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Endovascular Thrombectomy for Large Ischemic Stroke Across Ischemic Injury and Penumbra Profiles

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IMPORTANCE Whether endovascular thrombectomy (EVT) efficacy for patients with acute ischemic stroke and large cores varies depending on the extent of ischemic injury is uncertain.

OBJECTIVE To describe the relationship between imaging estimates of irreversibly injured brain (core) and at-risk regions (mismatch) and clinical outcomes and EVT treatment effect.

DESIGN, SETTING, AND PARTICIPANTS An exploratory analysis of the SELECT2 trial, which randomized 352 adults (18-85 years) with acute ischemic stroke due to occlusion of the internal carotid or middle cerebral artery (M1 segment) and large ischemic core to EVT vs medical management (MM), across 31 global centers between October 2019 and September 2022.

INTERVENTION EVT vs MM.

MAIN OUTCOMES AND MEASURES Primary outcome was functional outcome—90-day mRS score (0, no symptoms, to 6, death) assessed by adjusted generalized OR (aGenOR; values >1 represent more favorable outcomes). Benefit of EVT vs MM was assessed across levels of ischemic injury defined by noncontrast CT using ASPECTS score and by the volume of brain with severely reduced blood flow on CT perfusion or restricted diffusion on MRI.

RESULTS Among 352 patients randomized, 336 were analyzed (median age, 67 years; 139 [41.4%] female); of these, 168 (50%) were randomized to EVT, and 2 additional crossover MM patients received EVT. In an ordinal analysis of mRS at 90 days, EVT improved functional outcomes compared with MM within ASPECTS categories of 3 (aGenOR, 1.71 [95% CI, 1.04-2.81]), 4 (aGenOR, 2.01 [95% CI, 1.19-3.40]), and 5 (aGenOR, 1.85 [95% CI, 1.22-2.79]). Across strata for CT perfusion/MRI ischemic core volumes, aGenOR for EVT vs MM was 1.63 (95% CI, 1.23-2.16) for volumes ≥70 mL, 1.41 (95% CI, 0.99-2.02) for ≥100 mL, and 1.47 (95% CI, 0.84-2.56) for ≥150 mL. In the EVT group, outcomes worsened as ASPECTS decreased (aGenOR, 0.91 [95% CI, 0.82-1.00] per 1-point decrease) and as CT perfusion/MRI ischemic core volume increased (aGenOR, 0.92 [95% CI, 0.89-0.95] per 10-mL increase). No heterogeneity of EVT treatment effect was observed with or without mismatch, although few patients without mismatch were enrolled.

CONCLUSION AND RELEVANCE In this exploratory analysis of a randomized clinical trial of patients with extensive ischemic stroke, EVT improved clinical outcomes across a wide spectrum of infarct volumes, although enrollment of patients with minimal penumbra volume was low. In EVT-treated patients, clinical outcomes worsened as presenting ischemic injury estimates increased.

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Editorial
Supplemental content

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Endovascular thrombectomy (EVT) is proven to be safe and effective in patients with limited ischemic changes on baseline neuroimaging up to 24 hours after the patient was last known to be well.[1-3] Recently, 4 randomized clinical trials (RCTs) also established EVT superiority in patients with a large ischemic core, defined as ASPECTS (Alberta Stroke Program Early CT Score) of 3 to 5 and/or ischemic core volume of 50 mL or greater.[4-7] Two other trials, presented in abstract form, provided support for benefit of EVT in this population.[8,9]

Imaging eligibility criteria and qualifying modalities differed among trials, with large ischemic core defined variably using noncontrast computed tomography (CT), CT perfusion imaging, or diffusion magnetic resonance imaging (MRI).[4-6] Noncontrast CT assesses tissue hypodensity due to increased water content, perfusion imaging evaluates blood flow, and MRI detects restricted diffusion of water molecules due to cytotoxic edema.[10] Additionally, noncontrast CT and diffusion MRI were assessed using a semiquantitative score (ASPECTS),[11] while CT perfusion imaging was processed to provide a quantitative volumetric estimate.[12] While the aforementioned recent RCTs provided randomized evidence of thrombectomy benefit in patients with large ischemic core, the effect of ischemic core extent, using different imaging modalities, on EVT treatment effect and outcomes is not well established.

Perfusion imaging also provides estimates of salvageable ischemic penumbra (perfusion mismatch), which is the current guideline-recommended selection approach for thrombectomy beyond 6 hours of stroke onset.[13,14] However, there are limited data on the effect of mismatch selection on thrombectomy treatment benefits in patients with large cores. Further, EVT treatment effects and outcomes may differ by imaging selection modalities and are not well characterized in patients with large ischemic cores. The Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT2)[3,15] is unique in this approach. All patients received a noncontrast CT and either CT-perfusion imaging or, in a few cases, MR-diffusion-perfusion imaging at baseline, with no upper limit on eligible core volume, allowing simultaneous evaluation of 2 different imaging modalities and both semiquantitative and quantitative ischemic core definitions.

This exploratory analysis investigated the association of ischemic extent, estimated using different imaging modalities, with thrombectomy treatment effect and EVT outcomes in the SELECT2 trial. The trial also investigated the association of mismatch presence and concordance vs discordance between 2 imaging modalities with thrombectomy outcomes and treatment effect.

Key Points

Question Does the benefit from endovascular thrombectomy for patients with large ischemic strokes caused by large vessel occlusion vary by the extent of presenting ischemic injury?

Findings In an exploratory analysis of a randomized clinical trial that included 336 participants, while functional outcomes worsened as baseline ischemic core volumes increased, endovascular thrombectomy was associated with better clinical outcomes across a wide spectrum of ischemic changes and penumbra profiles on various imaging modalities compared with medical management.

Meaning Endovascular thrombectomy, compared with medical management, improved clinical outcomes across a wide spectrum of ischemic core volumes and penumbral profiles; however, large ischemic core volume is an important prognostic factor to consider when individualizing treatment decisions.

Methods

Ethical Considerations

The SELECT2 trial protocol was approved by local institutional review boards at all participating institutions prior to recruitment. All patients or their surrogates provided written informed consent for participation in the trial.

Study Population

The SELECT2[4,15] study was an open-label RCT with blinded outcome assessment, enrolling adults aged 18 to 85 years with no premorbid disability, presenting with acute ischemic stroke due to an occlusion of the internal carotid artery or proximal middle cerebral artery (M1 segment) and large core defined by either noncontrast CT (ASPECTS score 3-5) or by ischemic core 50 mL or greater on CT perfusion imaging (relative cerebral blood flow <30%) or diffusion MRI (apparent diffusion coefficient $<620 \times 10^{-6}$ mm^2/s) at 31 centers across US, Canada, Europe, Australia, and New Zealand between October 2019 and September 2022. Patients were eligible for the trial if they had a large core based on 1 or both imaging modalities. Race and ethnicity of the patients were classified among set response options by patients or family. Race and ethnicity are reported because stroke mechanisms, including intracranial atherosclerosis and atrial fibrillation, differ in frequency among racial and ethnic populations. The study protocol and eligibility criteria have been published.[4,15] The trial protocol is available in Supplement 2, the primary trial statistical analysis protocol in Supplement 3, and the statistical analysis protocol for this exploratory analysis in Supplement 4.

