JAMA Neurology | Original Investigation

Endovascular Thrombectomy Treatment Effect in Direct vs Transferred Patients With Large Ischemic Strokes

A Prespecified Analysis of the SELECT2 Trial

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IMPORTANCE Patients with large ischemic core stroke have poor clinical outcomes and are frequently not considered for interfacility transfer for endovascular thrombectomy (EVT).

OBJECTIVE To assess EVT treatment effects in transferred vs directly presenting patients and to evaluate the association between transfer times and neuroimaging changes with EVT clinical outcomes.

DESIGN, SETTING, AND PARTICIPANTS This prespecified secondary analysis of the SELECT2 trial, which evaluated EVT vs medical management (MM) in patients with large ischemic stroke, evaluated adults aged 18 to 85 years with acute ischemic stroke due to occlusion of the internal carotid or middle cerebral artery (M1 segment) as well as an Alberta Stroke Program Early CT Score (ASPECTS) of 3 to 5, core of 50 mL or greater on imaging, or both. Patients were enrolled between October 2019 and September 2022 from 31 EVT-capable centers in the US, Canada, Europe, Australia, and New Zealand. Data were analyzed from August 2023 to January 2024.

INTERVENTIONS EVT vs MM.

MAIN OUTCOMES AND MEASURES Functional outcome, defined as modified Rankin Scale (mRS) score at 90 days with blinded adjudication.

RESULTS A total of 958 patients were screened and 606 patients were excluded. Of 352 enrolled patients, 145 (41.2%) were female, and the median (IQR) age was 66.5 (58-75) years. A total of 211 patients (59.9%) were transfers, while 141 (40.1%) presented directly. The median (IQR) transfer time was 178 (136-230) minutes. The median (IQR) ASPECTS decreased from the referring hospital (5 [4-7]) to an EVT-capable center (4 [3-5]). Thrombectomy treatment effect was observed in both directly presenting patients (adjusted generalized odds ratio [OR], 2.01; 95% CI, 1.42-2.86) and transferred patients (adjusted generalized OR, 1.50; 95% CI, 1.11-2.03) without heterogeneity (*P* for interaction = .14). Treatment effect point estimates favored EVT among 82 transferred patients with a referral hospital ASPECTS of 5 or less (44 received EVT; adjusted generalized OR, 1.52; 95% CI, 0.89-2.58). ASPECTS loss was associated with numerically worse EVT outcomes (adjusted generalized OR per 1-ASPECTS point loss, 0.89; 95% CI, 0.77-1.02). EVT treatment effect estimates were lower in patients with transfer times of 3 hours or more (adjusted generalized OR, 1.15; 95% CI, 0.73-1.80).

CONCLUSIONS AND RELEVANCE Both directly presenting and transferred patients with large ischemic stroke in the SELECT2 trial benefited from EVT, including those with low ASPECTS at referring hospitals. However, the association of EVT with better functional outcomes was numerically better in patients presenting directly to EVT-capable centers. Prolonged transfer times and evolution of ischemic change were associated with worse EVT outcomes. These findings emphasize the need for rapid identification of patients suitable for transfer and expedited transport.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03876457

JAMA Neurol. doi:10.1001/jamaneurol.2024.0206
Published online February 8, 2024.

Supplemental content

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Group Information: The SELECT2 Collaborators appear at the end of the article, and members of the SELECT2 Investigators appear in Supplement 3.

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Four recent randomized clinical trials and a meta-analysis demonstrated better clinical outcomes with endovascular thrombectomy (EVT) in patients with a large ischemic stroke on noncontrast computed tomography (CT) or advanced diffusion-perfusion imaging.[1-5] Two additional trials provided evidence in support of EVT in patients with extensive ischemic changes assessed using the Alberta Stroke Program Early CT Score (ASPECTS) on CT or magnetic resonance (MR) imaging.[6,7] Implementation of these findings may have significant implications for stroke care infrastructure and systems of care. A significant proportion of patients with stroke present to non-EVT-capable centers,[8] which provide initial treatment and then coordinate transfers to EVT-capable centers after evaluating eligibility and the need for a higher level of care. While large ischemic core trials enrolled both directly presenting patients as well as those who were transferred to EVT-capable centers, important questions remain. Is the treatment effect maintained in patients with large ischemic cores presenting initially to an outside hospital? Does the effect of transit time and radiological deterioration during transfer alter the treatment effect? Additionally, transfer futility is often determined at the point of decision-making for transfer rather than at the arrival point at the destination center. If ineligibility for EVT or poor outcome regardless of treatment could be reliably assessed at the primary hospital, informed transfer decisions could be made, especially for those with already low ASPECTS (5 or less) seen on imaging at non-EVT-capable centers.

We aimed to provide a comprehensive evaluation of the association of transfer status with EVT outcomes and treatment effects in patients with large ischemic stroke in the Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT2) trial. Furthermore, we evaluated the association of interfacility transfer time, ASPECTS decay, and collateral flow with EVT outcomes and treatment effect in patients with large ischemic core. Additionally, we assessed EVT treatment effects in patients who presented with ASPECTS of 3 to 5 at referring hospitals.

Key Points

Question Did clinical outcomes and endovascular thrombectomy (EVT) treatment effect differ between directly presenting and transferred patients with large ischemic core stroke in the SELECT2 trial?

