined as a filling of ≥50% of the middle cerebral artery territory on computed tomography (CT) angiography. In the subset of patients with perfusion imaging (n=379), volumes were provided for 195 patients, and favorable perfusion profile was defined as mismatch ratio ≥1.8, whereas in one study (184 patients), volumes estimates were not available, and favorable perfusion profile was defined as core ≤50% of hypoperfusion extent or less than one-third of the middle cerebral artery territory according to Turk et al.[21]

In the subset of patients who underwent perfusion imaging, core and penumbra volumes were measured using the local software (Table S1). Mismatch volume was calculated by subtracting the core volume from the penumbra volume. To account for the smaller intracranial volume in women compared with men, we performed an additional analysis to adjust for a percentage difference in intracranial volume of 9.8% (according to a previous meta-analysis).[22]

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Successful reperfusion was defined as a Thrombolysis in Cerebral Infarction score of 2b to 3. All included studies were approved by the local review board at each participating center.

Outcomes

The functional outcome was 90 days functional independence defined as a modified Rankin Scale (mRS) score of ≤2 and the shift in the functional level assessed on the full mRS score. Safety outcomes were 90-day mortality and symptomatic intracranial hemorrhage (sICH) defined according to the ECASS2 (European Cooperative Acute Stroke Study 2).[23]

Statistical Analysis

We compared baseline characteristics between women and men using descriptive statistics. χ^2 test was used for categorical variables comparison and Mann-Whitney test for continuous variables.

To assess the association between sex and outcomes, multivariable logistic and ordinal regressions were performed adjusting for age, National Institutes of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT Score (ASPECTS), time from onset to puncture, occlusion location, intravenous thrombolysis administration, and successful reperfusion. Furthermore, we studied the effect modification of sex on variables known to be associated with outcomes (age and successful reperfusion) by including interactions terms in the regression models. Interaction terms with a *P* value of <0.05 were considered statistically significant.

To account for the possibility of studies clustering, we conducted a sensitivity analysis by including center as a cluster variable in the models.

Missing data were minimal (4% for mRS and mortality and 7% for sICH) and therefore no imputation was performed.

Statistical tests were 2-sided, and *P* values were considered significant if <0.05. Statistical analysis was performed using STATA 17 (StataCorp LP).

RESULTS

Baseline Characteristics

Among 608 patients recruited in the study, 307 (50.5%) were women. The study flow chart is displayed in Figure 1. Women were older, median age 72 years (interquartile range [IQR], 58–80) versus 68 years (IQR, 58–76), *P*=0.02, and had a lower prevalence of tandem occlusions than men, 43 out of 307 (14.0%) versus 69 out of 301 (22.9%), *P*=0.005. No significant difference was found between women and men in the NIHSS score (median 15 versus 16, *P*=0.35), ASPECTS (median 8 versus 8, *P*=0.60), or the proportion of patients with a favorable collateral profile. Baseline characteristics of included patients are provided in Table 1.

Among 101 women and 94 men who underwent perfusion imaging and had volumes available for analysis, infarct volumes were numerically lower in women than in