Randomization

Patients were randomized 1:1 to receive EVT vs standard medical management. A web-based centralized randomization module using minimization (covariate-adaptive randomization) algorithm was used to obtain randomized treatment assignment in real time. The minimization algorithm assigns values to each individual participant based on the observed characteristics including age, National Institutes of Health Stroke Scale (NIHSS) score at presentation (with scores ranging from 0-42 and higher scores indicating worse neurologic deficits), occlusion location, time window (the interval between the time that the patient was last known to be well and randomization), ischemic core volume estimate, ASPECTS score, presence or absence of target perfusion-diffusion mismatch profile (mismatch ratio [the ratio of critically hypoperfused tissue to the ischemic core estimate] of 1.8 or greater with a mismatch volume [the volumetric difference between critically hypoperfused tissue and

the ischemic core estimate] of ≥15 mL), affected brain hemisphere, and participating center and attempts to balance the overall values between treatment groups. Further details regarding the randomization module have been published.[4]

Intervention

Patients were randomized to receive EVT with medical care or best medical management only. Endovascular thrombectomy was provided by means of a stent retriever, aspiration catheter, or their combination, with details regarding primary approach, arterial access, use of balloon-guided catheter, anesthesia protocol, and periprocedure and postprocedure care deferred to the local neurointerventionalists. All patients received standard medical care, including thrombolytics, based on institutional protocols and regional guidelines.[13,14,16]

Imaging Evaluation

All patients received standardized neuroimaging evaluation, including a noncontrast CT, CT/MR angiography, and CT perfusion/MR diffusion-perfusion imaging at the time of presentation. CT perfusion imaging was processed locally at the enrollment sites using RapidAI software to obtain quantitative estimates of ischemic core (measured using relative cerebral blood flow <30% threshold) and critically hypoperfused tissue (tissue with time to maximum intensity >6 seconds).

Site investigators adjudicated noncontrast CT to calculate the ASPECTS, a 10-point ordinal scoring system in which ischemic injury on each territory represents a loss of 1 ASPECTS point. Thus, patients with ASPECTS score of 10 demonstrate no ischemic changes in the middle cerebral artery territory, and an ASPECTS score of 0 suggests that all ischemic territories supplied by middle cerebral artery show signs of ischemic injury. Patient eligibility was determined based on assessment of CT ASPECTS score by the enrolling investigator. Subsequently, all neuroimaging evaluations were collected and reviewed by the imaging core laboratory, with adjudication of baseline CT ASPECTS score by manual review of noncontrast CT. Occlusion location was also manually reviewed and adjudicated by the imaging core laboratory.

Additionally, CT perfusion and MR diffusion-perfusion images were retrospectively reprocessed using RapidAI v5.1.1R2 (research version) for potential correction of motion and arterial input function-related artifacts. CT hypodensity volumes were quantified by manual planimetry using ITK-Snap version 3.8 to draw regions of interest, using an iterative process by 3 reviewers blinded to treatment and outcome information. Two investigators (F.C.N., V.Y.) manually delineated CT hypodensity, then regions of interest were reviewed by another investigator (B.C.C.), with disagreements resolved by mutual decision. Follow-up infarct volume was measured by manual delineation of infarcted tissue on MR diffusion imaging or noncontrast CT (if MR diffusion imaging was unavailable), acquired 24 hours to 7 days after randomization by an investigator (V.Y.) with review by another (B.C.C.) and with disagreements resolved by mutual decision. ASPECTS score was assessed centrally by an investigator (C.W.S.) blinded to treatment assignment and outcomes. An illustration for the imaging evaluation process is provided in eFigures 1 and 2 in Supplement 5.

Because a substantial proportion of patients demonstrated volumetric differences between ischemic volume measured using CT hypodensity and CT perfusion imaging, analyses were performed using 3 sets of volumes: (1) CT perfusion/MR diffusion core volume, (2) CT hypodensity, and (3) composite ischemic core volume, defined as the larger of the 2 values (CT hypodensity or CT perfusion/MR diffusion volume). Critically hypoperfused tissue was defined as the volume of brain tissue with Tmax greater than 6 seconds. Two mismatch definitions were used: (1) mismatch volume (difference between critically hypoperfused tissue and ischemic core) 15 mL or greater and mismatch ratio (critically hypoperfused to ischemic core) 1.8 or greater[3]; and (2) mismatch volume 10 mL or greater and mismatch ratio 1.2 or greater.[17] Both CT perfusion and composite core volumes were used to calculate mismatch status.

Because quantitative ischemic changes seen on noncontrast CT and CT perfusion/MR diffusion-perfusion imaging do not always correlate, the study also aimed to identify and quantify the presence of imaging discordance and its association with EVT treatment effect and clinical outcomes. Discordant profiles were defined using both CT perfusion/MR diffusion core volume and composite core volume as (1) ASPECTS less than 6 but core volume less than 70 mL and (2) ASPECTS 6 or greater but core volume 70 mL or greater. Patients with ASPECTS less than 6 and core volume 70 mL or greater were deemed concordant.

Outcomes

Blinded assessment of functional status at 90-day follow-up was performed by trained evaluators. The primary outcome was the 90-day modified Rankin Scale (mRS) score distribution (range, 0 [no residual stroke symptoms] to 6 [death]). Scores of 5 (complete dependence) and 6 were merged to avoid considering a shift from 6 to 5 as an improvement. Secondary outcomes included functional independence (mRS score 0-2), independent ambulation (mRS score 0-3), complete dependence or death (mRS score 5-6 [not included in the primary trial analyses but found to be clinically relevant and thus included herein]), mortality, neurologic worsening defined as an increase of 4 or more points in NIHSS score at 24 hours (±6 hours) compared with baseline, and symptomatic intracerebral hemorrhage per SITS-MOST (Safe Implementation of Thrombolysis in Stroke Monitoring Study) criteria.[18]

Statistical Analysis

Patients were stratified using ischemic core volume thresholds of 70, 100, and 150 mL and ASPECTS thresholds of 2 and 5, in accordance with the primary analysis of the trial. Baseline clinical and imaging characteristics were described and compared between subgroups. Continuous variables were described using median (IQR). Categorical variables were described using counts and proportions.

EVT treatment effect for the primary outcome was evaluated using probabilistic index models (PIM). Adjusted PIMs[19,20]

differ from parametric ordinal logistic regression models in that PIMs estimate the odds of a random patient from the EVT group having better mRS outcome than a random patient receiving medical management, given the differences in covariates between these 2 patients. For the within-group analyses of association between covariates of interest and ordinal mRS outcomes, for a random pair of patients with a given difference in the covariate of interest from the same group (eg, per 10-mL increase in ischemic core volume or per 1-point decrease in ASPECTS score), PIM models estimate the adjusted odds of a patient with a higher value of the covariate having a better mRS outcome than a patient with a lower value of that covariate. Respective treatment effects are reported as adjusted generalized odds ratios (aGenORs) and 95% CIs, with ties split equally between groups. For secondary outcomes, EVT treatment effects for outcomes within individual subgroups were evaluated using modified Poisson regression models with robust standard errors, as per the statistical analysis protocol for the main trial analysis. Heterogeneity of treatment effect was evaluated using an interaction term between treatment group and characteristic of interest (conducted separately for subgroups based on imaging characteristics and for imaging characteristics across continuous scales where possible).