Findings In this prespecified analysis of the SELECT2 trial including 352 patients, both directly presenting and transferred patients had better clinical outcomes with EVT compared with medical management, without a significant effect modification. Treatment effect estimates favored thrombectomy in patients with a low Alberta Stroke Program Early CT Score (ASPECTS) at referring hospitals and in those who demonstrated a loss of 2 or more points in ASPECTS during transfer.

Meaning Thrombectomy was beneficial in transferred patients with large ischemic core stroke without heterogeneity in treatment effect vs those who presented directly and appeared to confer better outcomes even in those with low ASPECTS at outside hospitals or worsening ASPECTS during interfacility transfer.

Methods

Study Population

Data are from the SELECT2 trial, an international, multicenter, randomized clinical trial with blinded outcome assessment, conducted at 31 centers across North America, Europe, Australia, and New Zealand. The trial protocol and statistical analysis plan can be found in Supplement 1. Eligibility criteria included adults aged 18 to 85 years with an ischemic stroke due to occlusion of the internal carotid or first part of the middle cerebral artery and a large ischemic core on non-contrast CT (ASPECTS of 3 to 5) and/or CT perfusion (tissue with relative cerebral blood flow less than 30%) volume of 50 mL or greater or MR diffusion-perfusion (tissue with apparent diffusion coefficient less than 620×10^{-6} mm/s^2) volume of 50 mL or greater, presenting within 24 hours of last known well. Further details regarding inclusion and exclusion criteria as well as detailed trial protocol and primary results are published elsewhere.[2,9] All participating centers obtained approval from local institutional review boards or equivalent ethics committees prior to enrolling patients for the trial. All patients or their surrogates provided written informed consent. Patients were randomized to receive EVT or best medical care using a web-based centralized system with covariate adaptive randomization. Choice of EVT devices and approaches were at the discretion of the neurointerventional team. All patients received best medical management (MM), including intravenous thrombolytics if eligible based on national guidelines. For this analysis, patients were characterized based on whether they presented directly to an EVT-capable center or transferred from outside hospitals. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Imaging Evaluation

All patients received a uniform imaging protocol prior to enrollment, including a noncontrast CT, CT/MR angiography, and CT perfusion/MR diffusion-perfusion imaging. Ischemic core volume was defined as the larger of the CT hypodensity volume (manually outlined), CT perfusion volume (relative cerebral blood flow less than 30%), or MR diffusion-perfusion volume (tissue with apparent diffusion coefficient less than 620×10^{-6} mm/s^2) at baseline. Lesion volume was calculated by manual planimetry on follow-up imaging (diffusion-weighted imaging preferred; CT was used if diffusion-weighted imaging was not available) acquired within 24 hours to 7 days of randomization. Infarct growth was determined as the volumetric difference between baseline ischemic core and follow-up lesion volume. Collateral status was evaluated by a central core lab using the Tan collateral score,[10] with good collaterals defined as a collateral score of 2 to 3.

For transferred patients, transfer time was defined as the time between 2 imaging acquisitions, if available. For cases where imaging acquisition times were not available, the difference between arrival time at the EVT-capable center and arrival time at the outside hospital was used to approximate these

times. If outside noncontrast CT images were available, ASPECTS was scored by the imaging core lab. Otherwise, site-reported ASPECTS were considered for analyses. ASPECTS loss was defined as the difference in ASPECTS from the referring hospital to EVT hospital. A significant ASPECTS decay was defined as a loss of 2 or more points between outside hospital and EVT hospital. The rate of ASPECTS decay was defined using ASPECTS point loss divided by transfer time.

Outcomes

The primary outcome was shift in modified Rankin Scale (mRS) score at 90-day follow-up. Secondary clinical outcomes included functional independence (mRS score of 0 to 2), independent ambulation (mRS score of 0 to 3), and severe disability or death (mRS score of 5 to 6) at 90-day follow-up. Safety outcomes included mortality, parenchymal and symptomatic hemorrhage, and procedural complications. The proportion of patients receiving hemicraniectomy procedure, follow-up infarct volume, and infarct growth were also evaluated.

Statistical Analysis

Categorical variables were described using counts and proportions and compared using χ^2 or Fisher exact tests, as appropriate. Continuous variables were described using medians and IQRs and compared using Wilcoxon rank sum tests. The thrombectomy treatment effects for the primary and secondary outcomes were evaluated using probabilistic index model (PIM) and modified Poisson regression models with robust SEs, respectively. All models were adjusted for age, National Institutes of Health Stroke Scale score at presentation at the trial hospital, time from last known well to randomization, ASPECTS, and estimated ischemic core volume obtained at the EVT hospital. Adjusted PIM models differ from parametric ordinal logistic regression models in that PIMs estimate the odds of a random patient from the EVT group having a better mRS outcome than a random patient from the MM group, given the differences in covariates between these 2 patients.[11,12] The treatment effect estimates were reported using adjusted generalized odds ratios (ORs) and 95% CIs, with ties split equally between groups for ordinal outcomes and adjusted relative risk (aRR) with 95% CIs for dichotomous variables. A multiplicative interaction term between the characteristic of interest and received treatment was used to determine the heterogeneity of EVT treatment effect. Similar models were used to determine the associations of transfer time and ASPECTS decay in transfer with the outcomes. EVT treatment effect was also evaluated within the trial population with an ASPECTS of 5 or less at the referring hospital and those with significant ASPECTS decay (2 or more points) during the transfer.