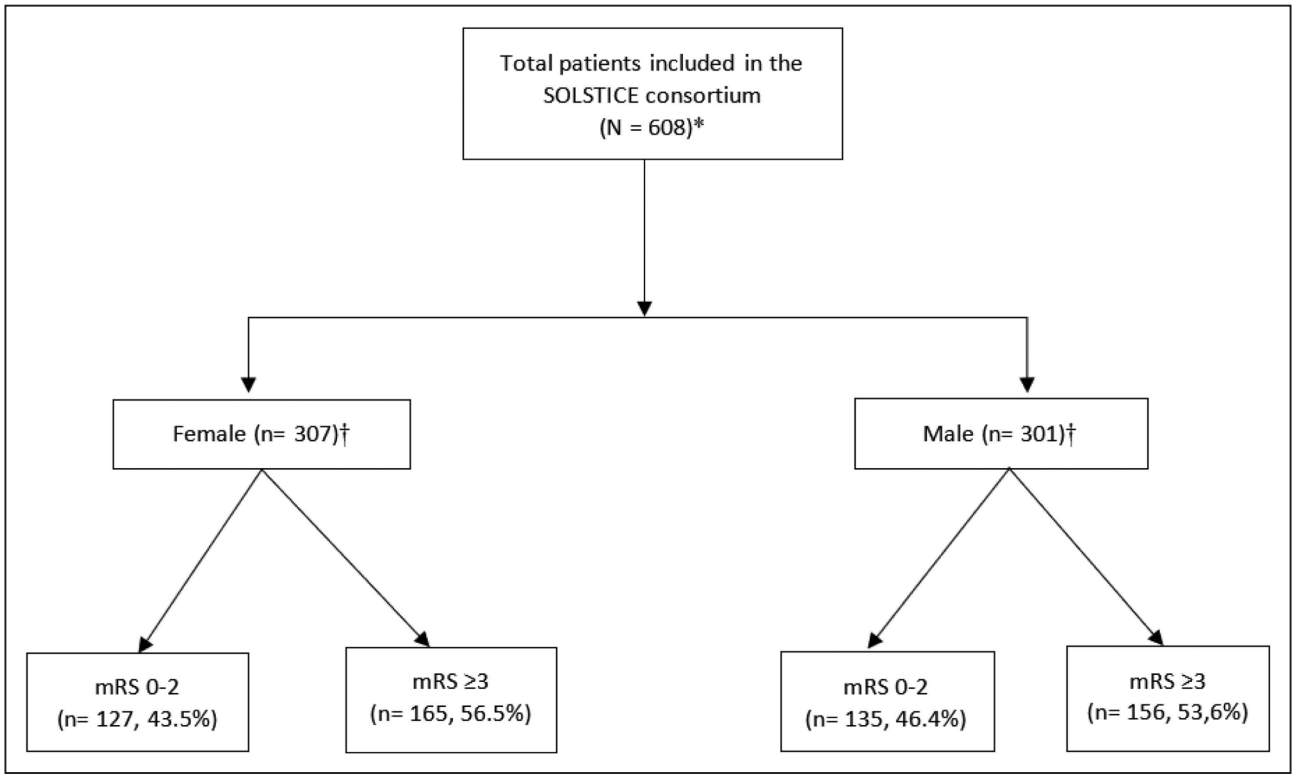

Figure 1. Study flow chart.
mRS indicates modified Rankin Scale; and SOLSTICE, Selection of Late-Window Stroke for Thrombectomy by Imaging Collateral Extent. *All patients underwent collateral imaging. Perfusion volumes were available in 195 patients. †Follow-up data at 90 d were missing for 25 patients (15 women and 10 men).

Table 1. Baseline Characteristics and Outcomes of Included Patients Stratified by Sex

Characteristic	Women (n=307)	Men (n=301)	*P* value
Age, y (median, IQR)	72 (58–80)	68 (58–76)	0.02*
Stroke presentation			
Wakeup stroke	160/291 (55.0)	150/292 (51.4)	0.38
Baseline NIHSS (median, IQR)	15 (10–19)	16 (11–20)	0.35
IV Alteplase	32(10.4)	23 (7.6)	0.23
Time metrics, min (median, IQR)			
Time from onset to ED door	540 (400–697), [n=279]	527 (395–685), [n=279]	0.68
Time from onset to CT scan	556 (438–720), [n=304]	561 (435–700), [n=293]	0.79
Time from onset to puncture	660 (521–843), [n=288]	623 (515–800), [n=285]	0.35
Time from onset to reperfusion	694 (565–868), [n=273]	675 (570–855), [n=274]	0.84
Time from ED door to CT scan	26 (15–45), [n=277]	25 (15–40), [n=271]	0.51
Time from CT to puncture	70 (40–115), [n=286]	63 (40–107), [n=277]	0.26
Imaging factors			
Imaging modality			
Single phase CTA	107 (34.8)	107 (35.5)	0.86
Multiphase CTA	200 (65.1)	194 (64.4)	0.86
CT perfusion	185 (60.3)	194 (64.4)	0.29
ASPECTS	8 (7–9)	8 (7–9)	0.60
ASPECTS 6–10	292 (95.1)	286 (95.0)	0.96
Occlusion site			
Terminal ICA	62 (20.2)	74 (24.6)	0.19
M1-MCA	193 (62.9)	174 (57.8)	0.20
M2-MCA	45 (14.7)	37 (12.3)	0.39
Tandem occlusion	43 (14.0)	69 (22.9)	0.005*
Favorable collateral profile	276/305 (90.5)	268/299 (89.6)	0.72
Favorable perfusion profile	167/185 (90.3)	172/194 (88.7)	0.61
Baseline perfusion volumes	[n=101]	[n=94]	
Core volume, mL	7 (1.2–23)	11.2 (0.8–34.7)	0.16
Adjusted core volume, mL†	7.7 (1.3–25.2)	11.2 (0.8–34.7)	0.26
Penumbra volume, mL	97 (60–130)	109 (73–189)	0.008*
Adjusted penumbra volume, mL†	106 (66–143)	109 (73–189)	0.11
Mismatch volume, mL	79 (49–101)	91 (57–158)	0.02*
Adjusted mismatch volume, mL†	86 (54–110)	91 (57–158)	0.17
Mismatch ratio	11.3 (4.2–36.2)	9.5 (3.9–34.2)	0.69