Similar models were used to evaluate the association of given clinical characteristics on primary and secondary outcomes within EVT and medical management strata. The generalized odds of having a better mRS outcome with EVT compared with medical management as a function of core volume, ASPECTS score, and mismatch volume was estimated using a g-computation approach based on the full ordinal scale with bootstrapped confidence intervals. Predicted margins and marginal probabilities were used to illustrate the association of 1 or more clinical characteristics on primary and secondary outcomes. Sensitivity analyses using site investigator-adjudicated ASPECTS score and excluding the limited number of patients enrolled based on MRI were also performed. Post hoc sensitivity analyses using composite core and CT hypodensity volumes, as well as comparing model information criteria and area under the receiver operating characteristic curve (AUC) values for key functional outcomes across different volumetric ischemic estimates, were performed. A post hoc analysis evaluating infarct volumes and growth from baseline core was also performed.

All analyses were performed using STATA release 17[21] and R version 4.2.2.[22] Patients were analyzed based on the groups to which they were randomized when evaluating the association of treatment group with outcomes across various imaging strata, and patients were analyzed based on their as-treated treatment received when evaluating the association of imaging characteristics with outcomes within the treatment groups. Missing data were not imputed. Patients with missing information regarding functional outcome at 90-day follow-up, baseline imaging on noncontrast CT or CT/MR perfusion, and/or follow-up infarct volume were excluded from this analysis (eFigure 3 in Supplement 5). All hypotheses were evaluated using 2-sided tests. $P < .05$ was considered statistically significant. Analyses were considered exploratory and no adjustments for multiple comparisons were performed.

Results

After publication of the results from the RESCUE Japan LIMIT trial, the data and safety monitoring board requested data review after the first 300 patients completed their 90-day follow-up. After review, the board declared that the study should be stopped since the prespecified efficacy boundary was crossed in favor of EVT. A total of 352 patients had been enrolled and randomized in the SELECT2 trial at the time the board recommended stopping the trial. Sixteen patients excluded from this exploratory analysis (12 for reasons related to imaging quality, 4 for loss to follow-up) (eFigure 3 in Supplement 5). Of 336 included, 168 (50%) were randomized to EVT and 2 additional patients crossed over from the medical management group to receive EVT (**Table 1**; eTables 1 and 2 in Supplement 5). Median age was 67 (IQR, 58.5-75) years, and 139 (41.4%) were female.

Noncontrast CT and CT/MR perfusion imaging were acquired within 60 minutes for 308 of 336 patients (92%), with median interval between noncontrast CT and CT/MR perfusion imaging of 6 (IQR, 2-13) minutes. Overall, median ASPECTS score was 4 (IQR, 3-5). Median CT hypodensity volume was 86 (IQR, 49-114) mL, whereas median CT perfusion/MR diffusion pretreatment ischemic core volume was 73 (IQR, 46-107) mL. In a post hoc analysis, CT hypodensity volume was larger than CT perfusion core in 203 patients (60%), and those patients had significantly longer time from last known to be well to randomization (CT hypodensity larger than CT perfusion/MR diffusion: 727 [422-1004] min; CT perfusion/MR diffusion core larger than CT hypodensity: 372 [251-664] min; $P < .001$). Of patients randomized 0 to 3 hours after onset, 81% had larger volume by CT perfusion/MR diffusion vs CT hypodensity but only 14% of those presenting at 21 to 24 hours had larger CT perfusion/MR diffusion core (eFigure 4 in Supplement 5). Median composite ischemic core volume was 101 (IQR, 72-138) mL. Follow-up imaging modality was MRI in 8 of 336 patients (2%) and CT in 328 of 336 patients (98%).

Association of Noncontrast CT-ASPECTS With EVT Treatment Effect

In 277 patients with adjudicated ASPECTS score 3-5, EVT was associated with significantly better functional outcomes than medical management (median mRS, 4 [IQR, 3-6] vs 5 [IQR, 4-6]; aGenOR, 1.82 [95% CI, 1.40-2.35]) (**Figure 1**). This was preserved in patients with ASPECTS score 3 (n = 73 [22%]; aGenOR, 1.71 [95% CI, 1.04-2.81]), ASPECTS score 4 (n = 88 [26%]; aGenOR, 2.01 [95% CI, 1.19 – 3.40]), and ASPECTS score 5 (n = 116 [35%]; aGenOR, 1.85 [95% CI, 1.22-2.79]) without significant heterogeneity ($P = .80$ for interaction). Similar results were obtained for functional independence, independent ambulation, and complete dependence or death (eFigures 7-9 in Supplement 5). Furthermore, a sensitivity analysis using site investigator-adjudicated ASPECTS scores also demonstrated similar results (eTable 3 in Supplement 5).

Table 1. Baseline Clinical and Imaging Characteristics of Study Population (Intention-to-Treat), Stratified by Treatment

Characteristic	Endovascular thrombectomy (n = 168)	Medical care only (n = 168)
Demographics		
Age, median (IQR), y	66 (59-75)	67 (58-75)
Sex, No. (%)		
Female	68 (40.5)	71 (42.3)
Male	100 (59.5)	97 (57.7)
Race and ethnicity, No. (%)[a]		
Asian	5 (3.0)	3 (1.8)
Black	24 (14.3)	24 (14.3)
Native Hawaiian or Pacific Islander	2 (1.2)	0
White	124 (73.8)	125 (74.4)
Other or unknown	13 (7.8)	16 (9.5)
Transferred to thrombectomy-capable center, No. (%)	97 (57.7)	103 (61.3)
Medical history, No. (%)		
Hypertension	131 (78.0)	121 (72.0)
Diabetes	50 (29.8)	54 (32.1)
Atrial fibrillation	44 (26.2)	38 (22.6)
Coronary artery disease	39 (23.5)	25 (15.4)
Congestive heart failure	19 (11.3)	19 (11.3)
Ischemic stroke	18 (10.7)	13 (7.7)
Transient ischemic attack	4 (2.4)	8 (4.8)
Physical examination		
Left hemisphere affected, No. (%)	76 (45.2)	71 (42.3)
NIHSS score at thrombectomy hospital, median (IQR)[b]	19 (15-23)	19 (15-22)
Neuroimaging findings		
Occlusion location, No. (%)		
ICA	75 (44.6)	64 (38.1)
MCA M1	86 (51.2)	96 (57.1)
MCA M2	7 (4.2)	8 (4.8)
Tandem occlusions	54 (32.1)	43 (25.6)
CT ASPECTS at thrombectomy hospital, median (IQR)[c]	4 (3-5)	4 (4-5)
Composite core volume, median (IQR), mL[d]	103 (70-139)	99 (74-137)
Imaging modality used to determine ischemic core volume at randomization		
CT perfusion, No. (%)	165 (98.2)	163 (97.0)
MR DWI, No. (%)	3 (1.8)	5 (3.0)
CT perfusion/MRI core volume, median (IQR), mL[e]	70 (40-110)	77 (48-104)
CT hypodensity volume, median (IQR), mL[f]	84 (46-114)	87 (49-113)
Critically hypoperfused (Tmax >6 s) volume, median (IQR), mL	161 (117-206)	166 (119-213)
Time metrics, median (IQR)		
Time from last known well to randomization, min	545 (307-919)	596 (347-934)
Time from arrival to CT acquisition, min	16 (9-27)	16 (7-24)
Time from arrival to CTP acquisition, min	26 (18-42)	25 (13-36)
Additional characteristics, No. (%)		
Intravenous thrombolytics administered	33 (19.6)	28 (16.8)
Tenecteplase used	4 (12.5)	1 (3.7)
General anesthesia used	100 (59.9)	

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; DWI, diffusion-weighted imaging; ICA, internal carotid artery; MCA, middle cerebral artery; MR, magnetic resonance; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; Tmax, time to maximum intensity.