All analyses were conducted based on the treatment received by the individual (as-treated analysis) regardless of the randomization assignment. Stata version 17 (StataCorp) and R version 4.2.2 (The R Foundation) were used to perform all statistical analyses. All hypotheses were tested using 2-sided statistical tests, and a *P* value less than .05 was considered significant. All analyses were considered hypothesis-generating. Missing data were not imputed.

Results

A total of 958 patients were screened and 606 patients were excluded from participation and/or did not provide consent. Of 352 enrolled patients, 145 (41.2%) were female, and the median (IQR) age was 66.5 (58-75) years. A total of 211 patients (59.9%) were transfers, of whom 108 (51.2%) received EVT, while 141 (40.1%) presented directly, of whom 72 (51.1%) received EVT (**Figure 1**). A comparison of the baseline characteristics based on transfer status is provided in eTable 1 in Supplement 2. The 2 populations were similar except that patients transferred were younger (median [IQR] age, 65 [58-74] years vs 69 [60-77] years) and received intravenous thrombolytics more frequently (51 of 210 [24.3%] vs 16 of 141 [11.3%]). Compared with directly presenting patients, transferred patients had longer median (IQR) times from last known well to arrival at an EVT-capable center (390 [118-703] minutes vs 518 [318-912] minutes) and randomization (516 [226-765] minutes vs 635 [364-979] minutes) but had shorter median (IQR) times from arrival to acquisition of CT perfusion/MR diffusion-perfusion (29 [19-40] minutes vs 24 [13-35] minutes) and arterial puncture (118 [92-146] minutes vs 99 [66-130] minutes) if they received EVT.

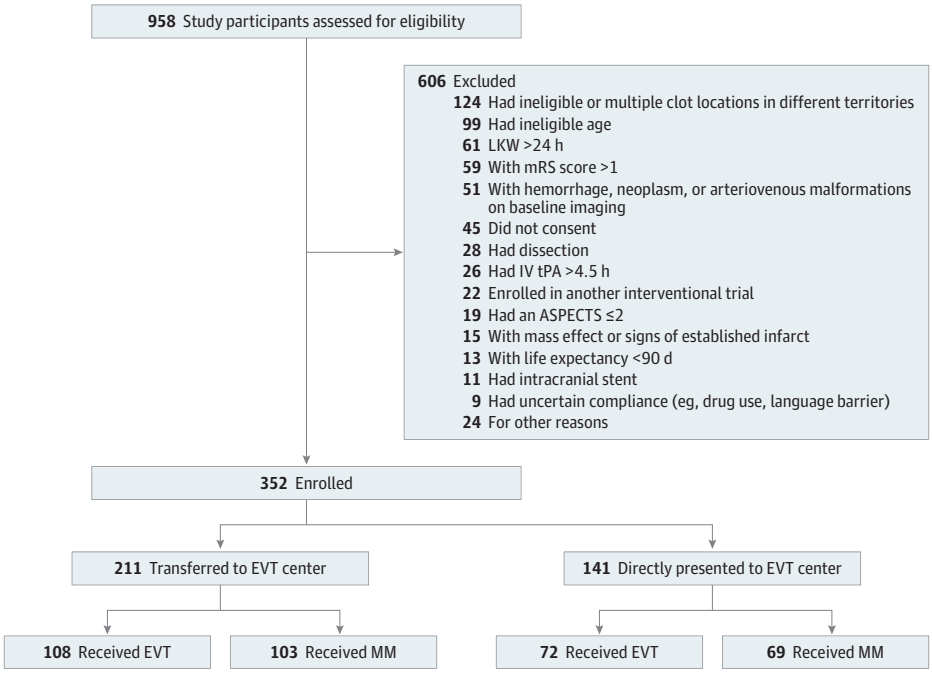
ASPECTS at both the referring hospital and EVT-capable center were available for 153 of 211 transferred patients (72.5%). The median (IQR) ASPECTS at the referring hospital (EVT, 5 [4-7]; MM, 5.5 [4-7]) and at an EVT-capable hospital (EVT, 4 [3-5]; MM, 4 [4-5]) were similar between the 2 treatment arms, as were the median (IQR) National Institutes of Health Stroke Scale score at the referring hospital (EVT, 18 [14-22]; MM, 17 [14-21]) and at an EVT-capable hospital (EVT, 18.5 [15-23]; MM, 19 [15-23]) (**Table**).

Functional and Safety Outcomes in Directly Presenting vs Transferred Patients

There was a shift toward improved mRS distribution with EVT for both directly presenting patients (median [IQR]: EVT, 4 [3-6]; MM, 5 [4-6]; adjusted generalized OR, 2.01; 95% CI, 1.42-2.86) and transferred patients (median [IQR]: EVT, 4 [3-6]; MM, 5 [4-6]; adjusted generalized OR, 1.50; 95% CI, 1.11-2.03). Treatment effect estimates also favored EVT for secondary functional outcomes (eTable 5 in Supplement 2). Sensitivity analyses after including intravenous thrombolysis as an additional covariate for adjustment demonstrated similar results (eTable 6 in Supplement 2). No evidence of heterogeneity between transfer status and treatment effect was observed across functional outcomes (eTable 5 in Supplement 2).