Values are expressed as median (IQR) or n (%). Data are for the entire population unless otherwise specified in square parentheses. ASPECTS indicates Alberta Stroke Program Early CT Score; CTA, computed tomographic angiography; ED, emergency department; ICA, internal carotid artery; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; and NIHSS, National Institutes of Health Stroke Scale.

*Significant results ($P<0.05$).

†Adjusted values in women were calculated by taking into account the smaller intracranial volume by 9.8% in women compared with men.

men, median (IQR) 7 mL (1.2–23) versus 11.2 mL (0.8–34.7), $P=0.16$. Women had significantly lower penumbra volumes (97 mL [60–130] versus 109 mL [73–189], $P=0.008$) and mismatch volumes (79 mL [49–101] versus 91 mL [57–158], $P=0.02$) than men. In the analysis accounting for intracranial volume difference between women and men, the significant differences in penumbra (106 mL [66–143] versus 109 mL [73–189], $P=0.11$) and mismatch volumes (86 mL [54–110] versus 91 mL [57–158], $P=0.17$) were no longer maintained (Table 1)

There was no significant difference in prehospital and intrahospital times and successful reperfusion rates between women and men (Table 1 and 2).

Functional and Safety Outcomes

Functional outcome data at 90 days were available for 583 out of 608 (96%) patients. The proportions were similar between sexes: median mRS (IQR): 3 (1–5) in women versus 3 (1-4) in men, $P=0.22$. Functional

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Table 2. Treatment Characteristics and Outcomes Stratified by Sex

	Women (n=307)	Men (n=301)	*P* value
Final TICI 2b–3	253/306 (82.7)	240/301 (79.7)	0.35
Final TICI 2c–3	106 (34.5)	87 (28.9)	0.14
sICH	37/278 (13.3)	33/285 (11.6)	0.53
90-d mRS (median, IQR)	3 (1–5), n=292	3 (1–4), n=291	0.22
90-d mRS=0–1	80/292 (27.4)	91/291 (31.3)	0.30
90-d mRS=0–2	127/292 (43.5)	135/291 (46.4)	0.48
90-d mortality	54/292 (18.5)	48/291 (16.5)	0.52

IQR indicates interquartile range; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage; and TICI, Thrombolysis in Cerebral Infarction.

independence at 90 days (mRS, 0–2) was achieved in 127 out of 292 (43.5%) of women versus 13 out of 291 (46.4%) of men, *P*=0.48 (Table 2).

Symptomatic ICH and mortality data were available for 563 out of 608 (93%) and 583 out of 608 (96%) patients, respectively. There was no significant difference in sICH (37/278 [13.3%] versus 33/285 [11.6%], *P*=0.53) or mortality (54/292 [18.5%] versus 48/291 [16.5%], *P*=0.52) between women and men.