[a] Classified using set response options by patients or family.

[b] The NIHSS is a 42-point scoring system measuring neurologic deficits, with higher score representing more neurologic deficits.

[c] ASPECTS is a 10-point ordinal scoring system measuring areas of hypoattenuation due to ischemic changes in the MCA territory on noncontrast computed tomography (CT) of brain, with 1 point deducted for each location demonstrating hypoattenuation. Thus, lower scores represent worse ischemic injury.

[d] Composite core volume indicates the larger of CT perfusion/MRI core volume and CT hypodensity volume estimates.

[e] CT perfusion/MRI core volume is a volumetric estimate obtained from CT perfusion using relative cerebral blood flow less than 30% threshold/MR perfusion imaging using apparent diffusion coefficient less than 620×10^{-6} mm/s^2 threshold using automated RapidAI processing.

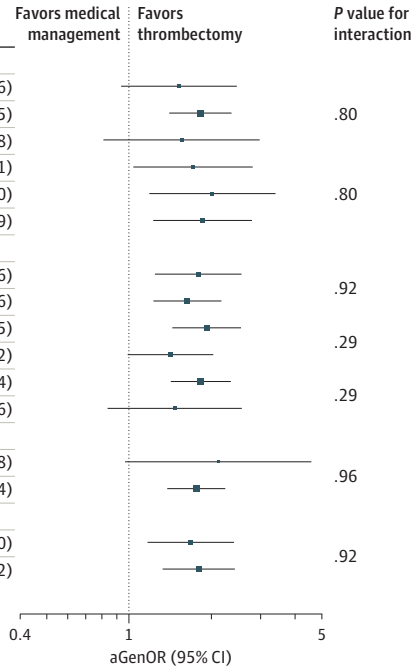
[f] CT hypodensity volume is a volumetric estimate of observed hypodensity on noncontrast CT by manual delineation of the region of interest by consensus from 3 expert readers using ITK-SNAP.

Association of CT Perfusion/MRI Core Volume With EVT Treatment Effect

Treatment effect estimates (median mRS scores) for EVT vs medical management across CTP/MRI core subgroups were 5 (IQR, 4-6) vs 6 (IQR, 4-6) for threshold 70 mL or greater (aGenOR, 1.63 [95% CI, 1.23-2.16]); 6 (IQR, 4-6) vs 6 (IQR, 5-6) for threshold 100 mL or greater (aGenOR, 1.41 [95% CI, 0.99-2.02]); and 6 (IQR, 4-6) vs 6 (IQR, 5-6) for threshold 150 mL or greater (aGenOR, 1.47 [95% CI, 0.84-2.56]) (Figure 1 and **Figure 2**). There was no significant heterogeneity in

Figure 1. Endovascular Thrombectomy Treatment Effect on mRS Score Distribution at 90-Day Follow-Up Across Various Imaging Strata, Reported Using Adjusted Generalized Odds Ratio

Measure	No. of patients	mRS score, median (IQR)		aGenOR (95% CI)	*P* value for interaction
		Thrombectomy	Medical management		
ASPECTS					
0-2	19	6 (5-6)	6 (5-6)	1.52 (0.94-2.46)	
3-5	277	4 (3-6)	5 (4-6)	1.82 (1.40-2.35)	.80
6-10	40	5 (3-6)	6 (4-6)	1.55 (0.81-2.98)	
3	73	4 (3-6)	6 (4-6)	1.71 (1.04-2.81)	
4	88	4 (3-6)	5 (4-6)	2.01 (1.19-3.40)	.80
5	116	3 (2-6)	4 (3-6)	1.85 (1.22-2.79)	
Core volume, mL					
<70	156	3 (2-6)	4 (3-6)	1.78 (1.24-2.56)	
≥70	180	5 (4-6)	6 (4-6)	1.63 (1.23-2.16)	.92
<100	236	4 (2-6)	5 (4-6)	1.91 (1.44-2.55)	
≥100	100	6 (4-6)	6 (5-6)	1.41 (0.99-2.02)	.29
<150	296	4 (3-6)	5 (4-6)	1.82 (1.42-2.34)	
≥150	40	6 (4-6)	6 (5-6)	1.47 (0.84-2.56)	.29
Mismatch ratio ≥1.2 and volume ≥10 mL					
No	29	4 (4-6)	5 (4-6)	2.11 (0.97-4.58)	
Yes	307	4 (3-6)	5 (4-6)	1.75 (1.38-2.24)	.96
Mismatch ratio ≥1.8 and volume ≥15 mL					
No	120	5 (4-6)	6 (4-6)	1.68 (1.17-2.40)	
Yes	216	4 (2-6)	5 (4-6)	1.79 (1.33-2.42)	.92



Treatment effect reported using adjusted generalized odds ratio (aGenOR), adjusted for age, National Institutes of Health Stroke Scale (NIHSS) score at presentation, time from last known well to randomization, and core volume. Core volume was not included as an adjustment covariate for analyses within core volume strata. aGenOR greater than 1 indicates better functional outcome (distribution of modified Rankin Scale [mRS] score) at 90-day follow-up with endovascular thrombectomy. The NIHSS is a 42-point scoring system measuring neurologic deficits, with higher score representing more neurologic deficits. The Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point ordinal scoring system measuring areas of hypoattenuation due to ischemic changes in the middle cerebral artery territory on noncontrast computed tomography (CT) of the brain, with 1 point deducted for each location demonstrating hypoattenuation. Thus, lower scores represent worse ischemic injury. The CT perfusion/magnetic resonance imaging (MRI) core volume is a volumetric estimate obtained from CT perfusion using relative cerebral blood flow less than 30% threshold or MR diffusion imaging using apparent diffusion coefficient less than 620×10^{-6} mm/s^2 threshold using automated RAPID-AI processing. The modified Rankin Scale (mRS) score is a 7-point ordinal scale measuring functional status, ranging from 0 (no residual deficit) to 6 (death).

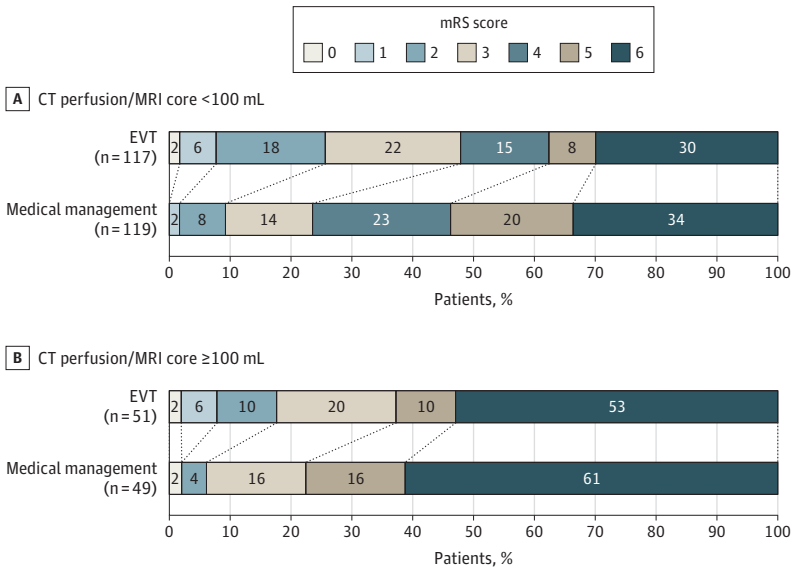
the treatment effect by core volume strata (interaction $P = .92$, $P = .29$, and $P = .29$ for stratifications using 70-mL, 100-mL, and 150-mL thresholds, respectively), although the aGenORs were numerically lower for 100 mL or greater vs less than 100 mL and 150 mL or greater vs less than 150 mL. Treatment effect estimates for secondary outcomes were also generally similar across CT perfusion/MRI core subgroups based on thresholds of 70 mL or greater, 100 mL or greater, and 150 mL or greater (eFigures 7-9 in Supplement 5). Sensitivity analyses restricted to patients who received CT perfusion only, excluding 8 patients who received MRI, also demonstrated similar results (eTable 4 in Supplement 5). Similar results were also observed using composite core and CT hypodensity volumes (post hoc) (eFigures 10-13 in Supplement 5).