Symptomatic hemorrhage (directly presenting, 1 [0 receiving EVT and 1 receiving MM]; transfers, 2 [1 receiving EVT and 1 receiving MM]) and parenchymal hemorrhage (directly presenting, 4 [3 receiving EVT and 1 receiving MM]; transfers, 4 [2 receiving EVT and 2 receiving MM]) were observed infrequently (eTable 3 in Supplement 2). Treatment effect estimates largely favored EVT in key clinical subgroups (age, stroke severity, and time from last known well to randomization) and imaging subgroups (ischemic core volume and ASPECTS strata), without heterogeneity in both directly presenting and transferred patients (**Figure 2**; eFigures 1 to 6 in Supplement 2).

Figure 1. Flow Diagram of the Study Participants



ASPECTS indicates Alberta Stroke Program Early CT Score; EVT, endovascular thrombectomy; LKW, last known well; MM, medical management; mRS, modified Rankin Scale; tPA, tissue plasminogen activator.

Table. Key Parameters at Outside and Endovascular Thrombectomy (EVT)–Capable Centers in Transferred Patients, Overall and Stratified by Type of Treatment Received

Parameter	Median (IQR)			*P* value
	Total (n = 211)	MM only (n = 103)	EVT plus MM (n = 108)	
Transfer time, min	178 (136-230)	180 (140-230)	176 (128-231)	.95
CT ASPECTS at outside hospital	5 (4-7)	6 (4-7)	5 (4-7)	.82
CT ASPECTS at EVT-capable hospital	4 (3-5)	4 (4-5)	4 (3-5)	.37
ASPECTS loss during transfer	1 (0-3)	1 (0-2)	1 (0-3)	.50
Rate of ASPECTS decay, points per h	0.3 (0.0-0.9)	0.3 (0.0-0.8)	0.4 (0.0-0.9)	.95
NIHSS score at outside hospital	18 (14-22)	17 (14-21)	18 (14-22)	.56
NIHSS at EVT-capable hospital	19 (15-23)	19 (15-22)	19 (15-23)	.72
Time from arrival to arterial puncture, min	109 (75-138)	NA	109 (75-138)	NA
Time from arterial puncture to reperfusion/ end of the procedure, min	38 (25-61)	NA	38 (25-61)	NA

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; MM, medical management; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale.

Association of Collateral Status With Thrombectomy Outcome Treatment Effect in Transferred Patients

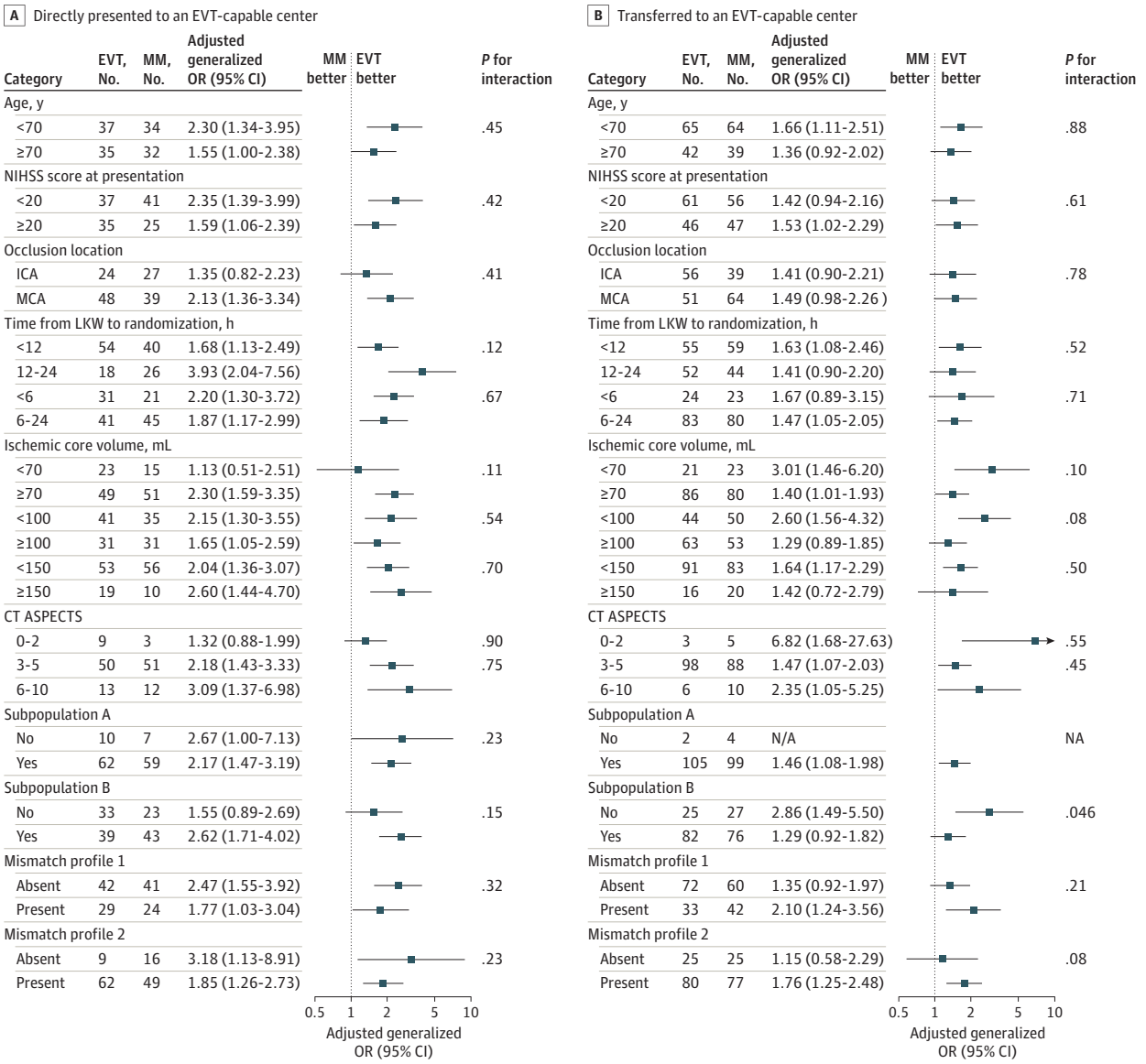
Of 211 transfers, 90 patients (49 receiving EVT and 41 receiving MM) demonstrated poor collaterals (collateral score of 0 to 1) on vascular imaging obtained at EVT trial centers, whereas 121 (59 receiving EVT and 62 receiving MM) demonstrated good collaterals (collateral score of 2 to 3). Baseline characteristics, including stroke severity and imaging findings, were otherwise similar between the 2 treatment arms with good and poor collateral scores (eTable 7 in Supplement 2).