Effect Modification of Sex on Functional and Safety Outcomes

Interaction Between Sex and Age

In the entire population, increasing age was independently associated with lower chances of 90-day functional independence and survival but not with sICH after adjusting for sex, NIHSS score, ASPECTS, time from onset to puncture, occlusion location, intravenous thrombolysis administration, and successful reperfusion. Similar results were maintained with the ordinal analysis of mRS score (Table S2).

We assessed for any effect modification of sex on the relationship between age and functional independence by including an interaction term (age×sex) in the logistic and ordinal regression models. This did not show a differential effect between women and men ($P_{interaction}$=0.17 and $P_{interaction}$=0.11 for the logistic and ordinal regression, respectively.). However, there was a significant interaction between sex and age for 90-day mortality ($P_{interaction}$=0.003) and sICH ($P_{interaction}$=0.017) as men had an increased likelihood of sICH and death with advancing age compared with women (Figure 2 and Table 3). This effect modification was marked in patients older than 80 years as shown by the intersection points of the predicted probabilities curves of both sexes in Figure 2B and 2C. For instance, in patients aged 80 years or older, men had higher odds of mortality (adjusted odds ratio, 2.69 [95% CI, 1.14–6.35], *P*=0.02), whereas women younger than 80 years were more at risk of death than men (adjusted odds ratio, 1.81 [95% CI, 1.02–3.23], *P*=0.04). Although not significant, sICH was more frequent in women younger than 80 years (adjusted odds ratio, 1.60 [95% CI, 0.82–3.13], *P*=0.16), and more frequent in men aged 80 years or older (adjusted odds ratio, 2.30 [95% CI, 0.75–6.99], *P*=0.14) (Figure 2)

Interaction Between Sex and Successful Reperfusion

Successful reperfusion was independently associated with a higher likelihood of 90-day functional independence and survival in the entire population after adjustment for age, sex, NIHSS score, ASPECTS, time from onset to puncture, occlusion location, and intravenous thrombolysis administration (Table S2). However, no association was found between successful reperfusion and sICH.

There was no interaction between sex and successful reperfusion on 90 days functional independence, ordinal mRS, mortality or sICH ($P_{interaction}$=0.88, $P_{interaction}$=0.45, $P_{interaction}$=0.65, $P_{interaction}$=0.81) (Table 3).

Sensitivity Analysis

We repeated the above analyses using center as a cluster variable in the models, and we found similar results.

DISCUSSION

In this multicenter individual-patient level analysis that included 608 patients with acute stroke presenting in the late time window and treated with EVT, we did not find significant sex-related disparities in functional outcome. However, there was a sex-by-age interaction as men had higher likelihood of mortality and sICH with advancing age compared with women.

The literature that addressed the same question in late presenters is limited.[11] In a substudy of the DEFUSE-3 trial on 182 patients presenting 6 to 16 hours from last known well, there was no interaction between sex and EVT, but the authors found that women in the EVT arm had worse 90-day mRS than men (median mRS [IQR], 3.5 [2–5] versus 2 [1–4], *P*=0.046). However, the analysis of the control arm showed no sex difference in functional outcomes. Possible explanations for the lack of difference between sexes in functional and angiographic outcomes in our study include the use of less strict imaging criteria before EVT, and the overall reasonable balance in the available baseline characteristics, such as NIHSS score, ASPECTS, collateral grade, and time to puncture; all are known to be associated with functional outcome.[24]

The effect of sex on outcomes in patients treated with EVT in the early time window was assessed in several studies, and the results varied. Some studies suggested worse outcomes in women,[2,5,9] whereas other studies found neutral results, and others described better outcomes in women.[1,3,8,25] The largest study is the post hoc