Association of ASPECTS and CT Perfusion/MRI Core Volume With Clinical Outcomes in EVT-Treated Patients

In multivariable models without adjusting for volumetric measures, decreasing ASPECTS score was associated with significantly worse clinical outcomes within EVT-treated patients (aGenOR, 0.91 [95% CI, 0.82-1.00] per 1-point ASPECTS score decrease) (**Table 2**). However, after adjusting for CT perfusion/MRI core volume (in addition to age, NIHSS score, and time), EVT functional outcomes did not differ significantly with decreasing ASPECTS score (aGenOR, 0.96 [95% CI, 0.86-1.07] per 1-point decrease) (eFigure 14 in Supplement 5).

Functional outcomes were significantly worse in EVT-treated patients as CT perfusion/MRI core volume increased (aGenOR, 0.92 [95% CI, 0.89-0.95] per 10-mL increase) (Table 2). Functional independence (absolute risk reduction [aRR], 0.89 [95% CI, 0.84-0.95] per 10-mL increase) and independent ambulation (aRR, 0.91 [95% CI, 0.87-0.95] per 10-mL increase) also decreased significantly, whereas complete dependence or death (aRR, 1.05 [95% CI, 1.02-1.08] per 10-mL increase) increased significantly with increasing ischemic core volume in the EVT group (**Figure 3**). Results using composite core volume and CT hypodensity volumes (post hoc) were similar (eFigures 15-16, eTable 5 in Supplement 5). Furthermore, composite core volume demonstrated better Akaike information criterion, Bayesian information criterion, and AUC values, compared with CT perfusion core volume or CT hypodensity volume (eTable 6 in Supplement 5).

Figure 2. Distribution of Modified Rankin Scale Score at 90-Day Follow-Up in the Study Population (Intention to Treat)



The modified Rankin Scale (mRS) score is a 7-point ordinal scale measuring functional status, ranging from 0 (no residual deficit) to 6 (death).

Table 2. Association of Extent of Ischemic Injury on CT ASPECTS and CT Perfusion/MRI Core Volumes and Clinical Outcomes Within Patients Receiving Endovascular Thrombectomy and Medical Management (As-Treated Analysis)

	aGenOR or aRR (95% CI)[a]		
	Endovascular thrombectomy (n = 170)	Medical care only (n = 166)	*P* value for interaction
mRS distribution[b]			
Median (IQR)	4 (3-6)	5 (4-6)	
ASPECTS (per 1-point decrease)[c]	aGenOR, 0.91 (0.82-1.00)	aGenOR, 0.89 (0.80-0.99)	.83
CT perfusion or MRI core volume (per 10-mL increment)	aGenOR, 0.92 (0.89-0.95)	aGenOR, 0.95 (0.92-0.98)	.20
mRS 0-2[b]			
No./total (%)	34/170 (20.0)	12/166 (7.2)	
ASPECTS (per 1-point decrease)[c]	aRR, 0.94 (0.81-1.09)	aRR, 0.81 (0.57-1.14)	.41
CT perfusion or MRI core volume (per 10-mL increment)	aRR, 0.89 (0.84-0.95)	aRR, 0.91 (0.80-1.03)	.58
mRS 0-3[b]			
No./total (%)	66/170 (38.8)	30/166 (18.1)	
ASPECTS (per 1-point decrease)[c]	aRR, 1.00 (0.90-1.12)	aRR, 0.92 (0.72-1.19)	.73
CT perfusion or MRI core volume (per 10-mL increment)	aRR, 0.91 (0.87-0.95)	aRR, 0.91 (0.85-0.98)	.25
mRS 5-6[b]			
No./total (%)	77/170 (45.3)	101/166 (60.8)	
ASPECTS (per 1-point decrease)[c]	aRR, 1.04 (0.93-1.15)	aRR, 1.03 (0.95-1.11)	.86
CT perfusion or MRI core volume (per 10-mL increment)	aRR, 1.05 (1.02-1.08)	aRR, 1.03 (1.01-1.05)	.37

Abbreviations: aGenOR, adjusted generalized odds ratio; aRR, absolute risk reduction; ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; MRI, magnetic resonance imaging; mRS, modified Rankin Scale score.

[a] Analyses are adjusted for age, National Institutes of Health Stroke Scale score, and time from last known well to randomization. aGenOR greater than 1 indicates better functional outcome (distribution of mRS score) at 90-day follow-up with endovascular thrombectomy. aRR greater than 1 indicates higher rate ratio for mRS 0-2, 0-3, and 5-6 with endovascular thrombectomy.

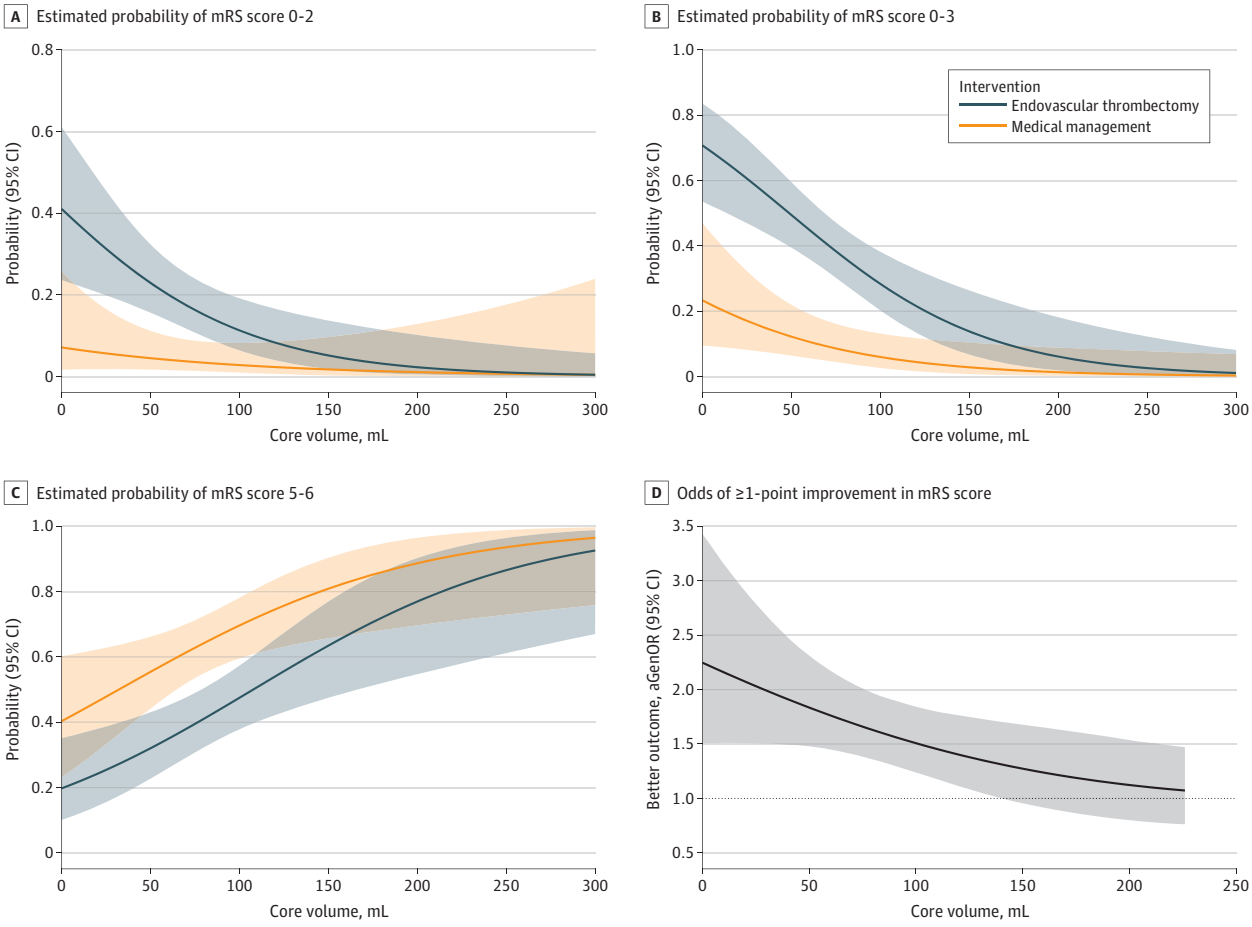
[b] The mRS is a 7-level ordinal scoring system representing functional status, with higher scores representing worse functional status (0 indicating without any deficits and 6 indicating dead).