EVT was associated with better functional outcomes in transferred patients with good collateral scores (adjusted generalized OR, 1.94; 95% CI, 1.29-2.92), higher independent ambulation (EVT, 29 of 58 [50%]; MM, 17 of 62 [27%]; aRR, 1.80; 95% CI, 1.19-2.72), and reduced severe disability or death (EVT, 20 of 58 [34%]; MM, 33 of 62 [53%]; aRR, 0.63; 95% CI, 0.43-0.92) (eTable 8 in Supplement 2). However, among transferred patients with poor collateral scores, no association between treatment arm and functional outcomes distribution was observed (adjusted generalized OR, 0.94; 95% CI, 0.62-1.44; *P* for interaction = .047). Independent ambulation was numerically higher with EVT (EVT, 14 of 49 [29%]; MM, 4 of 41 [10%]; aRR, 2.60; 95% CI, 0.99-6.85), while no difference in complete dependence or death was observed (EVT, 29 of 49 [59%]; MM, 24 of 41 [59%]; aRR, 1.23; 95% CI, 0.98-1.69).

Thrombectomy Treatment Effect in Transferred Patients Based on Referring Hospital ASPECTS

Among transfers, 82 patients (44 receiving EVT and 38 receiving MM) demonstrated an ASPECTS of 5 or less on initial noncontrast CT at the referring hospital (eTable 9 in Supplement 2). Points estimates favored functional outcomes in

Figure 2. Forest Plot of the Association of Endovascular Thrombectomy (EVT) With Distribution of 90-Day Modified Rankin Scale Scores in Patients Directly Presenting and Transferring to an EVT-Capable Center



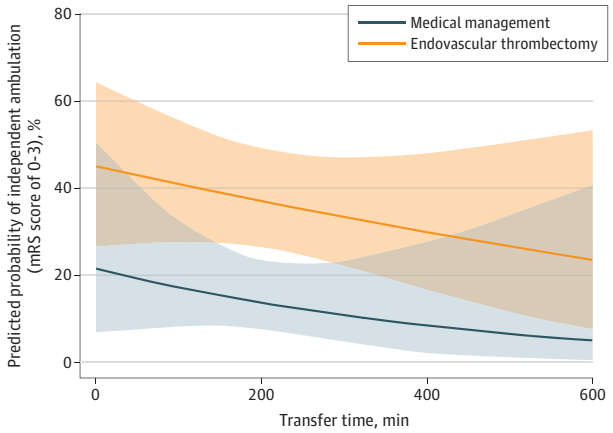
ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; ICA, internal carotid artery; LKW, last known well; MCA, middle cerebral artery; MM, medical management; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

patients receiving EVT (median [IQR] ASPECTS: EVT, 4 [3-6]; MM, 4 [3-5.5]; adjusted generalized OR, 1.52; 95% CI, 0.89-2.58) and independent ambulation (EVT, 21 of 44 [48%]; MM, 10 of 38 [26%]; aRR, 1.52; 95% CI, 0.93-2.49). Additionally, EVT was associated with better functional independence (EVT, 10 of 44 [23%]; MM, 2 of 38 [5%]; aRR, 4.28; 95% CI, 1.09-16.81) (eTable 10 in Supplement 2). A sensitivity analysis excluding 3 patients with outside ASPECTS less than 3 demonstrated similar results (eTable 11 in Supplement 2). There was no interaction between referral hospital ASPECTS (ASPECTS greater than 5 vs ASPECTS of 5 or less) and EVT treatment benefit observed across all outcomes (eFigure 7 and eTable 10 in Supplement 2).