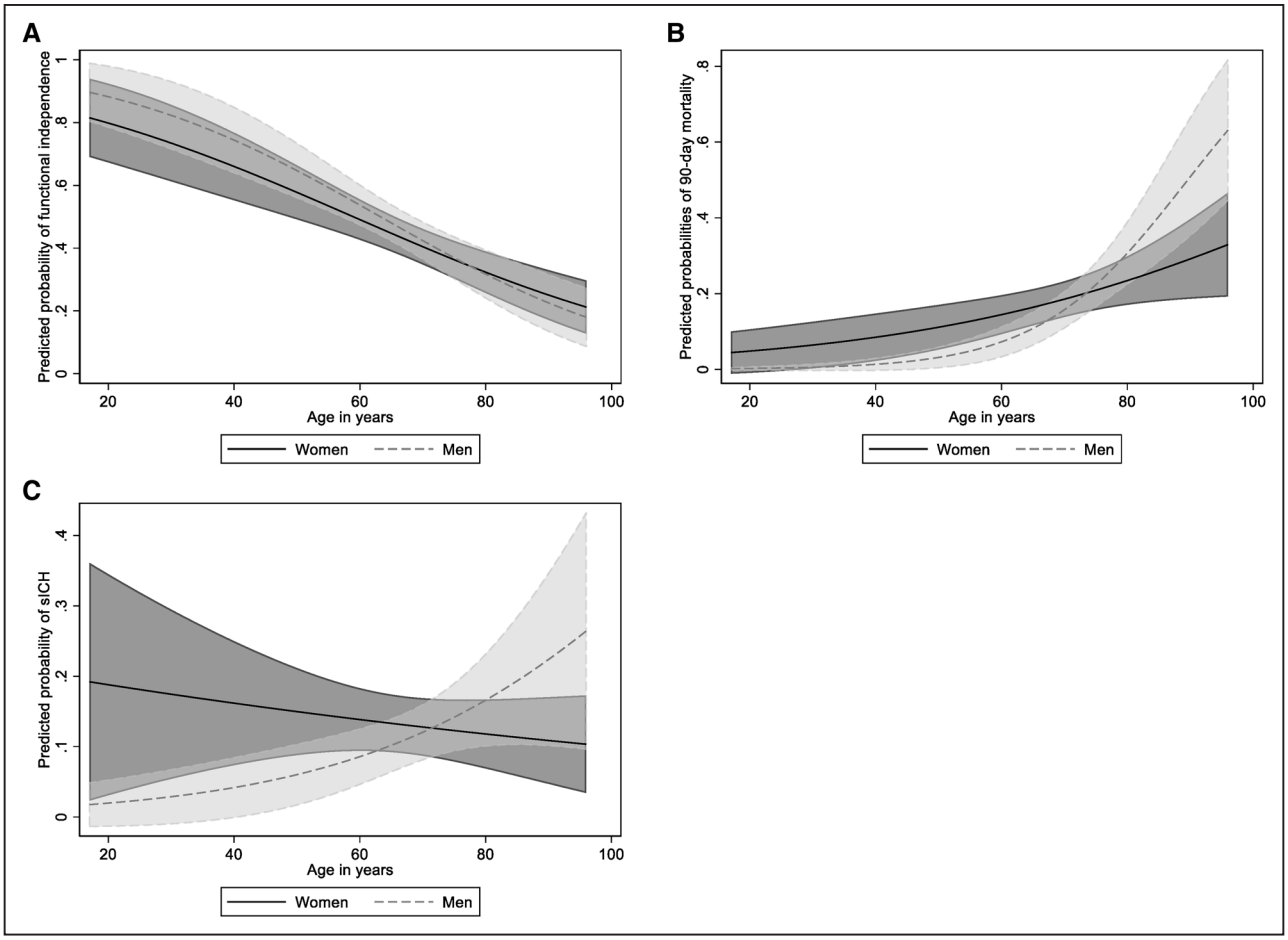

Figure 2. Effect of age on outcomes in women and men.
Likelihood of 90-d functional independence (**A**), 90-d mortality (**B**), and symptomatic intracranial hemorrhage (**C**) were calculated using multivariable logistic regressions adjusting for age, National Institutes of Health Stroke Scale score, Alberta Stroke Program Early CT Score, time from onset to puncture, occlusion location, intravenous thrombolysis administration, successful reperfusion, and AGE x SEX interaction term. sICH indicates symptomatic intracranial hemorrhage.

analysis of the HERMES collaboration, which included 1762 patients and found a similar 90-day functional independence in both sexes (39%), which is in line with our results.[1] Moreover, a Japanese prospective registry study of 2399 patients with stroke with large vessel occlusion showed that women were less likely to receive EVT (47.9% versus 57.7%, $P<0.001$) and to achieve functional independence at 90 days (27.3% versus 44.2%, $P<0.001$).[9]