[c] ASPECTS is a 10-point ordinal scoring system measuring areas of hypoattenuation due to ischemic changes in the middle cerebral artery territory on noncontrast computed tomography (CT) of brain, with 1 point deducted for each location demonstrating hypoattenuation. Thus, lower scores represent worse ischemic injury.

Association of Mismatch With EVT Treatment Effect and Functional Outcomes

Using CT perfusion/MRI core volume, a total of 29 patients (8.6%) demonstrated no mismatch profile based on mismatch ratio 1.2 or greater/mismatch volume 10 mL or greater, and 120 patients (35.7%) demonstrated no mismatch based on mismatch ratio 1.8 or greater/mismatch volume 15 mL or greater (**Table 3**). No association between time from last known well

Figure 3. Association of Increasing CT Perfusion/MRI Core Volume and Functional Outcomes at 90-Day Follow-Up in Patients Receiving Endovascular Thrombectomy and Medical Management



The modified Rankin Scale (mRS) score is a 7-point ordinal scale measuring functional status, ranging from 0 (no residual deficit) to 6 (death). Panels A, B, and C illustrate estimated probability of mRS score 0-2, 0-3, and 5-6, respectively. Panel D illustrates the generalized odds of having an improvement of 1 point or more in mRS outcome as a function of computed tomography (CT) perfusion/magnetic resonance imaging (MRI) core volume.

to randomization and the proportion of patients with presence or absence of mismatch profile was observed based on mismatch ratio 1.2 or greater/mismatch volume 10 mL or greater (P = .71 for trend) (eFigure 5A in Supplement 5), but patients with absence of mismatch profile (based on mismatch ratio ≥1.8/mismatch volume ≥15 mL definition) decreased as time to randomization increased (P < .001 for trend) (eFigure 5B in Supplement 5). Furthermore, the proportion of patients without mismatch (based on both definitions) increased as CT perfusion/MRI core estimates increased (P < .001 for trend for both definitions) (eFigure 6, panels A and B, in Supplement 5). No heterogeneity of EVT treatment effect was observed with presence or absence of mismatch using definition based on CT perfusion/MR diffusion core (Figure 1 and Table 3; eFigures 7-9 in Supplement 5). However, the absolute proportion of patients achieving mRS score 0 to 2 or 0 to 3 was numerically higher in EVT-treated patients with mismatch vs no mismatch. Furthermore, as mismatch volume increased, the marginal probability of functional independence and independent ambulation increased for patients receiving EVT but decreased in patients receiving medical management only (eFigure 17 in Supplement 5). In a post hoc analysis, when composite core volume was used to calculate mismatch, 262 patients (78.0%) and 125 (37.2%) demonstrated presence of mismatch based on the mismatch ratio 1.2 or greater/mismatch volume 10 mL or greater and the mismatch ratio 1.8 or greater/mismatch volume 15 mL or greater definitions, with largely similar results (eTable 7 in Supplement 5), but the paradoxical tendency for increased mismatch in patients treated later was no longer observed, suggesting that CT perfusion was underestimating core in regions of noncontrast hypodensity (eFigure 5 in Supplement 5).

Association of Ischemic Changes on Noncontrast CT and Perfusion (Together) With EVT Treatment Effect and Functional Outcomes

The presence of discordance between ASPECTS score and core volume estimates was not associated with heterogeneity in EVT treatment effect. However, favorable outcomes were more frequent in patients with ASPECTS score 0 to 5 and core

Table 3. Association of Presence or Absence of CT Perfusion Mismatch Profile With Clinical Outcomes Within Patients Receiving Endovascular Thrombectomy and Medical Management (As-Treated Analysis)[a]