Transfer Time Association With EVT Outcomes and Treatment Effect

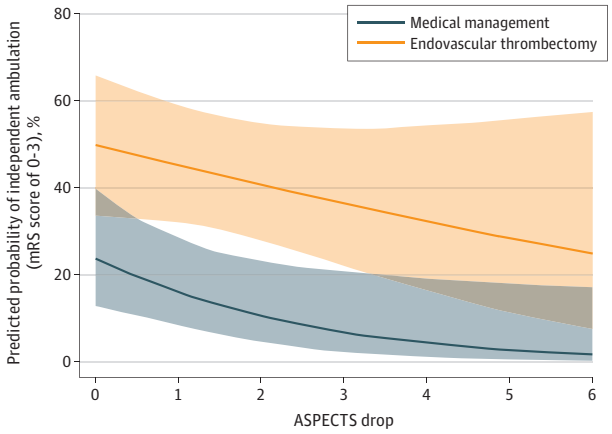
The median (IQR) transfer time was 176 (128-231) minutes for patients who were randomized to EVT and 180 (140-230) minutes for those who received MM. Patients with transfer time less than 3 hours demonstrated better functional outcomes (adjusted generalized OR, 1.92; 95% CI, 1.21-3.04), functional independence (EVT, 12 of 49 [25%]; MM, 5 of 47 [11%]; aRR, 2.55; 95% CI, 1.00-6.49) and independent ambulation (EVT, 22 of 49 [45%]; MM, 10 of 47 [21%]; aRR, 2.47; 95% CI, 1.45-4.22) (eTable 14 in Supplement 2). In those with transfer time of 3 hours or more, treatment effect estimates were reduced but still favored EVT for better functional outcomes (adjusted generalized OR, 1.15; 95% CI,

Figure 3. Predicted Marginal Probabilities of Independent Ambulation (Modified Rankin Scale [mRS] Score of 0 to 3) by Transfer Time in Those Receiving Endovascular Thrombectomy and Medical Management



As transfer time increased, the predicted probability of independent ambulation decreased in both arms, but treatment effects were largely preserved. Shaded areas indicate 95% CIs.

Figure 4. Predicted Marginal Probabilities of Independent Ambulation (Modified Rankin Scale [mRS] Score of 0 to 3) by Loss of Alberta Stroke Program Early CT Score (ASPECTS) Points During Transfers in Those Receiving Endovascular Thrombectomy and Medical Management



As ASPECTS loss increased, the predicted probability of independent ambulation decreased in arms, but treatment effects were largely preserved. Shaded areas indicate 95% CIs.

0.73-1.80) and independent ambulation (EVT, 16 of 45 [36%]; MM, 11 of 47 [23%]; aRR, 1.58; 95% CI, 0.89-2.80). There was no significant interaction between EVT treatment effect and transfer time strata (*P* for interaction = .19) (**Figure 3**).

ASPECTS Decay Association With EVT Outcomes and Treatment Effect

The median (IQR) ASPECTS loss between outside and EVT-capable center imaging was 1 (0-3) for the EVT arm and 1 (0-2) for the MM arm, with ASPECTS decay at a median (IQR) rate of 0.4 (0-0.9) points per hour and 0.3 (0-0.8) points per hour, respectively. ASPECTS loss was associated with numerically worse functional outcomes in patients receiving EVT (adjusted generalized OR per 1-ASPECTS point loss, 0.89; 95% CI, 0.77-1.02) but not in patients receiving MM (adjusted generalized OR per 1-ASPECTS point loss, 0.99; 95% CI, 0.86-1.13) (**Figure 4**). However, the interaction term was not significant (*P* for interaction = .45) (eTable 12 in Supplement 2).

Discussion

We found that among patients with large ischemic stroke at the time of evaluation, both directly presenting patients and patients transferred to EVT-capable centers benefited from thrombectomy. This benefit was consistent for improvement on mRS score, functional independence, and independent ambulation. Furthermore, treatment effect estimates favored EVT in transferred patients with ASPECTS of 5 or less prior to transfer on referring hospital images. Median ASPECTS loss was almost 1 point for every 3 hours of transfer time, and ASPECTS loss during interfacility transfer was associated with numerically worse outcomes in patients receiving EVT but not MM. Patients with transfer times less than 3 hours demonstrated better functional outcomes with EVT, whereas treatment effect estimates were lower but still favored EVT in those with longer transfer time.

Additionally, collateral scores appeared to modify EVT treatment effects in this population, since EVT resulted in improved functional outcomes in transferred patients with good collateral scores but there was no consistent association of EVT with better functional outcomes in transferred patients with poor collateral scores. Collateral status, as with perfusion imaging, only provides assessment of blood flow status at the time of imaging acquisition. We could not evaluate changes before and after transfer in this dataset. Other than transferred patients with poor collateral scores, all clinical and imaging subgroups favored EVT without heterogeneity between transferred and directly presenting patients.

We observed a trend toward potential effect modification of thrombectomy treatment in transferred patients by mismatch status, as patients with an absence of mismatch (defined as an adjusted generalized OR of 1.2 or greater or ischemic core volume of 10 mL or greater) demonstrated a reduction in EVT association with better clinical outcomes compared with those with a presence of mismatch. However, no such association was observed in patients presenting directly to EVT-capable centers. Similarly, when the definition of mismatch was analyzed as an adjusted generalized OR of 1.8 or greater or ischemic core volume of 15 mL or greater, the effect modification disappeared. Transfer status was not one of the covariates in the adaptive randomization algorithm used for the trial, and further evaluation from other large ischemic core trials and pooled patient-level meta-analyses may help explain the findings.