Overall, the baseline characteristics in our study were balanced between sexes except for age. Collateral flow grade was not different between sexes which is consistent with a previous report.[26] We found that women had smaller baseline penumbra and mismatch volumes compared with men in the subset of patients with available perfusion volumes. However, this difference did not persist after adjustment for the smaller intracranial volume in women. This differs from the aforementioned substudy of DEFUSE-3 which found lower penumbra volumes in women before and after adjustment for intracranial volume. In addition, such difference, if true, could confirm the numerous animal studies,[27,28] suggesting a possible neuroprotective role for female steroid hormones after ischemic stroke in mice. This has not been yet shown in human studies.[29]

Previous reports found no interaction between sex and EVT outcomes.[1,10] A study by Sheth et al[8] of 389 patients treated with EVT in the early time window showed no differential effect of age on functional outcome (mRS score of 0–2) in women versus men. We expand on these results by showing similar outcomes in the late time window. We also show that men had higher likelihood of 90-day mortality and sICH with advancing age compared with women. Similar observations were reported in the Northwestern German Stroke Registry as women exhibited lower hospital mortality compared with men.[25] Numerous factors could account for the variability in reporting any interaction between sex and EVT including biological, genetic, and socio-economic.[1,30] Future studies are warranted to identify sex-specific differences in elderly patients receiving EVT.

Our study has several limitations. First, some baseline characteristics were not captured in this study, such as

Table 3. Interaction Analyses of Sex on the Relationship of Age and Successful Reperfusion With Outcomes

Outcome	aOR in women (95% CI)	aOR in men (95% CI)	*P* interaction
Functional independence (mRS 0–2)			
Age, per 10 y	0.70 (0.57–0.84)	0.52 (0.41–0.66)	0.17
Successful reperfusion	3.95 (1.63–9.53)	3.87 (1.76–8.47)	0.88
Shift to better outcome (ordinal regression)*			
Age, per 10 y	0.71 (0.62–0.83)	0.56 (0.47–0.67)	0.11
Successful reperfusion	3.30 (1.85–5.89)	2.59 (1.48–4.50)	0.45
90-d mortality			
Age, per 10 y	1.28 (1.01–1.63)	2.52 (1.75–3.64)	0.003†
Successful reperfusion	0.45 (0.21–0.99)	0.49 (0.21–1.13)	0.65
sICH			
Age, per 10 y	0.91 (0.71–1.17)	1.67 (1.16–2.41)	0.017†
Successful reperfusion	1.48 (0.47–4.70)	1.28 (0.45–3.64)	0.81

Adjusted odds ratios were calculated from multivariable logistic regression models adjusting for age, NIHSS score, ASPECTS, time from onset to puncture, occlusion location, intravenous thrombolysis administration, and successful reperfusion. Successful reperfusion was defined as final Thrombolysis in Cerebral Infarction 2b–3. ASPECTS indicates Alberta Stroke Program Early CT Score; aOR, adjusted odds ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and sICH, symptomatic intracranial hemorrhage.

*The effect estimates are adjusted common odds ratios.

†Significant results.

history of prestroke disability, comorbidities (eg, hypertension, diabetes, atrial fibrillation), use of antithrombotic drugs, or the cohabitation status. Therefore, we were unable to adjust for them in the analyses. Moreover, our results may have not been significant if these confounders were available, Second, we did not assess the effect of sex on long-term disability, as mRS score does not capture poststroke quality of life. In a study by Sheth et al,[8] females had a relative advantage over males in optimal life years after EVT, whereas the 90-day mRS score was not different between sexes.[8] Third, the retrospective and nonrandomized design of some of the included studies may have introduced selection bias. However, our sample formed of patients from multinational registries reflects routine clinical practice and real-world data better than trials.

CONCLUSIONS

In this multicenter pooled data of patients treated with EVT in the late time window, we found no influence of sex on functional outcomes. We observed a higher likelihood of symptomatic intracranial hemorrhages and death with increasing age among men compared with women.

ARTICLE INFORMATION

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Supplemental Material

STROBE Checklist
Tables S1–S2

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