Outcome	Endovascular thrombectomy (n = 170)	Medical care only (n = 166)	*P* value for interaction
Presence of mismatch profile (mismatch volume ≥10 mL and mismatch ratio ≥1.2)—based on CTP/MRI core volume			
mRS distribution[b]			
No mismatch, median (IQR) [reference]	4 (3.5-6) [n = 8]	5 (4-6) [n=21]	
Mismatch, median (IQR)	4 (3-6) [n = 162]	5 (4-6) [n = 145]	
Effect size with uncertainty estimates	aGenOR, 0.84 (95% CI, 0.39 to 1.82)	aGenOR, 0.78 (95% CI, 0.48 to 1.27)	.88
Functional independence (mRS 0-2[b])			
No mismatch, No./total (%) [reference]	0/8	1/21 (4.8)	
Mismatch, No./total (%)	34/162 (21.0)	11/145 (7.6)	
Effect size with uncertainty estimates		aRR, 1.01 (95% CI, 0.21 to 4.92) aRD, −0.001 (95% CI, −0.138 to 0.136)	
Independent ambulation (mRS 0-3[b])			
No mismatch, No./total (%) [reference]	2/8 (25.0)	4/21 (19.0)	
Mismatch, No./total (%)	64/162 (39.5)	26/145 (17.9)	
Effect size with uncertainty estimates	aRR, 1.04 (95% CI, 0.26 to 4.21) aRD, 0.010 (95% CI, −0.344 to 0.364)	aRR, 0.49 (95% CI, 0.22 to 1.05) aRD, −0.139 (95% CI, −0.289 to 0.012)	.47
Complete dependence or death (mRS 5-6[b])			
No mismatch, No./total (%) [reference]	3/8 (37.5)	14/21 (66.7)	
Mismatch, No./total (%)	74/162 (45.7)	87/145 (60.0)	
Effect size with uncertainty estimates	aRR, 1.33 (95% CI, 0.52 to 3.44) aRD, 0.178 (95% CI, −0.109 to 0.465)	aRR, 1.10 (95 % CI, 0.78 to 1.56) aRD, 0.075 (95% CI, −0.129 to 0.279)	.65
Presence of mismatch profile (mismatch volume ≥15 mL and mismatch ratio ≥1.8)—based on CTP/MRI core volume			
mRS distribution[b]			
No mismatch, median (IQR) [reference]	5 (4-6) [n = 59]	5 (4-6) [n = 61]	
Mismatch, median (IQR)	4 (2-6) [n = 111]	5 (4-6) [n = 105]	
Effect size with uncertainty estimates	aGenOR, 0.89 (95% CI, 0.57 to 1.38)	aGenOR, 0.92 (95% CI, 0.63 to 1.32)	.92
Functional independence (mRS 0-2[b])			
No mismatch, No./total (%) [reference]	6/59 (10.2)	2/61 (3.3)	
Mismatch, No./total (%)	28/111 (25.2)	10/105 (9.5)	
Effect size with uncertainty estimates	aRR, 1.20 (95% CI, 0.44 to 3.28) aRD, 0.033 (95% CI, −0.124 to 0.191)	aRR, 1.09 (95% CI, 0.26 to 4.57) aRD, 0.003 (95% CI, −0.097 to 0.103)	.75
Independent ambulation (mRS 0-3[b])			
No mismatch, No./total (%) [reference]	14/59 (23.7)	6/61 (9.8)	
Mismatch, No./total (%)	52/111 (46.8)	24/105 (22.9)	
Effect size with uncertainty estimates	aRR, 1.03 (95% CI, 0.56 to 1.88) aRD, 0.009 (95% CI, −0.164 to 0.181)	aRR, 0.87 (95% CI, 0.39 to 1.92) aRD, −0.032 (95% CI, −0.155 to 0.090)	.60
Complete dependence or death (mRS 5-6[b])			
No mismatch, No./total (%) [reference]	31/59 (52.5)	43/61 (70.5)	
Mismatch, No./total (%)	46/111 (41.4)	58/105 (55.2)	
Effect size with uncertainty estimates	aRR, 1.18 (95% CI, 0.82 to 1.70) aRD, 0.092 (95% CI, −0.071 to 0.255)	aRR, 1.05 (95% CI, 0.79 to 1.38) aRD, 0.037 (95% CI, −0.117 to 0.191)	>.99

Abbreviations: aRD, absolute risk difference; aRR, absolute risk reduction; CT, computed tomography; MRI, magnetic resonance imaging; mRS, modified Rankin Scale.

[a] Analyses are adjusted for age, National Institutes of Health Stroke Scale score, time from last known well to randomization, and CT perfusion/MRI core volume. aGenOR greater than 1 indicates better functional outcome (distribution of mRS score) at 90-day follow-up with endovascular thrombectomy. aRR greater than 1 indicates higher rate ratio for mRS 0-2, 0-3, and 5-6 with endovascular thrombectomy.

[b] mRS is a 7-level ordinal scoring system representing functional status, with higher scores representing worse functional status (0 indicating without any deficits and 6 indicating dead).

volume less than 70 mL vs 70 mL or greater (eTables 8-10 in Supplement 5).

Association of Follow-Up Infarct Volume and Infarct Growth With EVT Outcomes

In a post hoc analysis, infarct volume on follow-up imaging did not differ significantly between EVT (median, 170 [IQR, 123-268] mL and medical management (median, 168 [IQR, 110-253] mL) (*P* = .43). In patients with MR diffusion follow-up (n = 204 [61%]), infarct growth from baseline CT perfusion/MRI core volumes was smaller with successful reperfusion (median, 68 [IQR, 37-142] mL) than with medical management (median, 95 [IQR, 56-125] mL) and unsuccessful reperfusion (median, 125 [IQR, 76-179] mL) (eTable 11 in Supplement 5). Additionally, infarct growth from baseline CT perfusion/MRI core volume estimates was smaller in those

who achieved functional independence and independent ambulation as compared with those who did not (eTable 12 in Supplement 5). Overestimation of ischemic core on CT perfusion/MR diffusion imaging was infrequent, with 3 patients (<1%) demonstrating CT perfusion/MR diffusion core that was 10 mL or greater larger than follow-up infarct volume (eTable 13 in Supplement 5).

Association of Age and Time With Functional Outcome After EVT

With increasing age (aRR, 0.97 [95% CI, 0.96-0.99] per 1-year increment) and time from CT perfusion acquisition to reperfusion or end of the procedure (aRR, 0.97 [95% CI, 0.93-1.00] per 10-minute increment), the predicted probability of achieving independent ambulation significantly decreased (eFigure 18 in Supplement 5). However, time from last known to be well to reperfusion or end of the procedure did not exhibit a significant association with the odds of independent ambulation (aRR, 1.00 [95% CI, 0.99-1.00]) (eFigure 19 in Supplement 5). The relationship was consistent across estimated CT perfusion/MRI core volumes set at 70 mL, 100 mL, and 150 mL, but absolute predicted probabilities reduced with increasing core volumes. As age increased and time from imaging to reperfusion or end of the procedure lengthened, the probability of independent ambulation decreased. Although the probability graphs represent point estimates without confidence intervals, it is evident that a patient with a 150-mL core would be unlikely to achieve independent ambulation, unless they are young and treated very rapidly.

Discussion

In this exploratory analysis of the SELECT2 trial, EVT improved functional outcomes in ordinal analysis of the mRS score across a wide spectrum of ischemic injury extent when compared with medical management only. Point estimates of outcomes were better with EVT even in patients with ASPECTS score of 3 and ischemic core of 150 mL or larger, noting wide confidence intervals in the 150 mL or greater core volume group. However, within the EVT group, proportion of patients achieving functional independence and independent ambulation decreased as ischemic core increased and ASPECTS score decreased, and very few patients with ischemic core 100 mL or greater and 150 mL or greater achieved functional independence or independent ambulation.

Patients who received EVT demonstrated better clinical outcomes compared with those who received medical care only, with or without presence of a mismatch profile (based on mismatch ratio ≥1.8 and mismatch volume ≥15 mL). A limited number of patients without a mismatch profile based on mismatch ratio 1.2 or greater and mismatch volume 10 mL or greater (n = 29 [8.6%], of whom 8 received EVT) were included in the trial, precluding definitive conclusions. Although lack of mismatch was not an exclusion criterion, we cannot exclude the possibility that investigators may have chosen not to randomize some patients without mismatch or to treat some early-presenting patients with large core but mismatch with thrombectomy outside the trial. However, this was not evident in the screening logs. EVT association with functional outcomes did not significantly differ between those with concordant vs discordant imaging profiles.

EVT benefit in ordinal analysis of functional outcome appeared maintained, even in patients with very large cores, with no clear upper threshold, albeit with lower rates of functional independence and independent ambulation. Functional outcomes in those with core volume 100 mL or greater who received EVT were poor, with approximately 80% having moderately severe disability (mRS score 4) or worse at 90-day follow-up. However, 1 in 5 patients still achieved independent ambulation after EVT.

The SELECT2 trial used automated perfusion image processing using RapidAI to obtain ischemic core and critically hypoperfused tissue estimates. Other software platforms are also available for postprocessing of perfusion imaging and have shown performance similar to RapidAI.[23-25] Further validation of the study findings using perfusion core estimates from other software platforms may help extend the study generalizability.