Prior analyses have demonstrated improved clinical outcomes with EVT in patients with large vessel occlusion stroke who presented initially to non–EVT-capable centers and then transferred for thrombectomy, both in the early and late time

window.[8,13] However, these cohorts included patients with limited ischemic changes prior to EVT. Furthermore, many patients were excluded due to deterioration on neuroimaging, suggesting infarct expansion and large ischemic stroke. In our current analyses, transferred patients had better functional outcomes with EVT vs MM, which was persistent in various ischemic injury strata based on volumetric core or ASPECTS without significant heterogeneity.

Treatment of patients with large vessel occlusion stroke who already demonstrate established large strokes is challenging for hospitals without EVT capability due to perceived poor outcomes. Furthermore, EVT-capable centers frequently dissuade transfers of such patients owing to concerns regarding EVT eligibility and potential further radiologic deterioration during interfacility transfers. The lack of advanced imaging capabilities at referring hospitals, which are recommended by current guidelines[14] for EVT in the late time window, also make transfer decisions challenging. Our results demonstrated that these patients may still benefit from EVT despite having large ischemic core strokes, as defined as an ASPECTS of 5 or less, on initial images at referring hospitals. Furthermore, the treatment effect estimates were largely similar for patients with high (6 to 10) and low (5 or less) ASPECTS at referral hospitals, without significant heterogeneity.

Potential radiological deterioration during transfer remains a valid concern regarding EVT outcomes for patients with large ischemic core stroke. In our study, worsening ASPECTS was associated with numerically worse clinical outcomes in patients receiving EVT. Our findings support the transfer and treatment consideration of patients with large ischemic core stroke presenting to non–EVT-capable centers as well as exploration of opportunities to further optimize clinical outcomes by reducing potential stroke evolution on neuroimaging during transfer through other therapeutic approaches, such as neuroprotection. On the other hand, a 2023 meta-analysis demonstrated that EVT improves outcomes even in patients with very low ASPECTS (0 to 2).[15] A randomized clinical trial has included patients with ASPECTS of 0 to 2 and their findings, if confirming beneficial effects of EVT in this population, may further support the notion of transferring patients even with very low ASPECTS or longer transfer times for consideration of thrombectomy procedures. These findings also raise important questions about stroke system of care design. Approximately 1 in 5 patients with stroke due to large vessel occlusion present with estimated large ischemic cores at initial evaluation,[16] suggesting that these expanded EVT eligibility criteria will substantially increase the number of procedures. On the other hand, futile transfers are also expected to rise because of patients demonstrating a very large stroke and fast progression[17] before they reach an EVT-capable center. All these factors are expected to significantly challenge the current stroke systems, and thus proactive measures should be considered to ensure an adequate workforce and necessary support as we gear toward incorporating EVT for large ischemic core strokes in our treatment protocols.

Patients with longer transfer times demonstrated decreased EVT treatment effect estimates for functional outcomes and independent ambulation. Optimizing transfer times may be another strategy to improve EVT outcomes and treatment effects in these patients but is a complex and challenging endeavor. A recent analysis from American Heart Association/American Stroke Association Get With The Guidelines registry suggested that median door-in-door-out times for patients with stroke were approximately 3 hours, and 3 of 4 patients with stroke exceeded the recommended time of less than 2 hours.[18] On the other hand, a significant proportion of the US population reside outside of a 30-minute drive-time distance to EVT-capable centers.[19] In our study, the median transfer time was approximately 3 hours, and more than 80% of patients with available transfer times took at least 2 hours for transfers.

While thrombectomy benefit was preserved in both directly presenting and transferred patients, the treatment effect estimates were lower for transferred patients. A portion of this decrease could be attributed to the time it takes to transfer patients to an EVT-capable center and potential ASPECTS decay that may occur during transfer. The expected transfer times and distances may provide ancillary information to estimate potential ASPECTS and eventual EVT eligibility by the time the transfer is completed. Combining all these prognostic markers (ASPECTS decay, transfer time, and collateral status) into a clinically relevant scoring system may potentially segregate individuals with very low likelihood of treatment benefit and/or reasonable clinical outcomes. However, we do not have sufficient data to derive and validate such a score at present. A thorough discussion with patients and/or their surrogates regarding the extent of ischemic changes on outside hospital imaging, potential for further worsening, expected outcomes, and individuals' wishes regarding the quality of life and advanced directives should further help individualize transfer and treatment decision-making in this unique population.

Limitations

This study has limitations. The SELECT2 trial was not primarily designed to evaluate the potential impact of transfer status on EVT treatment effect. As such, while the study was prespecified in concept, randomization and treatment assignments were not based on transfer status (transfer status was not accounted for in the covariate adaptive randomization scheme for the SELECT2 trial). Thus, analyses presented in this article are underpowered and exploratory in nature, and the results should be considered preliminary. A significant proportion of patients did not have available data regarding imaging findings at referring hospitals. Additional limitations to our analysis include unavailability of perfusion imaging findings at referring hospitals and a relatively low number of patients with outside ASPECTS less than 5. Furthermore, evaluation of potential effect modification through collateral status was limited by our inability to account for potential changes in collaterals during transfer. We also did not have information regarding how many patients with low ASPECTS at outside hospitals were not considered for transfer, nor how many transferred patients were rendered ineligible for participation in the trial due to very low ASPECTS at EVT hospitals.

Conclusions

In a randomized clinical trial of patients with large ischemic core stroke, both directly presenting and transferred patients benefited from EVT. However, the association of EVT with better functional outcomes was numerically better in patients presenting directly to EVT-capable centers. The treatment effect estimates favored EVT even in patients with low ASPECTS at the referring hospital. Prolonged transfer times and ASPECTS loss was associated with numerically worse functional outcomes after EVT, but the treatment effect was preserved. These findings may impact stroke systems of care infrastructure, highlighting the need for rapid identification of patients suitable for transfer and expedited transport and reperfusion on arrival.

ARTICLE INFORMATION

Accepted for Publication: January 11, 2024.

Published Online: February 8, 2024. doi:10.1001/jamaneurol.2024.0206

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Conflict of Interest Disclosures: Dr Sarraj reported grants from Stryker Neurovascular during the conduct of the study. Dr Hill reported grants from Medtronic and personal fees from Microvention outside the submitted work. Dr Hussain reported grants from Medtronic Core Lab as well as personal fees from Stryker Neurovascular, Rapid Medical, and Cerenovus outside the submitted work. Dr Abraham consulted for Stryker Neurovascular and Q'Apel outside the submitted work. Dr Ortega-Gutierrez reported grants from Stryker Neurovascular, National Institute of Neurological Disorders and Stroke, and MicroVention as well as personal fees from Medtronic and Stryker Neurovascular outside the submitted work. Dr Kasner reported grants from Stryker during the conduct of the study; grants from Bayer, Bristol Myers Squibb, Diamedica, and Genentech as well as personal fees from NovoNordisk, Artivion, and UpToDate outside the submitted work. Dr Herial

reported honorarium from Medtronic outside the submitted work. Dr Budzik reported grants from Stryker Neurovascular during the conduct of the study. Dr Arenillas reported grants from the Spanish Ministry of Science, Spanish Ministry of Science, European Commission, Castilla-Leon Department of Health, University Valladolid, and AstraZeneca as well as personal fees from AstraZeneca, Medtronic, Medtronic, Amgen, BMS-Pfizer, Daiichi Sankyo, and University Valladolid outside the submitted work. Dr Tsai reported personal fees from Medtronic, MicroVention, Cerenovus, Q'Apel, and Imperative Care outside the submitted work. Dr Manning reported personal fees from Medtronic, Stryker, and MicroVention outside the submitted work. Dr Cheung reported personal fees from Medtronic outside the submitted work. Dr Hanel reported grants from the National Institutes of Health, Interline Endowment, MicroVention, Stryker, and CNX; personal fees from Medtronic, Stryker, Cerenovous, MicroVention, Balt, Phenox, Rapid Medical, Q'Apel, MIVI Neuroscience, eLum, Three Rivers Medical, Shape Medical, and Corindus; and holds stock in InNeuroCo, Cerebrotech, eLum, Endostream, Three Rivers Medical, Scientia, RisT, BlinkTBI, Corindus, and NTI outside the submitted work. Dr Gibson serves on the clinical advisory board for iSchemaView outside the submitted work. Dr Sahlein reported grants from MicroVention; personal fees from Medtronic and Kaneka; and holds stock in Scientia, Vasorum, and Emboa outside the submitted work; and has a patent for TRAP pending. Dr Warach reported grants from the University Hospital Cleveland and The University of Texas Health Science Center at Houston during the conduct of the study as well as personal fees from Genentech outside the submitted work. Dr Arthur reported personal fees from Balt, Johnson and Johnson, Medtronic, Microvention, Penumbra, Perfuze, Scientia, Siemens, and Stryker and holds stock in Bendit, Cerebrotech, Magneto, and Vastrax outside the submitted work. Dr Sitton reported grants from Stryker during the conduct of the study. Dr Nguyen serves on the advisory board of Idorsia and Brainomix and is an Associate Editor of *Stroke* for the American Stroke Association outside the submitted work. Dr Fifi reported personal fees from University of Houston during the conduct of the study; personal fees from Cerenovus, MicroVention, Stryker, MIVI Neuroscience, and Medtronic; and holds stock in Imperative Care outside the submitted work. Dr Tjoumakaris reported personal fees from MicroVention outside the submitted work. Dr Mendes Pereira reported personal fees from Stryker outside the submitted work. Dr Sila reported grants from University Hospitals during the conduct of the study. Dr Bambakidis reported grants from Idorsia outside the submitted work. Dr Davis reported personal fees from Boehringer Ingelheim and Medtronic outside the submitted work. Dr Wechsler reported personal fees from Astellas Pharma, Athersys, Silk Road Medical, and Forest Devices outside the submitted work. Dr Albers reported personal fees from iSchemaView and Genentech outside the submitted work. Dr Hassan reported personal fees from Medtronic, MicroVention, Stryker, Penumbra, Cerenovus, Genentech, GE Healthcare, Scientia, Balt, Viz.ai, Insera Therapeutics, Proximie, NeuroVasc, NovaSignal, Vesalio, Rapid Medical, Imperative Care, Galaxy Therapeutics, Route 92, and Perfuze outside the submitted work. No other disclosures were reported.

Funding/Support: The SELECT2 trial was funded by Stryker Neurovascular through grants to University Hospitals Cleveland Medical Center and UT McGovern Medical School.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: Members of the SELECT2 Investigators appear in Supplement 3.

Data Sharing Statement: See Supplement 4.

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