Substantial volumetric overestimation (≥10 mL) of the infarct by CT perfusion imaging was rare (<1%). However, more than one-half of the patients had CT perfusion ischemic core estimates smaller than the CT hypodensity volume (particularly in the later time window), for reasons including (1) distal clot migration from a more proximal initial occlusion, (2) partial recanalization, (3) recruitment of collaterals, or (4) infarct outside of CT perfusion coverage area. Conversely, 40% of patients had larger CT perfusion/MR diffusion core estimates than CT hypodensity estimates. These patients tended to be in the earlier window, likely due to the time required for the ionic edema that causes hypodensity through increased water content to evolve on CT.[26] Thus, combining information from both imaging modalities best estimates the extent of ischemic injury and prognosis. Automated software to measure CT hypodensity is evolving,[27] but, regardless, clinicians are able to recognize individuals in whom there are substantial noncontrast CT changes outside of the current CT perfusion core and account for these changes when assessing treatment decisions and prognosis. Imaging discordance between the 2 modalities was frequent and did not alter EVT treatment effect.

No treatment effect modification was observed with the presence or absence of mismatch profile on perfusion imaging, albeit with very few patients in the no mismatch group for a ratio of 1.2, where the absolute proportion of patients achieving mRS score 0 to 2 or 0 to 3 was numerically lower in EVT-treated patients without mismatch (as compared with those with mismatch). The proportion of patients without mismatch in this study was smaller than in prior reports.[28,29] However, most of the patients in those studies had MRI-based core measurements. CT perfusion imaging estimates the ischemic core indirectly using reduced cerebral blood flow and thus may result in undersegmentation of regions with noncontrast CT hypodensity that have subsequent improvement in perfusion due to collateral recruitment or clot migration. This would

lead to overestimation of mismatch volume, and the proportion of patients with mismatch was reduced from 91% when calculated using the CT perfusion definition to 78% when calculated using the composite core definition (ratio ≥1.2/volume ≥10 mL). The proportion of patients without mismatch using the ratio 1.8 or greater and volume 15 mL or greater definition, calculated using CT perfusion core volume, was higher in those presenting very early and decreased as time progressed, in contrast to the usual increase in patients without mismatch observed over time. It is possible that investigators' equipoise to randomize vs perform standard-care EVT was reduced in early-presenting patients, especially those with mismatch or good ASPECTS score.

As with previous analyses, patients without mismatch had a lower absolute proportion of favorable outcomes.[30] However, the treatment benefit in ordinal analysis was preserved. The penumbral hypothesis is that the region of mismatch indicates tissue that is potentially salvageable with rapid reperfusion. In prior trials that included patients with predominantly small core, the volume of salvaged penumbra was large and therefore more strongly linked to outcomes, compared with SELECT2, which focused on large core and hence proportionately less mismatch. The significance of mismatch in patients with large core and receiving EVT will be further informed by a larger sample size with a planned pooling of trial data in patients assessed with advanced imaging. Furthermore, it is likely that a gradient of injury exists within the region of estimated core,[31] and, particularly in large ischemic core, a reduction in the severity of tissue injury is another possible mechanism of reperfusion benefit. This hypothesis is one possible explanation for the limited mediation of functional outcome by follow-up infarct volume[32] and deserves further investigation. Additionally, the concept of mismatch using the larger of noncontrast CT hypodensity core and CT perfusion core differs from that in prior studies,[30,33] and reperfused hypodense regions before treatment may have different recovery potential to persistently hypoperfused hypodense regions.

The benefits of assessing ischemic core volumes prior to EVT could be questioned based on the apparent generalized benefit of EVT across the SELECT2 population. However, there were few patients with very large core (>150 mL) or no mismatch, and real-world treatment decisions are more complex, with many patients having comorbidity and frailty that would have excluded them from the randomized trials. Patient preferences for quality of life should be considered in individualized decision-making, which requires the most accurate prognostic information available. The proportion of patients with core volume greater than 150 mL who regained independent ambulation after EVT was relatively low, and our data indicate that the combination of ischemic core volume, age, and imaging-to-reperfusion time significantly affected that probability, potentially informing discussions with next of kin or interpretation of advance health directives. These findings also bring up important challenges in regard to potential judicious use of limited clinical resources for transfer, operative capacity, and acute and postacute care in the setting of publicly funded health care systems.

These results showed maintained benefit with EVT across ASPECTS strata, including patients with ASPECTS score of 3, which was maintained in a sensitivity analysis using site-adjudicated ASPECTS score. A secondary analysis from the RESCUE Japan LIMIT trial[34] demonstrated loss of treatment effect in patients with ASPECTS score of 3. Most patients were, however, enrolled based on MR diffusion–weighted imaging ASPECTS score, which is shown to be on average 1 point lower than CT ASPECTS score.[35] Additionally, the latter analysis did not adjust for key prognostic characteristics.

In SELECT2, lower baseline ASPECTS score was associated with worse clinical outcomes in patients who received EVT; however, the association was no longer significant when core volume estimates were included as a covariate for adjustment. While no evidence of EVT treatment effect modification was observed based on either imaging modality, quantitative volumetric assessment of core size appeared to provide better prognostication that semiquantitative ASPECTS volume assessment. ASPECTS score remains a viable treatment selection measure to identify EVT-eligible patients with large core in settings where core volume estimates are not readily available.

There was no significant difference in follow-up infarct volume and infarct growth between EVT and medical management. However, patients who achieved functional independence or independent ambulation demonstrated smaller infarct growth. Additionally, in patients with MR diffusion follow-up (comprising two-thirds of the study population), infarct growth was smaller in patients who achieved successful reperfusion with EVT compared with the medical management group or those who did not achieve successful reperfusion after EVT. However, these findings are post hoc in nature.

No significant association was observed between time from onset to reperfusion with independent ambulation. However, time from imaging to reperfusion was significantly associated with independent ambulation. These findings are consistent with previous analysis in patients with smaller core volume in a 0- to 6-hour time window,[36] indicating that baseline imaging accounted for the progression of infarct up to the time of scan, but time-sensitive progression continued to occur between imaging and reperfusion.

Limitations

The study has several limitations. First, while the assessment of CT hypodensity and composite ischemic core concept were preplanned and the broad analysis plan with subgroup definitions were prespecified,[4,15] some analyses were post hoc. Second, a small proportion of patients had significant interval between CT and CT perfusion imaging acquisition. Third, the presented results largely relate to CT-based imaging because too few patients had pretreatment MRI to draw conclusions in that subgroup. Fourth, the follow-up imaging acquisition times varied from 1 to 7 days after stroke, which may have increased heterogeneity in final infarct volume and infarct growth assessment. Fifth, specific predicted probabilities result from models that have not been independently validated and calibrated and hence

need to be interpreted with caution. Sixth, the modest within-subgroup sample size restricts precision for analyses in different volume and ASPECTS strata and power to detect interactions. Seventh, because CT hypodensity volumes were obtained iteratively with readings determined by consensus, interrater and intrarater reliability of these estimates could not be assessed. Furthermore, the process is manual and feasibility in clinical workflow remains limited. Semiautomated and automated software can provide hypodensity volume with reasonable reliability, and the accuracy of the measurement is improving steadily.

Conclusions

In this exploratory analysis of a randomized clinical trial of patients with extensive ischemic stroke, endovascular thrombectomy, compared with medical management, improved clinical outcomes across a wide spectrum of infarct volumes, although enrollment of patients with minimal penumbra volume was low. However, in EVT-treated patients, clinical outcomes worsened as presenting ischemic injury estimates increased.

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